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SCIENTIFIC INVESTIGATIONS

Association of sleep disturbance and freezing of gait in Parkinson disease: prevention/delay implications

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Study Objectives: Freezing of gait (FOG) severely impairs life quality of Parkinson disease (PD) patients. The relationship between sleep disturbance and FOG in PD remains unclear, so in this study, we aimed to investigate that relationship.

Methods: First, we assessed clinical characteristics of freezers and nonfreezers among PD patients. Next, we assessed clinical characteristics of PD patients with different PDSS1 scores (score on first item of Parkinson's Disease Sleep Scale). Finally, we prospectively followed a cohort of nonfreezers from a baseline clinical visit and to a maximum of 18 months and performed a Cox regression analysis to further investigate the relationship between PDSS1 score and FOG in PD.

Results: A total of 163 participants with PD were included in the baseline analysis. The freezers had significantly worse sleep compared with the nonfreezers. The proportion of freezers in the patients with low PDSS1 score (PDSS1 < 6) was significantly higher than that in the patients with high PDSS1 score (PDSS1 ≥ 6). A total of 52 nonfreezers were prospectively followed. During a maximum 18-month follow-up, FOG incidence (73%) in the PDSS1 < 6 group was significantly higher than that (24%) in the PDSS1 ≥ 6 group (P = .008). Low PDSS1 score (hazard ratio = 4.23, 95% CI 1.64–10.92, P = .003) and high levodopa equivalent daily dose (hazard ratio = 4.18, 95% CI 1.62–10.75, P = .003) were significantly associated with an increased hazard of FOG.

Conclusions: Our study indicated that low PDSS1 score may be a risk indicator for the development of FOG and provided important insights into potential targets for the prevention/delay of FOG in PD.

Keywords: Parkinson disease, sleep disturbance, freezing of gait, levodopa, risk indicator

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Freezing of gait (FOG) is a debilitating symptom in patients with Parkinson disease (PD) and severely impairs their quality of life. Increasing evidence shows that sleep disturbance may be related to a higher risk of PD, but the relationship between sleep disturbance and FOG in PD remains unclear.

Study Impact: Our study indicated that low PDSS1 score may be a risk indicator for the development of FOG and provides important insight into potential targets for the prevention/delay of FOG in PD.

INTRODUCTION

Freezing of gait (FOG), clinically characterized as a brief, episodic absence or a marked reduction of forward progression of the feet despite the intention to walk, is a common and debilitating symptom in Parkinson disease (PD).[1,2] Patients feel as if their feet are "glued" to the floor.[3] Previous research reported that approximately 80% of PD patients ultimately developed FOG.[4] FOG is closely related to the risk of falling and worse quality of life. However, to date, the etiology and pathogenesis of FOG are poorly understood and few approaches have been identified to effectively treat it.

While sleep is essential to health,[5] sleep disturbance is commonly observed in patients with PD,[6–8] who experience such symptoms as inability to fall asleep and remain asleep, rapid eye movement (REM) sleep behavior disorder (RBD), and excessive daytime sleepiness. Increasing evidence shows that sleep disturbance may be related to a higher risk of neurodegenerative diseases, such as PD. People with idiopathic REM sleep behavior disorder are at very high risk of neurodegenerative synucleinopathy, including PD.[9] Excessive daytime sleepiness is more frequent in PD even before treatment initiation compared with control participants.[10] Sleep disturbance may precede the typical motor system impairment of PD.[11] Disrupted slow-wave sleep could accelerate and consolidate neurodegeneration and PD progression.[12] The ability of sleep disturbance to predict neurodegenerative diseases has important implications for development of neuroprotective treatment.[13] Treatment of sleep disturbance is associated with improved overall nonmotor symptoms.[14] In addition, recent studies suggest that circadian rhythm disruption may be associated with postural instability and gait initiation impairment in PD patients.[15] REM sleep behavior disorder and excessive daytime sleepiness were shown to be more common in freezers

compared to nonfreezers.[16,17] Although increasing attention has been paid to seeking therapeutic approaches that delay or even prevent the development of FOG and sleep disturbance, the clinical characteristics of freezers and nonfreezers are unclear. In addition, we are unclear about the relationship between sleep disturbance and FOG in PD.

Here, we assessed clinical characteristics of freezers and nonfreezers in PD patients. We also assessed clinical characteristics of PD patients with different PDSS1 score [score on the first item of the Parkinson's Disease Sleep Scale (PDSS)]. Finally, we prospectively followed a cohort of nonfreezers from a baseline clinical visit to a maximum of 18 months and performed a Cox regression analysis to further investigate the relationship between PDSS1 score and FOG in PD.

