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ORIGINAL COMMUNICATION

Sexual dysfunction is associated with postural instability gait difficulty subtype of Parkinson's disease

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Abstract The pathophysiology of the postural instability gait difficulty (PIGD) subtype of Parkinson's disease (PD) is unclear. Information on the spectrum of non-motor symptoms (NMS) in PIGD phenotype is limited. Our objective is to compare the spectrum of NMS in PIGD subtype compared to non-PIGD subgroup in PD patients and to determine predictive factors that are associated with PIGD phenotype. A total of 432 PD patients comprising 158 PIGD and 274 non-PIGD patients were recruited. NMS burden (frequency and severity) was assessed using non-motor symptom scale (NMSS). In the univariable analysis, NMSS total score ($P = 0.0132$), NMSS domain 3 (mood/apathy) score ($P = 0.0108$), NMSS domain 5 (attention/memory) score ($P = 0.0048$) and NMSS domain 8 (sexual function) score ($P = 0.0052$) were significantly higher in the PIGD group than in the non-PIGD group. Using multivariable logistic regression, UPDRS tremor score, UPDRS PIGD score, H&Y staging score and NMSS domain 8 (sexual function) score were found to be significantly different in the PIGD group compared to the non-PIGD group. We disclosed for the first time that PIGD patients demonstrated a greater overall NMS burden and sexual dysfunction and was an independent predictor of PIGD phenotype. Early intervention of sexual dysfunction symptoms in PIGD patients may improve their clinical management.

Keywords Parkinson's disease · Postural instability gait difficulty · Non-motor symptoms

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that affects 1 % of the population worldwide after the age of 65 years [1]. PD is a systemic neurodegenerative disorder with a broad spectrum of motor and non-motor symptoms (NMS). It is well known that PD motor symptoms contain rigidity, resting tremor, bradykinesia and postural instability which are due to the loss of dopaminergic neurons from the substantia nigra.

Increasing studies indicate that PD patients also experience numerous NMS including neuropsychiatric symptoms, cognitive impairment, behavioral changes, sleep disorders and autonomic and sensory symptoms [2, 3]. NMS occur across all stages of PD and some symptoms, such as depression and anxiety could even precede the diagnosis of PD [4]. Such symptoms usually do not or poorly respond to dopaminergic therapy. It is suggested that these may be a result of non-dopaminergic involvement in the extra-nigral lesion and the peripheral autonomic nervous system [5]. The burden of NMS is a key determinant of quality of life in PD patients [2].

Among the subtypes of [6, 7], the pathophysiology underlying postural instability gait difficulty (PIGD) is unclear. PIGD is characterized by axial symptom

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involvement and is likely to be mediated by brainstem lesions affecting non-dopaminergic systems [8]. The PIGD phenotype usually associates with more rapid disease progression and predicts a worse prognosis [9, 10]. Cognitive impairment, depression and apathy are often correlated with non-tremor-dominant PD subtype [11, 12]. Recent studies reported that the PIGD subtype experienced a greater number of NMS based on Non-Motor Symptom Questionnaire (NMSQ), which focused on the quantity of NMS [13, 14]. It is not known if there is a greater NMS burden in PIGD compared to non-PIGD patients, which has not been investigated previously. To address these gaps in knowledge, we used motor symptom scale (NMSS), including severity and frequency to identify clinical predictive factors of the PIGD phenotype in PD patients.

Patients and methods

Study population

A total of 432 idiopathic PD patients, (as defined by the UK PD Brain Bank criteria [15]), aged between 40 and 85 years, were recruited from movement disorder outpatient clinics in Singapore General Hospital (SGH), a tertiary referral center. The exclusion criteria for this study were as follows: (1) PD patients with significant cognitive impairment, as defined by Elderly Cognitive Assessment Questionnaire (ECAQ) [16] score of five points or less (maximum score of ten points); (2) not idiopathic parkinsonism; (3) patients with a severe chronic debilitating condition (e.g., congestive cardiac failure, central nervous system disorders, renal failure, diabetes mellitus with advanced complications). Our study was approved by Singhealth Centralized Institutional Review Board and was carried out in accordance with the approved guidelines.

