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ORIGINAL RESEARCH

Non-Motor Symptoms of the Postural Instability and Gait Difficulty Subtype in De Novo Parkinson's Disease Patients: A Cross-Sectional Study in a Single Center

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Background and Purpose: Little is known about non-motor symptoms (NMSs) associated with the postural instability and gait difficulty (PIGD) phenotype, especially in de novo Parkinson's disease (PD) patients. The aims of this study were to compare NMSs between the tremor dominant (TD) and PIGD phenotypes in de novo PD patients and to determine factors that are associated with the PIGD subtype.

Patients and Methods: In a cross-sectional study conducted at our single center, 226 de novo PD patients with a median disease duration of 2 years were recruited. Data, including comprehensive demographics, motor subtypes and NMSs were obtained. Motor subtypes were classified as PIGD and non-PIGD (TD and indeterminate) by Jankovic's method. NMSs were evaluated by the non-motor symptoms questionnaire (NMSQuest).

Results: We identified 73 (32.3%), 34 (15.0%) and 119 (52.7%) patients with TD, intermediate and PIGD subtypes, respectively. Patients with the PIGD subtype had poorer ADL, motor, depression, anxiety, sleep, and non-motor scores compared with those with the TD subtype. In the NMSQuest, the prevalence of cardiovascular, sleep, mood/cognitive and miscellaneous domains was increased in patients with the PIGD subtype compared with patients with the TD subtype. Multivariable forward stepwise logistic regression revealed that the Hamilton Depression Scale (HAMD) [odds ratio (OR), 1.059; 95% confidence interval (CI), 1.016–1.104, $p = 0.007$] and pain (OR, 3.175; 95% CI, 1.695–5.947, $p < 0.001$) exhibit significant discriminative power in differentiating PIGD and non-PIGD groups.

Conclusion: The PIGD group had more severe cardiovascular symptoms, sleep impairments, mood disturbances and pain. We demonstrated for the first time that pain was associated with the PIGD phenotype. Prompt detection and early treatment of NMSs related to the PIGD phenotype may improve patient outcomes.

Keywords: de novo Parkinson's disease, motor subtypes, non-motor symptoms, tremor dominant, postural instability and gait difficulty

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Introduction

Parkinson's disease (PD) is a chronically progressive neurodegenerative disorder with a wide variety of clinical manifestations that encompass both motor and non-motor symptoms (NMSs).[1] The heterogeneity in clinical manifestations of PD has been conceptualized by a taxonomy of subgroups based on family history, age at onset, variable progression, patterns in motor symptoms, and NMSs, such as dementia and

depression.[2–5] The clinical phenotypes of PD can be subdivided into postural instability and gait difficulty (PIGD) and non-PIGD (tremor dominant (TD) and indeterminate) subtypes empirically according to the presence of prominent motor symptoms.[2] Compared to the non-PIGD phenotype, the PIGD phenotype is associated with more rapid disease progression and less favorable outcomes.[2,6] However, the pathophysiology underlying the PIGD phenotype remains unclear.

In addition to motor disturbances, various NMSs, including sleep disorders, neuropsychiatric symptoms, and cognitive impairment, are experienced by PD patients.[7] The onset of some NMSs, such as hyposmia, REM sleep behavior disorder (RBD) and constipation, may precede the diagnosis of PD by years and significantly increase the risk of developing PD, as they are prodromal PD markers.[8–10] In addition, some NMSs are insensitive to dopaminergic therapy, which may result from extensive nondopaminergic neurodegeneration.[11] As the disease progresses, NMSs, rather than motor disability, have a major detrimental effect on patients' prognoses and quality of life.[12,13] Despite their clinical significance, NMSs remain under-recognized and consequently undertreated.[14]

Therefore, a comprehensive understanding of NMSs related to the PIGD subtype has the potential to provide further insights into the pathogenesis, clinical progression, and personalized treatment of the PIGD subtype. Previous studies have reported that patients with the PIGD subtype exhibit a wide variety of NMSs, especially in patients with advanced PD.[15–17] Nevertheless, to the best of our knowledge, there is a paucity of work on NMSs of the PIGD subtype in de novo PD patients. To address these gaps in knowledge, the goals of this study were to examine NMSs of the PIGD phenotype in de novo PD patients and to identify factors that are related to the PIGD phenotype. We hypothesized that specific NMSs are associated with the PIGD subtype.