METHODS

Participants

A total of 188 participants with PD were consecutively recruited between August, 2017, and January, 2018, at the Department of Neurology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. Most participants were Shanghai urban residents. They had been diagnosed by experts in our department based on the Unified Kingdom PD Society Brain Bank Clinical Diagnostic Criteria.[18] Exclusion criteria included: atypical and secondary Parkinsonism, severe mental diseases, self-reported sleep apnea syndrome, a history of deep brain stimulation surgery, inability to walk independently, or inability to complete clinical evaluation due to cognitive impairment. As a result, 25 patients were excluded and 163 patients were left for the baseline analysis (**Figure 1**).

To further explore the relationship between sleep disturbance and FOG in PD, we conducted a prospective study by including a subset of nonfreezers at baseline clinical visit who consented to participate in the subsequent follow-up. The patients were followed up once every 3 months until the end of the study in August, 2019. However, follow-up was terminated once a patient became a freezer. The number of follow-ups ranged from 3 to 7 with a median of 7. Data were also excluded for the patients who did not develop FOG at the end of follow-up. As a result, a total of 52 PD patients were included in the follow-up analysis (**Figure 1**). This study was approved by Xinhua Hospital Ethics Committee Affiliated to Shanghai Jiao Tong University School of Medicine (Approval No. XHEC-F-2016-209). Written informed consent was obtained from all patients.

Assessment of FOG

For each patient, the presence of FOG was classified based on the individual's response to question 1 of the New Freezing of Gait Questionnaire (NFOG-Q) and direct observation of a FOG episode during a clinical or laboratory visit.[19] Before the inquiry, we fully explained the meaning of FOG to all patients with the help of videos to ensure their understanding of FOG—"your feet get glued to the floor while walking, making a turn or when trying to initiate walking." If the presence of FOG was in doubt, the participant was asked to turn in place multiple times to the right and left. In addition, medical records were consulted for a reported history of FOG.[20,21] During the 18-month follow-up, phone inquiry was performed once every 3 months. Based on the previous study[22] suggesting that patients' self-detection may be more reliable than observation by a lay person, ratings were made only by the patients. The total NFOG-Q, which is the sum of parts I, II, and III of the NFOG-Q, reflects the severity of global gait disturbance. Both the baseline and follow-up NFOG-Q were collected and used for our current analyses. Once a patient became a freezer, his NFOG-Q collection was terminated.

Assessment of sleep

Sleep was assessed by the following 4 sleep scales: Pittsburgh Sleep Quality Index (PSQI),[23] the PDSS,[24] REM Sleep Behavior Disorder Questionnaire (score ≥ 19 means RBD),[25] and Epworth Sleepiness Scale (ESS, ≥ 10 means excessive daytime sleepiness).[26] Based on PDSS1score, patients were divided into 2 groups: 1 group with low PDSS1 score (PDSS1 < 6) and the other group with high PDSS1 score (PDSS1 ≥ 6).