All subjects were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS PIGD score is the sum of scores of five items contributing to postural instability and gait difficulties, such as falling, walking and freezing of gait, while the UPDRS tremor score is the sum of scores from nine items, which include rest, postural, action tremor, and so on. Motor phenotypes in our study were defined as either PIGD or non-PIGD using the approach proposed by Jankovic and colleagues [17]. In the present study, there were 158 patients in the PIGD group and 274 patients in the non-PIGD group (including 93 tremor dominant and 181 indeterminate subtypes).

Data collection and assessments

Demographic data were collected from all subjects. NMS burden was evaluated by non-motor symptom scale (NMSS) [18]. NMSS comprises 30 items which are grouped into nine domains (cardiovascular domain, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function and miscellaneous). Olfaction impairment and autonomic failures are included in the miscellaneous domain. Each item is rated with a different level of severity (scored from 0 to 3) and frequency (scored from 1 to 4) over the past month, and the burden of that symptom is the result of severity rating multiplied by frequency rating. A domain score is the sum of the relevant items scores within that domain. The NMSS total score is calculated by the sum of all the domain scores, indicating the overall NMS burden in a patient and the maximum NMSS score of 360.

The quality of life (QoL) was assessed by the Parkinson's Disease Questionnaire-39 item version (PDQ-39), which contains 39 questions grouped into eight domains (mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognitive impairment, communication and bodily discomfort). Summary index (SI) is calculated for the total PDQ-39 scale (PDQ-39 SI) and the eight domains. The range of each domain SI is from 0 to 100. A higher PDQ-39 SI reflects poorer quality of life in PD patients.

Along with NMSS and PDQ-39, modified Hoehn and Yahr (H&Y) staging scale, Schwab and England activities of daily living scale (ADL scale) were used to assess disease severity and daily living ability, respectively. The levodopa-equivalent daily dose (LEDD) was calculated from the standardized formula [19].

Statistical analysis

The R version 3.0.2 (http://www.r-project.org) was used to do all the analyses. Frequency together with proportion was reported for categorical data, while mean with standard deviation (SD) or median with interquartile range (IQR) was reported for continuous variables, where applicable. Fisher's exact test was carried out to compare the categorical variables between the PIGD and non-PIGD groups, while student's T test or Mann–Whitney U test was performed to compare continuous variables between the PIGD and non-PIGD patients.

Univariable and multivariable logistic regression was performed to identify those potential factors in differentiating between the PIGD and non-PIGD group. Backward elimination involving starting with all candidate factors identified by univariable logistic regression at cutoff of 0.2 was carried out to build the final multivariable model. Only those factors with P value less than 0.05 were included in the final model. The primary aim of our study is to identify potential factors to differentiate the PIGD and non-PIGD patients using logistic regression and this requires at least 15 patients for one coefficient in the smallest group. We had 158 PIGD patients and this gave us sufficient power

(>80 %) to develop a multivariable logistic regression model with at least ten coefficients. Our current model included four coefficients only.

Results

In total, 158 patients in the PIGD group and 274 patients in the non-PIGD group were included in the study. The mean age was 66.6 ± 9.8 years in the PIGD group and 65.1 ± 9.8 in the non-PIGD group.

Patients in both groups were similar in terms of age, age of onset, disease duration and other morbidity conditions (all $P > 0.05$).

More patients in the PIGD group (65.8 %) were male compared to the non-PIGD group (55.5 %) ($P = 0.0419$). A higher percentage of patients (12.2 %) had PD family history in the PIGD group than non-PIGD group (5.1 %) ($P = 0.0132$). More patients were prescribed levodopa in the PIGD group (PIGD: 89.9 %, non-PIGD: 72.8 %) ($P < 0.0001$), while more patients were given selegiline in the non-PIGD group (PIGD 20.3 %, non- PIGD: 36.8 %) ($P = 0.0003$). The mean levodopa-equivalent daily dose (LEDD) was 428.5 ± 304.85 mg/day in the PIGD group and 258.8 ± 240.12 mg/day in the non-PIGD group ($P < 0.0001$). A summary of the demographic data of both groups are listed in Table 1.