Patients and Methods
Patients
A total of 226 idiopathic PD patients diagnosed on the basis of the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria were recruited from the Department of Neurology at the Affiliated Brain Hospital of Nanjing Medical University from January 2012 to December 2019.[18] Patients were followed up at least once and exhibited positive responsiveness to levodopa. The exclusion criteria for this study were as follows: (1)

individuals who were undergoing or underwent treatment with antiparkinsonian agents, (2) those with middle- or late-stage PD (modified H-Y stage ≥3), (3) those with atypical or secondary parkinsonism, (4) those with clinically significant lesions visible on brain magnetic resonance imaging (MRI) scans, (5) those with a severe chronic condition (eg, renal failure, cardiac failure, diabetes with complications), and (6) those who were unable to complete clinical evaluations.

This research was approved by the Medical Ethics Committee of Affiliated Brain Hospital of Nanjing Medical University, and the approval numbers were "2011-KY003 and 2015-KY030." This study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to the experiment.

Clinical Evaluation
Demographic and clinical characteristics of the patients were recorded before dopaminergic medication was started. The participants answered questions about their age, gender, years of formal education, age at onset of PD, and disease duration in years. The participants' level of independence during activities of daily living (ADL) was assessed using ADL (part II) subscales of the Unified Parkinson's Disease Rating Scale (UPDRS). The state of parkinsonism was evaluated by the motor (part III) subscales of the UPDRS and the modified Hoehn-Yahr (H-Y) staging system. General cognition was measured with the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Mood was assessed with the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA). Sleep was measured with the Parkinson Disease Sleep Scale (PDSS). NMSs were evaluated by the non-motor questionnaire (NMSQuest).[19] The NMSQuest consists of 30 items that are divided into nine domains (cardiovascular, sleep, mood/cognitive, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function and miscellaneous).[20]

Subtype Classifications
The patients were included in either the PIGD or non-PIGD (TD and indeterminate) subtype groups based on the method proposed by Jankovic.[2] The ratio of the mean UPDRS tremor scores (UPDRS III items 20–21 and UPDRS II item 16) to the mean UPDRS PIGD scores (UPDRS III items 29 and 30 and UPDRS II items 13–15) was used to identify PIGD PD patients (ratio ≤1), TD PD patients (ratio ≥1.5) and indeterminate PD patients (ratios >1.0 and <1.5).

Statistical Analysis

IBM SPSS software version 25.0 was used to perform all statistical analyses. The Kolmogorov–Smirnov test was used to determine the normality of quantitative data. The differences in the gender distributions were evaluated using chi-square tests. Among TD/indeterminate/PIGD subtypes, one-way analysis of variance (ANOVA) was performed to compare the differences in demographic and clinical variables other than gender when both sets of data followed a normal distribution; for non-normally distributed data, the Kruskal–Wallis H-test was used. A two-sample t-test was performed to compare the differences in demographic and clinical variables other than gender between the TD and PIGD groups when both sets of data followed a normal distribution; for non-normally distributed data, the Mann–Whitney U-test was used. Statistical comparisons of the prevalence of NMSs between the TD and PIGD groups were performed using the chi-square test. Univariable and multivariable forward stepwise logistic regressions were performed to identify potential factors to differentiate the PIGD motor phenotype versus the non-PIGD motor phenotype. All variables with $p < 0.20$ in the univariate logistic regression were included in a forward stepwise procedure to build the final multivariable model. $P < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of all 226 patients with de novo PD are summarized in Table 1. To elucidate the features of the PIGD subtype, we compared the distributions of demographic and clinical characteristics between the TD and PIGD groups. No significant differences in age, gender, years of formal education, age at onset, disease duration, H-Y stage, MMSE score or MoCA score were noted. Scores related to ADL, motor symptoms, and NMSs, including the UPDRS ADL, UPDRS motor, HAMD, HAMA, PDSS and NMSQuest scores, were significantly different between the two groups. The patients with the PIGD subtype had poorer ADL ($p = 0.004$), motor ($p = 0.013$), depression ($p < 0.001$), anxiety ($p = 0.003$), sleep ($p = 0.040$), and non-motor scores ($p = 0.001$) compared with TD subtype patients (Table 1).