Assessment of other clinical characteristics

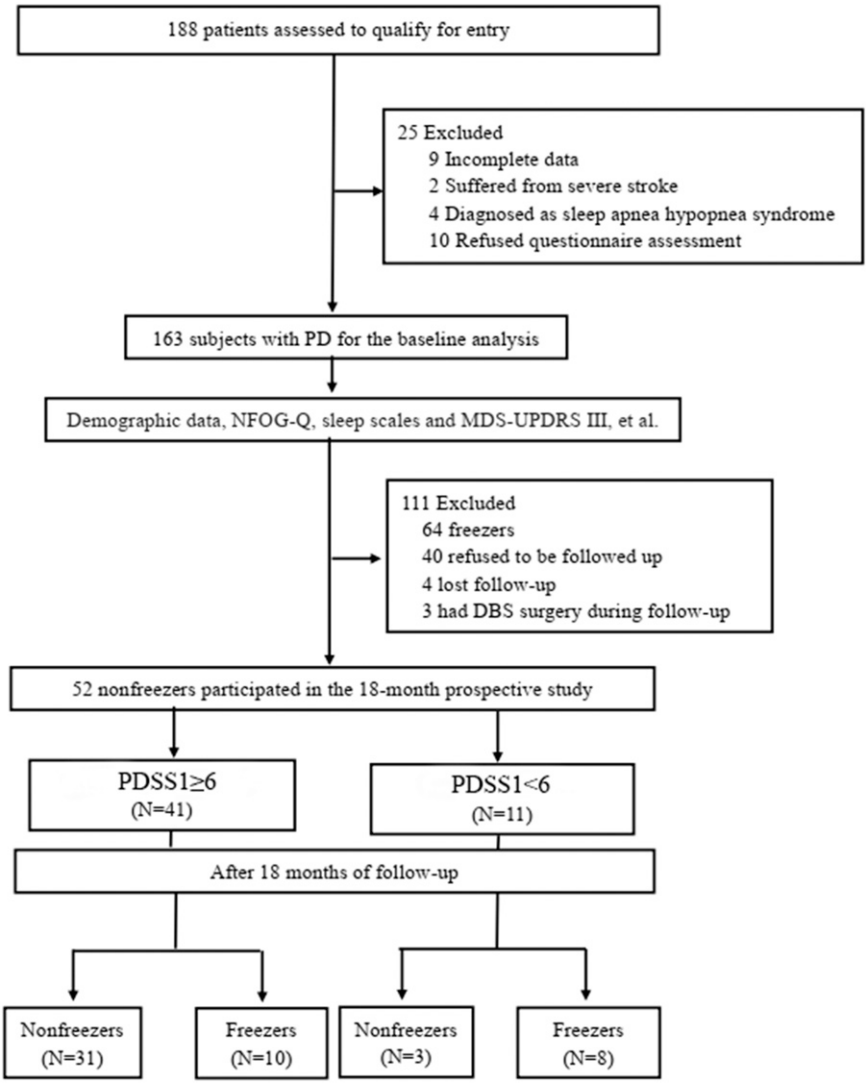
Demographic information included age, sex, age at PD onset, years of education, PD disease duration, and body mass index. The Movement Disorders Society Unified Parkinson Disease Rating Scale part III (MDS-UPDRS III) and Hoehn and Yahr stage were used to assess motor symptoms. The total levodopa equivalent daily dosage (LEDD) was calculated according to the established method.[27] The PD phenotype is defined by the ratio of tremor-dominant (TD) to postural instability/gait difficulty (PIGD) based on some items of MDS-UPDRS III and MDS-UPDRS II, with a ratio of TD/PIGD ≥ 1.15 being classified as TD, ≤ 0.9 as PIGD, and other values as indeterminate.[28] A patient was identified as having motor fluctuation if he/she showed positive response to at least 1 symptom of the 9-Symptom Wearing-off Questionnaire, and if clinical symptoms improved after the patient took medicine or appeared to be an on-off phenomenon. The Non-Motor Symptom Scale (NMSS) was performed to assess global nonmotor symptoms. The Mini-Mental State Examination was used to measure global cognitive function. Anxiety and depression were assessed using Hamilton Anxiety Rating Scale (HAMA) and Hamilton Depression Rating Scale (HAMD), respectively. Parkinson Disease Questionnaire-8 was used to determine patients' quality of life.

In our study, the raters were blinded to patient's group information. All patients were assessed when in a "medication-on" state, and all evaluators received homogeneity training to reduce inter-rater disagreement.

Statistical analyses

Continuous data were presented as mean ± standard deviation or median (interquartile range) and compared by using independent samples *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables were presented as numbers and percentages, and compared by chi-squared or Fisher's exact test, as appropriate. For Cox proportional hazards regression

Figure 1—Flow diagram of the study cohorts.



DBS = deep brain stimulation, MDS-UPDRS III = part III of the Movement Disorders Society Unified Parkinson Disease Rating Scale, NFOG-Q = New Freezing of Gait Questionnaire, PDSS1 = the first item of the Parkinson's Disease Sleep Scale.

analyses, continuous variables were transformed to categorical variables by the corresponding medians when necessary. Annual changes of the continuous variables were also calculated; for example, annual change in HAMA was calculated as annual ΔHAMA = (the ultimate HAMA − the baseline HAMA)/time of follow-up (year).

We used Cox proportional hazards regression to analyze incident FOG. We first used univariable Cox analysis for variables. All baseline variables with values of $P < .1$ in the univariable Cox models were included in a subsequent multivariable Cox model. We then performed a forward stepwise (likelihood ratio) regression for the multivariable Cox regression with a removal P value being .05. The assumption of proportional hazard was assessed by the Schoenfeld residuals test.