In the univariable analysis, Mann–Whitney *U* test found that UPDRS PIGD score ($P < 0.0001$), UPDRS motor sum ($P < 0.0001$), NMSS total score ($P = 0.0132$), NMSS domain 3 (mood/apathy) score ($P = 0.0108$), NMSS domain 5 (attention/memory) score ($P = 0.0048$), NMSS domain 8 (sexual function) score ($P = 0.0052$), PDQ-39 domain 7 SI ($P = 0.0488$) and H&Y stage ($P < 0.0001$) were significantly higher in the PIGD group than in the non-PIGD group, while UPDRS tremor score, ADL score and ECAQ score were significantly higher in the non-PIGD patients ($P < 0.0001$). H&Y stage score and UPDRS motor sum in the PIGD group were significantly higher than in the non-PIGD group based on the similar disease duration among the two groups. Differences of NMS and other clinical assessments in the PIGD and non-PIGD group are shown in Table 2.

In the multivariable logistic regression model, the following factors [gender, positive PD family history, LEDD, UPDRS motor sum, NMSS domain 3 (mood/apathy) score, NMSS domain 5 (attention/memory) score, PDQ-39 domain 7 SI, ADL, ECAQ] were excluded as potential risk factors. UPDRS tremor score, UPDRS PIGD score, H&Y stage and NMSS domain 8 (sexual function) were found to have significant discriminative power in differentiating the PIGD group from the non-PIGD group (Table 3).

Patients with higher UPDRS PIGD score [OR = 2.789, 95 % CI (1.925, 4.418)], higher H&Y stage [OR = 9.326, 95 % CI (3.174, 30.109)] and higher NMSS domain 8 (sexual function) score [OR = 1.485, 95 % CI (1.031, 2.142)] had positive association with the PIGD subtype. However, those with higher UPDRS tremor score [OR = 0.142, 95 % CI (0.079, 0.224)] had negative correlation with PIGD phenotype.

Discussion

In this study, we used NMSS (eight different domains and NMS burden) to assess the comprehensive aspects of NMS in the PIGD subtype of PD patients. The univariable analysis suggested that PIGD patients suffered from more severe cognitive impairment, memory problem, apathy and mood disorders. This is consistent with studies that focused on cognitive and mood evaluation of the PIGD phenotype [11, 20, 21]. There have been various hypotheses on neural basis for such an association. Gray matter (GM) atrophy, especially in the frontal gyrus, is more apparent in PIGD patients on magnetic resonance imaging (MRI) [22]. This finding might partially explain the more severe cognitive impairment in the PIGD group, as the frontal region usually correlates with the development of cognitive functions [23]. White matter lesion is another important factor which may contribute to the strong association of the NMS and PIGD phenotype. A higher prevalence of leukoaraiosis has been found in the PIGD subgroup on MRI study. This may explain why more patients in the PIGD group have cognitive and memory problems, since leukoaraiosis indicates a higher risk to develop cognitive impairment and early dementia [24]. The fact that the PIGD phenotype is prone to depression might also be due to white matter damage, especially in the cortico-limbic and medial thalamic areas [25, 26]. There is also significant impairment of the corpus callosum in the PIGD phenotype of PD patients on diffusion tensor imaging [27]. It has been known that impairment of the corpus callosum (serving as the largest fiber pathway and central interconnecting structure in the brain) associates with major depressive disorder [28]. In addition to anatomical evidence, we postulate that similar pathophysiological processes underlie these associations. The results of cerebrospinal fluid transmitter levels in PD patients showed that non-dopaminergic transmitter deficits were more remarkable in patients who developed axial symptoms than those with tremor-dominant symptoms [29]. The cause of NMS in PD patients was reported to correlate with widespread non-dopaminergic involvement. Taylor and colleagues also suggested that aggregation of symptoms, which consists of cognitive, attention and motor impairments, result from common neurodegenerative processes, such as gradual loss of cholinergic function [21]. Taken together, we reason that the PIGD phenotype is