Table 1 Demographic and Clinical Characteristics of Overall Study Population

Variables	Overall (n=226) (100%)	TD (n=73) (32.3%)	Intermediate (n=34) (15.0%)	PIGD (n=119) (52.7%)	p-value[a]	p-value[b]
Age (years)	61.07±10.22	59.48±11.31	63.91±8.78	61.23±9.79	0.109	0.259
Gender (male)	111 (49.1%)	39(53.4%)	18(52.9%)	54(45.4%)	0.495	0.279
Formal education	9.0 (6.0, 12.0)	9.0 (6.0, 12.0)	11.5 (5.8, 15.0)	9.0 (6.0, 12.0)	0.747	0.723
Age at onset	58.50±10.31	57.03±11.65	60.79±9.18	58.74±9.67	0.199	0.273
Disease duration	2.0 (1.0, 3.0)	2.0 (1.0, 3.5)	1.0 (1.0, 5.0)	2.0 (1.0, 3.0)	0.521	0.218
H-Y stage	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)	0.629	0.560
UPDRS ADL	8.0 (5.0, 12.0)	7.0 (4.0, 11.0)	9.5 (6.0, 13.5)	9.0 (5.0, 13.0)	**0.011**	**0.004**
UPDRS motor	20.0 (14.0, 27.0)	18.0 (10.0, 25.5)	23.0 (12.75, 28.75)	21.0 (15.0, 27.0)	**0.043**	**0.013**
MMSE	28.0 (26.0, 29.0)	28.0 (26.0, 29.0)	29.0 (26.0, 30.0)	28.0 (26.0, 29.0)	0.522	0.660
MoCA	24.0 (20.0, 26.0)	24.0 (20.0, 26.8)	25.0 (21.0, 27.0)	24.0 (20.0, 26.0)	0.169	0.525
HAMD	8.0 (4.0, 13.0)	6.0 (2.0, 11.0)	7.0 (4.0, 12.0)	9.0 (5.0, 16.0)	**0.001**	**<0.001**
HAMA	6.0 (3.0, 11.0)	4.0 (2.0, 9.0)	5.0 (3.0, 11.0)	7.0 (4.0, 12.0)	**0.008**	**0.003**
PDSS	128.5 (109.8, 140.3)	130.0 (114.0, 143.5)	136.5 (111.5, 144.5)	124.0 (100.0, 138.0)	**0.030**	**0.040**
NMSQuest	8.0 (5.0, 12.0)	6.0 (4.0, 9.0)	8.0 (4.8, 12.3)	9.0 (6.0, 12.0)	**0.004**	**0.001**

Notes: Data are presented as the mean±SD, n (%) and median (interquartile range). Bold values are statistically significant ($p < 0.05$). [a]Comparisons of variables among TD, PIGD, and intermediate subtypes. Univariate p-values calculated using ANOVA, Kruskal–Wallis H-test, or Chi-square test. [b]Comparisons of variables between TD and PIGD subtypes. Univariate p-values calculated using Student's t test, Mann–Whitney U-test, or Chi-squared test.
Abbreviations: TD, tremor dominant; PIGD, postural instability and gait difficulty; H-Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; NMSQuest, Non-motor Questionnaire.

NMSs Between TD and PIGD Motor Subtypes

As the total NMSQuest score significantly differed between the TD and PIGD groups, the prevalence of symptoms corresponding to each domain and item of the NMSQuest in the two groups was further compared in Table 2. "Orthostatic symptoms" in the cardiovascular domain ($p = 0.003$), "vivid dream imagery" in the sleep domain ($p = 0.023$), "low mood" and "anxiety" in the mood domain ($p = 0.045$, $p = 0.011$), and "pain" in the miscellaneous domain ($p = 0.001$) were more prevalent in patients with the PIGD subtype compared with patients with the TD subtype. No differences between the TD and PIGD subtypes were noted in the remaining NMSQuest items.