A 2-sided P-value < .05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY), GraphPad Prism 8 (GraphPad Corp., San Diego, CA), and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics of freezers and nonfreezers in PD

The 163 participants included 99 nonfreezers and 64 freezers. Demographics and clinical characteristics of both groups were presented in **Table 1**. No significant differences in age, sex, age at PD onset, years of education, and body mass index were observed between the nonfreezers and freezers. The freezers had significantly longer disease duration of PD (6.4 vs 4.4, $P = .002$) and higher LEDD (514.3 vs 375.0, $P < .001$) compared with the nonfreezers. Regarding motor symptoms, the freezers had significantly higher MDS-UPDRS III (27.9 vs 21.1, $P < .001$)

Table 1—Clinical characteristics of freezers and nonfreezers in PD.

Baseline	Groups		*P*
	Nonfreezers (n = 99)	Freezers (n = 64)	
Age, y	66.4 ± 6.2	68.2 ± 7.7	.116[a]
Male, n (%)	53 (54%)	36 (56%)	.734[b]
Age at onset of PD, y	61.4 ± 6.6	61.6 ± 8.7	.901[a]
Education years, y	9.0 (8.0–14.0)	9.5 (8.0–13.5)	.810
BMI	23.6 ± 2.6	23.5 ± 2.9	.850[a]
Disease duration, y	4.4 (2.2–7.2)	6.4 (4.2–9.9)	.002
Hypnotics, n (%)	11 (11%)	14 (22%)	.063[b]
H-Y	2.0 ±.6	2.6 ± .6	< .001[a]
MDS-UPDRS III	21.1 ± 9.7	27.9 ± 11.9	< .001[a]
NMSS score	200.0 (91.0–374.0)	608.0 (351.3–818.5.0)	< .001
HAMA score	5.0 (3.0–8.0)	8.5 (6.0–13.0)	< .001
HAMD score	7.0 (4.0–11.0)	10.5 (8.0–14.8)	< .001
MMSE score	28.2 ± 2.2	26.8 ± 3.4	.005[a]
TD, n (%)	68 (69%)	9 (14%)	< .001[b]
Motor fluctuation, n (%)	28 (28%)	33 (52%)	.003
Dyskinesias, n (%)	5 (5%)	13 (20%)	.002[b]
PDQ-8 score	3.0 (1.0–5.0)	5.0 (2.0–7.0)	< .001
LEDD	375.0 (262.5–625.0)	514.3 (400.0–684.4)	< .001
NFOG-Q	NA	14.63 ± 6.45	NA
PSQI total	5.0 (2.0–10.0)	9.5 (6.0–12.8)	< .001
PDSS total	130.0 (120.0–138.0)	119.5 (109.3–128.8)	< .001
ESS total	5.0 (3.0–7.0)	8.0 (5.3–10.8)	< .001
RBD, n (%)	47 (48%)	28 (44%)	.641[b]
Sleep quality	1.0 (0.0–2.0)	2.0 (1.0–2.0)	< .001
Sleep onset latency	0.0 (0.0–1.0)	1.0 (0.0–2.0)	.001
Sleep disturbances	1.0 (1.0–1.0)	1.0 (1.0–1.0)	.001
Daytime dysfunction	1.0 (0.0–2.0)	2.0 (1.0–2.0)	< .001
Sleep duration	1.0 (0.0–2.0)	2.0 (1.0–2.8)	.007
Sleep efficiency	1.0 (0.0–2.0)	1.0 (0.0–3.0)	.038
Sleep medication	0.0 (0.0–0.0)	0.0 (0.0–0.0)	.125

Results expressed as mean scores ± standard deviation (normally distributed data) or median (interquartile range) (nonnormally distributed data). [a]Independent samples *t* test; [b]Pearson chi-squared test; otherwise Mann-Whitney *U* test used. BMI = body mass index, ESS = Epworth Sleepiness Scale, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, H-Y = Hoehn and Yahr, LEDD = levodopa equivalent daily dose, MDS-UPDRS III = part III of Movement Disorder Society Unified Parkinson's Disease Rating Scale, MMSE = Mini-Mental State Examination, NA = no answer, NFOG-Q = New Freezing of Gait Questionnaire, NMSS = Non-Motor Symptom Scale, PDQ-8 = Parkinson's Disease Questionnaire-8, PDSS = Parkinson's Disease Sleep Scale, PSQI = Pittsburgh Sleep Quality Index, RBD = Rapid Eye Movement Sleep Behavior Disorder Questionnaire, TD = tremor-dominant.

and Hoehn and Yahr score (2.6 vs 2.0, $P < .001$) compared with the nonfreezers. The proportion of TD in the freezers was significantly lower than that in the nonfreezers (14% vs 69%, $P < .001$). Moreover, the proportion of motor fluctuation (52% vs 28%, $P = .003$) and dyskinesias (20% vs 5%, $P = .002$) in the freezers was significantly higher than that in the nonfreezers, respectively. Regarding nonmotor symptoms, the total score of NMSS (608.0 vs 200.0, $P < .001$), HAMA (8.5 vs 5.0, $P < .001$), and HAMD (10.5 vs 7.0, $P < .001$) in the freezers was significantly higher than that in the nonfreezers, respectively. In addition, Mini-Mental State Examination score in the freezers was significantly lower than that in the nonfreezers (26.8 vs 28.2, $P = .005$).