Table 1 Comparison of demographic data between the PIGD and non-PIGD group

	PIGD ($n = 158$)	Non-PIGD ($n = 274$)	P value
Age	66.6 ± 9.8	65.1 ± 9.8	0.1299
Age of onset	60.8 ± 10.7	60.3 ± 9.9	0.6968
Age of diagnosis	61.7 ± 10.4	61.2 ± 10.0	0.6718
Disease duration	5.0 (2.0, 8.8)	4.0 (1.0, 7.0)	0.8461
Gender			**0.0419***
Male	104 (65.8 %)	152 (55.5 %)	
Female	54 (34.2 %)	122 (44.5 %)	
Ethnicity			0.4172
Chinese	139 (88.0 %)	248 (90.5 %)	
Non-Chinese	19 (12.0 %)	26 (9.5 %)	
PD family history			**0.0132***
No	137 (87.8 %)	259 (94.9 %)	
Yes	19 (12.2 %)	14 (5.1 %)	
Young onset			1.0000
No	130 (85.5 %)	225 (85.9 %)	
Yes	22 (14.5 %)	37 (14.1 %)	
Hypertension (%)			0.3658
No	80 (51.0)	151 (55.7)	
Yes	77 (49.0)	120 (44.3)	
Hyperlipidemia (%)			0.4073
No	94 (59.9)	174 (64.2)	
Yes	63 (40.1)	97 (35.8)	
Diabetes mellitus (%)			0.3724
No	123 (78.3)	223 (82.3)	
Yes	34 (21.7)	48 (17.7)	
Ischemic heart disease (%)			0.4182
No	138 (87.9)	245 (90.4)	
Yes	19 (12.1)	26 (9.6)	
Levodopa administration			**<0.0001***
No	16 (10.1 %)	74 (27.2 %)	
Yes	142 (89.9 %)	198 (72.8 %)	
Dopamine agonist administration			0.5982
No	133 (84.2 %)	223 (81.7 %)	
Yes	25 (15.8 %)	50 (18.3 %)	
Selegiline			**0.0003***
No	126 (79.7 %)	172 (63.2 %)	
Yes	32 (20.3 %)	100 (36.8 %)	
Trihexyphenidyl administration			0.4683
No	104 (65.8 %)	169 (62.1 %)	
Yes	54 (34.2 %)	103 (37.9 %)	
Amantadine			0.0688
No	136 (86.1 %)	250 (91.9 %)	
Yes	22 (13.9 %)	22 (8.1 %)	
LEDD (mg/day)	428.5 ± 304.85	258.8 ± 240.12	**<0.0001***

Bold values are statistically significant ($P <$ Fisher's exact test was carried out to compare the categorical variables between PIGD and non-PIGD groups; frequency together with proportion was reported for categorical data

Student's T test was performed to compare continuous variables which followed normal distribution. Mean with standard deviation (SD) was reported for such continuous data

PD Parkinson's disease, *LEDD* levodopa-equivalent daily dose

Table 2 Differences of non-motor symptoms and other clinical assessments in the PIGD and non-PIGD group