Potential Factors of the PIGD Motor Phenotype

With univariate logistic regression, the following candidate factors of the PIGD motor phenotype were identified: UPDRS ADL ($p = 0.005$), UPDRS motor ($p = 0.013$), HAMD ($p = 0.001$), HAMA ($p = 0.008$), PDSS ($p = 0.008$), NMSQuest ($p = 0.007$), cardiovascular domain ($p = 0.021$), sleep domain ($p = 0.027$), mood/cognitive domain ($p = 0.035$), weight change ($p = 0.199$) and pain ($p < 0.001$) (Table 3). Then, with multivariable forward step-wise logistic regression, the following factors were excluded as potential risk and protective factors: the UPDRS ADL, UPDRS motor, HAMA, PDSS, NMSQuest, cardiovascular domain, sleep domain, mood/cognitive domain and weight change. The HAMD [odds ratio (OR), 1.059; 95% confidence interval (CI), 1.016–1.104, $p = 0.007$] and pain (OR, 3.175; 95% CI, 1.695–5.947, $p < 0.001$) had significant discriminative power in differentiating the PIGD group from the non-PIGD group (Table 4). Patients with higher HAMD score and incidence of pain exhibited a positive correlation with the PIGD phenotype.

Discussion

Our research deepens the understanding of NMSs related to the PIGD subtype by exploring the characteristics of NMSs in the PIGD subtype and determining potential factors of the PIGD subtype in de novo PD patients. The results in previous studies evaluating NMSs of the PIGD phenotype are limited by the utilization of medications with known anti-dopaminergic effects, long durations from PD diagnosis to study recruitment and differences in the severity of PD in patients.[15,16,21,22] In addition, it is worth noting that the prevalence of PIGD in this study (52.7%) was significantly increased compared with that of the Parkinson's Progression Biomarker Initiative (PPMI) cohort (17.5%) and Deprenyl

Table 2 Comparison of Non-Motor Symptoms (NMS) Between the Tremor Dominant (TD) and Postural Instability and Gait Difficulty (PIGD) Groups of Patients with De Novo Parkinson's Disease (PD)

Variables	TD (n=73) (32.3%)	PIGD (n=119) (52.7%)	*p*-value
D1. Cardiovascular	19 (26.0)	57 (47.9)	**0.003**
1. Orthostatic symptoms	17 (23.3)	53 (44.5)	**0.003**
2. Falls	5 (6.8)	9 (7.6)	0.854
D2. Sleep	54 (74.0)	102 (87.7)	**0.043**
3. Daytime somnolence	12 (16.4)	25 (21.0)	0.436
4. Insomnia	24 (32.9)	50 (42.0)	0.207
5. Vivid dream imagery	30 (41.1)	69 (58.0)	**0.023**
6. Somnambulate	20 (27.4)	45 (37.8)	0.139
7. Restless legs	20 (27.4)	36 (30.3)	0.673
D3. Mood/cognitive	39 (53.4)	85 (71.4)	**0.011**
8. Loss of interest	25 (34.2)	48 (40.3)	0.399
9. Low mood	29 (39.7)	65 (54.6)	**0.045**
10. Anxiety	28 (38.4)	68 (57.1)	**0.011**
D4. Perceptual problems/ hallucinations	24 (32.9)	43 (36.1)	0.646
11. Hallucinations	3 (4.1)	6 (5.0)	1.000
12. Delusions	2 (2.7)	4 (3.4)	1.000
13. Impaired taste or smell	11 (15.1)	28 (23.5)	0.157
14. Diplopia	11 (15.1)	22 (18.5)	0.542
D5. Attention/memory	53 (72.4)	87 (73.1)	0.939
15. Forgetfulness	44 (60.3)	80 (67.2)	0.328
16. Impaired attention	29 (39.7)	55 (46.2)	0.379
D6. Gastrointestinal	45 (61.6)	83 (69.7)	0.248
17. Dysphagia	14 (19.2)	28 (23.5)	0.479
18. Nausea	6 (8.2)	13 (10.9)	0.542
19. Constipation	27 (37.0)	60 (50.4)	0.069
20. Bowel incontinence	2 (2.7)	2 (1.7)	0.618
21. Incomplete bowel emptying	19 (26.0)	43 (36.1)	0.146
22. Sialorrhea	9 (12.3)	27 (22.7)	0.074
D7. Urinary	29 (39.7)	48 (40.3)	0.933
23. Urinary urgency	22 (30.1)	33 (27.7)	0.720
24. Nocturia	17 (23.3)	28 (23.5)	0.969
D8. Sexual function	12 (16.4)	21 (17.6)	0.829
25. Impaired libido	12 (16.4)	18 (15.1)	0.392
26. Sexual dysfunction	8 (11.0)	16 (13.4)	0.613
D9. Miscellaneous	32 (43.8)	83 (69.7)	**<0.001**
27. Weight change	9 (12.3)	27 (22.7)	0.074
28. Pain	15 (20.5)	52 (43.7)	**0.001**
29. Lower limb swelling	7 (9.6)	16 (13.4)	0.424
30. Excessive sweating	22 (30.1)	41 (34.5)	0.536

Notes: Data are expressed as n (%). Bold values are statistically significant ($p < 0.05$). Univariate *p*-values calculated using Chi-square test.

Table 3 Univariate Logistic Regression for Potential Factors of the Postural Instability and Gait Difficulty (PIGD) Phenotype in De Novo Parkinson's Disease (PD)

Variables	β	SE	p-value	OR	95% CI
Age	0.003	0.013	0.803	1.003	0.978–1.029
Gender (male)	−0.316	0.267	0.236	0.729	0.432–1.231
Formal education	−0.002	0.028	0.938	0.998	0.945–1.053
Age at onset	0.005	0.013	0.707	1.005	0.980–1.031
Disease duration	−0.009	0.043	0.838	0.991	0.910–1.079
UPDRS ADL	0.094	0.034	**0.005**	1.099	1.029–1.174
UPDRS motor	0.036	0.015	**0.013**	1.037	1.008–1.067
H-Y stage	0.196	0.294	0.506	1.216	0.683–2.164
MMSE	−0.021	0.034	0.541	0.979	0.915–1.048
MoCA	−0.026	0.026	0.312	0.974	0.926–1.025
HAMD	0.066	0.020	**0.001**	1.068	1.027–1.112
HAMA	0.064	0.024	**0.008**	1.066	1.017–1.117
PDSS	−0.016	0.006	**0.008**	0.984	0.973–0.996
NMSQuest	0.083	0.031	**0.007**	1.086	1.023–1.154
D1. Cardiovascular	0.637	0.276	**0.021**	1.891	1.101–3.248
D2. Sleep	0.755	0.342	**0.027**	2.127	1.088–4.158
D3. Mood/cognitive	0.596	0.282	**0.035**	1.815	1.044–3.154
D4. Perceptual problems/hallucinations	0.027	0.278	0.923	1.027	0.596–1.771
D5. Attention/memory	−0.086	0.304	0.777	0.918	0.506–1.664
D6. Gastrointestinal	−0.061	0.292	0.833	0.940	0.531–1.667
D7. Urinary	−0.109	0.270	0.686	0.897	0.528–1.523
D8. Sexual function	0.126	0.357	0.724	1.134	0.563–2.286
D9. Miscellaneous					
Weight change	0.441	0.343	**0.199**	1.554	1.945–6.642
Pain	1.279	0.313	**<0.001**	3.595	1.945–6.642
Lower limb swelling	0.031	0.393	0.936	1.032	0.478–2.229
Excessive sweating	0.254	0.287	0.378	1.289	0.734–2.264

Notes: Bold values are statistically significant ($p < 0.20$). P-values calculated using univariate logistic regression analysis.
Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living; H-Y, Hoehn and Yahr; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS, Parkinson Disease Sleep Scale; NMSQuest, Non-motor Questionnaire.

Table 4 Multivariable Forward Logistic Regression for Potential Factors of the Postural Instability and Gait Difficulty (PIGD) Phenotype in De Novo Parkinson's Disease (PD)

Variables	β	SE	p-value	OR	95% CI
HAMD	0.057	0.021	0.007	1.059	1.016–1.104
Pain	1.155	0.320	<0.001	3.175	1.695–5.947

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; HAMD, Hamilton Depression Scale.

and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) cohort (29.1%),[2,23] which may be partly because an increasing number of TD patients will enter the PIGD subgroup as the duration of the disease increases.[24] In this study, the median disease duration of patients with de novo PD was 2 years. In comparison, based on the goals of PPMI, the study recruited very early PD patients with an average disease duration starting at 6.7 months after

diagnosis. Similarly, the average disease duration of the DATATOP cohort, which is the basis of the TD/PIGD classi- fication, was 1.0 years.[25]