	PIGD ($n = 158$)	Non-PIGD ($n = 274$)	P value
UPDRS TREMOR score	0 (0, 1.0)	2.0 (1.0, 5.0)	**<0.0001***
UPDRS PIGD score	4.0 (4.0, 6.0)	2.0 (0.5, 4.0)	**<0.0001***
UPDRS motor sum	29.0 (21.6, 36.0)	13.0 (7.0, 29.8)	**<0.0001***
NMSS total score	27.5 (13.6, 50.0)	20.0 (9.0, 39.0)	**0.0132***
NMSS total prevalence	8.5 (5.0, 12.0)	7.0 (4.0, 11.0)	0.1074
NMSS domain 1 score (cardiovascular)	0 (0, 1.0)	0 (0, 1.0)	0.9443
NMSS domain 2 score (sleep/fatigue)	4.0 (1.0, 12.0)	4.0 (1.0, 11.0)	0.5946
NMSS domain 3 score (mood/apathy)	3.0 (0, 11.0)	1.0 (0, 7.8)	**0.0108***
NMSS domain 4 score (perceptual problems)	0 (0, 0)	0 (0, 0)	0.0655
NMSS domain 5 score (attention/memory)	2.0 (0, 5.0)	1.0 (0, 3.0)	**0.0048***
NMSS domain 6 score (gastrointestinal)	1.0 (0, 4.0)	0 (0, 4.0)	0.4687
NMSS domain 7 score (urinary)	4.0 (0, 8.0)	3.0 (0.3, 7.0)	0.1625
NMSS domain 8 score (sexual function)	0 (0, 2.0)	0 (0, 0)	**0.0052***
NMSS domain 9 score (miscellaneous)	1.0 (0, 4.0)	1.0 (0, 4.0)	0.6770
PDQ total score	22.0 (9.3, 42.0)	17.0 (6.3, 37.8)	0.0763
PDQ-39 SI	13.2 (5.5, 25.2)	10.8 (4.2, 23.7)	0.0956
PDQ-39 domain 1 SI (mobility)	13. 8 (2.5, 45.0)	7.5 (0, 35.0)	0.0828
PDQ-39 domain 2 SI (activities of daily living)	8.3 (0, 29.2)	8.3 (0, 24.0)	0.0793
PDQ-39 domain 3 SI (emotional well-being)	10.4 (0, 29.2)	8.3 (0, 25.0)	0.5202
PDQ-39 domain 4 SI (stigma)	0 (0, 12.5)	0 (0, 6.3)	0.1550
PDQ-39 domain 5 SI (social support)	0 (0, 8.3)	0 (0, 0)	0.4446
PDQ-39 domain 6 SI (cognitive impairment)	18.8 (6.3, 37.5)	12.5 (0, 31.3)	0.1330
PDQ-39 domain 7 SI (communication)	0 (0, 31.3)	0 (0, 16.7)	**0.0488***
PDQ-39 domain 8 SI (bodily discomfort)	16.7 (0, 31.3)	16.7 (0, 33.3)	0.6403
H&Y [median (IQR)]	2.5 (2.5, 2.9)	2.0 (1.0, 2.5)	**<0.0001***
ADL scale	80.0 (70.0, 90.0)	90.0 (80.0, 90.0)	**<0.0001***
ECAQ	9.0 (8.0, 10.0)	9.0 (8.0, 10.0)	**<0.0001***

Bold values are statistically significant ($P < 0.05$)

Mann–Whitney U tests was carried out to compare the continuous variables which were not distributed normally between PIGD and non-PIGD. Median with interquartile range (IQR) was reported for such continuous variables

UPDRS Unified Parkinson's disease Rating Scale, *NMS* non-motor symptom, *PDQ-39* Parkinson's Disease Questionnaire-39 item version, *H&Y* Hoehn and Yahr staging scale, *ADL scale* Schwab and England Activities of Daily Living Scale, *ECAQ* Elderly Cognitive Assessment Questionnaire

Table 3 Potential determinants in differentiating between the PIGD group and non-PIGD group

Variable	OR (95 % CI)	P value
UPDRS tremor score	0.142 (0.079, 0.224)	<0.0001
UPDRS PIGD score	2.789 (1.925, 4.418)	<0.0001
H&Y stage	9.326 (3.174, 30.109)	<0.0001
NMSS domain 8 score (sexual function)	1.485 (1.031, 2.142)	0.0340

Bold values are statistically significant ($P < 0.05$)

Multivariable logistic regression was performed to identify those potential factors in differentiating between the PIGD and non-PIGD group

more likely to experience NMS, as they might share similarity in both neurological anatomy and pathophysiology. Prospective clinical pathological correlation studies are useful to confirm and provide new insights into the pathogenesis.

Previous studies have used NMSQ to explore the comprehensive relationship between NMS and the PIGD phenotype. Herman and colleagues reported that the majority of cognitive assessments were not significantly different between the PIGD group and the tremor-dominant group

[14]. In our study, cognitive impairment was eliminated in the multivariable regression model which was consistent with their conclusion. Khoo and colleagues reported that only sialorrhea was significantly more common in the PIGD phenotype than in the tremor-dominant subtype [13]. The differences with our study may partially be explained by different disease stages, since their subjects were early PD patients and ours were advanced PD patients.

In our study, we demonstrated for the first time that the overall burden of NMS was more severe among patients in the PIGD group, which was agreeable with the proposal that NMS and axial impairment arise from similar neuropathology. Importantly, we found that the PIGD phenotype of PD patients experienced heavier burden in NMSS domain 8 (sexual function). Sexual dysfunction is common in PD and usually correlate with depression [30]. In addition, depressive disorders negatively influence cognition in PD patients [31]. The cause and effect between these factors are hard to determine. In our study, sexual dysfunction was retained while the potential determinants (cognition and mood) were removed from the multivariable regression model, which indicated that sexual dysfunction was strongly associated with the development of the PIGD phenotype and may be partially responsible for depression and cognitive dysfunction in PIGD patients. This finding suggested that a detailed assessment and proper treatment of sexual dysfunction might help to improve the clinical management of PD patients, especially in the PIGD subgroup. Allcock and colleagues reported that the PIGD phenotype was related to greater severity of autonomic symptoms, though detailed association was not available in terms of PIGD phenotype-related autonomic symptoms [32]. In our study, the PIGD phenotype experienced significantly worse sexual dysfunctions compared to the non-PIGD group. While the other autonomic functions, such as NMSS domain 1 (cardiovascular) and NMSS domain 9 (miscellaneous, e.g., pain, smelling, sweating, weight), were not significantly affected in the PIGD group. Sexual dysfunction identified by us and autonomic symptoms revealed by Allcock and colleagues among PIGD patients indicate that the PIGD phenotype was indeed associated with more severe autonomic symptoms. Our results were acquired from patients' questionnaire interview during ON state. The relationship between autonomic symptoms and the PIGD phenotype needs to be further confirmed by enlarging the patient pool and applying more comprehensive methods to assess autonomic symptoms.

The role of genetic factors in the PIGD phenotype is still under debate. Healy and colleagues found that leucine-rich repeat kinase 2 gene (LRRK2) mutation carriers of PD are more likely to manifest the tremor-dominant motor phenotype, which has slower motor progression and less cognitive impairment compared to the PIGD phenotype [33]. However, accumulating evidence indicates that G2019S LRRK2 carriers generally present with the PIGD phenotype [10, 34]. In our study, 12.2 % of the patients in the PIGD group had a positive PD family history. The percentage was significantly higher than 5.1 % in the non-PIGD group, which indicated a strong association between familial PD patient and PIGD phenotype. It is useful to further screen PIGD patients for genes linked to PD.

Hariz and colleagues also reported that the PIGD subtype of newly diagnosed PD patients had already experienced worse conditions in ADL and quality of life (especially in mobility, communication area) at the first visit compared to the tremor-dominant type [35], mainly due to impairment of axial symptoms. We also found that PD patients with the PIGD phenotype have a poorer daily living ability through ADL scale assessment and worse QoL scores in communication aspects. We could not find significant difference in the PDQ-39 summary index and the mobility scores between the PIGD phenotype and the non-PIGD group. QoL was affected by many factors, including disease stage, motor fluctuation and treatment. The patients in our study had mean disease duration over 5 years, which is different from early PD patients without any treatment in the above study. The different disease stage and treatment condition may account for the differences in QoL.

Factor and colleagues have reported that postural instability with falling (PIF) and freezing of gait (FOG) is a distinct subtype in the PIGD form of PD. FOG was associated with psychotic symptoms, while PIF was related to depression [36]. For our study, it was difficult to separate these two different subtypes from the PIGD group completely since a large number of patients showed mixed symptoms between these two phenotypes.

In conclusion, we demonstrated for the first time that PIGD patients presented a greater overall NMS burden, and sexual dysfunction was strongly associated with the PIGD phenotype of PD patients. In addition, PIGD patients experienced more severe cognitive, memory and mood problems and faster disease progression than non-PIGD patients. Early intervention of sexual dysfunction symptoms may help to improve the clinical management of the PIGD phenotype of PD patients.

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Compliance with ethical standards

Conflicts of interest The authors declare no competing financial interests.

Ethical statement Compliance with ethical standards from Singhealth Centralised Institutional Review Board.

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