Norepinephrine (NE) deficiency in the central and per- ipheral nervous systems of PD patients correlates with the PIGD phenotype, sleep impairment, affective disorders and cardiovascular symptoms.[26] Diagnosed PD patients with bradykinesia and rigidity exhibit a more extensive NE defi- ciency in the brain.[27] Further, freezing of gait (FOG), a unique subtype of the PIGD subtype, can also be caused by a reduction in NE innervation in the brain.[28] Therefore, central NE deficiency tends to be noted in the PIGD subtype rather than the TD subtype in PD patients. In addition, central NE deficiency is also related to sleep impairment and affec- tive disorders. A reduction in LC and its projections to the cerebral cortex, basal forebrain, thalamus, dorsal raphe, ped- unculopontine and laterodorsal tegmental nucleus cause

sleep disorders.[29] Emotions, including depression and anxiety are partly governed by NE activity.[30] In addition to central NE degeneration, peripheral noradrenergic cardiac denervation is one of the earliest pathophysiological characteristics of PD and causes cardiovascular symptoms.[26,31–33] PIGD subtype patients had more severe sleep impairments, mood disturbances and cardiovascular symptoms, indicating that the PIGD subtype is connected with more widespread and diffuse neurodegeneration of NE in the central and peripheral nervous systems. Therefore, treatment strategies based on dopaminergic treatment with increased NE enhancement may improve these symptoms of the PIGD subtype. A detailed understanding of NMSs related to the PIGD subtype may improve research on its etiology, subtype-specific biomarkers and therapeutic paradigms of the PIGD subtype.

HAMD and pain are associated with the PIGD subtype. As depression and pain became more severe, the proportion of patients with the PIGD subtype of PD increased. Depression can occur in patients throughout early stages of PD, including the preclinical, prodromal and clinical stages. In preclinical PD, the occurrence of depression is an integral component of progressive neurodegeneration, which eventually leads to dopaminergic neuron death.[34] In prodromal PD, depression, an important prodromal marker, markedly increases an individual's risk of developing PD and occurs within five years before PD is clinically diagnosed.[9,35] In clinical PD, depression is associated with the PIGD subtype rather than the non-PIGD subtype in early PD patients, which may be attributed to the similar pathophysiology of NE deficiency between depression and the PIGD subtype.[26,36,37] Therefore, we believe that depression is an independent risk factor for the PIGD subtype. Importantly, we demonstrated for the first time that pain is related to the PIGD phenotype. To the best of our knowledge, there is no detailed report on the relationship between pain and the PIGD phenotype of PD. Pain is not only an early symptom of PD but also a premotor symptom, and the incidence of pain increases as the disease progresses. A recent systematic review and meta-analysis proposed that pain in PD patients is attributable to a dopamine deficiency leading to obvious hyperalgesia.[38] Dopaminergic striatal denervation in a PIGD group of de novo PD patients was significantly increased compared with that of a non-PIGD group at baseline.[39] Therefore, pain is more common in patients with the PIGD subtype compared with patients with the non-PIGD subtype. Additionally, in a previous retrospective study on self-perceived premotor symptoms

and a cross-sectional study using the King's Parkinson's Disease Pain Scale (KPPS), PIGD patients exhibited an increased frequency of pain compared with non-PIGD patients.[40,41] These evidences suggest that pain is connected with the PIGD subtype. Patients with depression and pain may be warned of a risk of developing the PIGD subtype.

Several caveats must be taken into consideration when interpreting our findings. First, this cross-sectional study was only applicable to PD patients who were newly diagnosed and followed up in our single center and therefore does not reflect general PD patients, especially those in the prodromal, middle or late stage of PD. Nonetheless, the sample size for this study was large enough for analysis. Second, a previous study strongly suggested that a certain proportion of PD patients can develop different motor subtypes of PD after long periods of time.[42] A longitudinal study should be conducted to verify our results. Third, we did not use a detailed instrument to validate the relationship between pain and the PIGD phenotype. In the future, it will be helpful to use more comprehensive methods (such as KPPS) to assess pain.

Conclusion
Patients with the PIGD subtype exhibited more severe cardiovascular symptoms, sleep impairments, and mood disturbances compared with those with the non-PIGD subtype, which could be largely attributed to an underlying NE deficiency in PIGD subtype patients. Furthermore, we demonstrated for the first time that pain is associated with the PIGD phenotype. Prompt detection and early treatment of these NMSs in PIGD patients may improve their treatment and management outcomes.

Data Sharing Statement
The authors declare that data in the manuscript are available from the corresponding author via email under reasonable requests.

Disclosure

The authors declare no financial or other types of conflict of interest.

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