Furthermore, the freezers had significantly higher total PSQI (9.5 vs 5.0, $P < .001$) and ESS (8.0 vs 5.0, $P < .001$) scores and lower total PDSS (119.5 vs 130.0, $P < .001$) score compared with the nonfreezers. In addition, for the subitems of PSQI, the freezers had significantly reduced sleep quality ($P < .001$), sleep duration ($P = .007$), and sleep efficiency ($P = .038$), and increased sleep onset latency ($P = .001$), sleep disturbances ($P = .001$), and daytime dysfunction ($P < .001$) compared with the nonfreezers. However, there was no significant difference in the

Table 2—Clinical characteristics of PD patients with different PDSS1 scores.

Baseline	Groups		*P*
	PDSS1 ≥ 6 (n = 121)	PDSS1 < 6 (n = 42)	
Age, y	67.04 ± 6.92	67.40 ± 6.71	.768[a]
Male, n (%)	67 (55%)	22 (52%)	.737[b]
Onset age, y	62.0 (57.0–66.0)	61.0 (57.3–67.0)	.735
Education years, y	10.0 (8.5–14.0)	9.0 (8.0–11.0)	.060
BMI	23.52 ± 2.51	23.78 ± 3.13	.579[a]
Disease duration, y	4.6 (2.8–7.3)	6.9 (3.4–10.7)	.029
Hypnotics, n (%)	11 (9%)	14 (33%)	< .001[b]
H-Y	2.5 (1.5–3.0)	2.5 (2.0–3.0)	.238
MDS-UPDRS III	22.0 (16.0–30.0)	22.0 (16.8–32.0)	.563
NMSS score	253.0 (108.5–494.0)	608.0 (321.8–811.0)	< .001
HAMA score	6.0 (3.0–9.0)	8.5 (6.0–17.0)	< .001
HAMD score	7.0 (4.0–12.0)	13.0 (9.0–18.0)	< .001
MMSE score	29.0 (27.0–30.0)	28.0 (26.0–30.0)	.548
TD, n (%)	60 (50%)	17 (41)%	.334[b]
Motor fluctuation, n (%)	37 (31%)	24 (57%)	.002
Dyskinesias, n (%)	11 (9%)	7 (17%)	.117[b]
PDQ-8 score	3.0 (1.0–6.0)	4.5 (2.0–8.0)	.008
LEDD	400.0 (300.0–650.0)	450.0 (346.9–650.0)	.291
FOG, n (%)	42 (35%)	22 (52%)	.043[b]
NFOG-Q	14.41 ± 5.73	15.05 ± 7.77	.709[a]
PSQI total	5.0 (3.0–8.0)	12.0 (10.0–15.0)	< .001
PDSS total	130.0 (121.0–136.5)	113.0 (97.8–118.5)	< .001
ESS total	6.0 (3.0–9.0)	8.0 (5.0–11.3)	.001
RBD, n (%)	58 (48%)	17 (41%)	.403[b]
Sleep quality	1.0 (.5–2.0)	2.0 (2.0–2.0)	< .001
Sleep onset latency	.0 (.0–1.0)	2.0 (1.0–2.0)	< .001
Sleep disturbances	1.0 (1.0–1.0)	1.0 (1.0–1.0)	.009
Daytime dysfunction	1.0 (.0–2.0)	2.0 (1.0–3.0)	< .001
Sleep duration	1.0 (.0–2.0)	2.0 (2.0–3.0)	< .001
Sleep efficiency	1.0 (.0–2.0)	3.0 (2.0–3.0)	< .001
Sleep medication	.0 (.0–.0)	.0 (.0–3.0)	< .001

Results expressed as mean scores ± standard deviation (normally distributed data) or interquartile range (not normally distributed data). [a]Independent samples *t* test; [b]Pearson chi-squared test; otherwise Mann-Whitney *U* test used. BMI = body mass index, ESS = Epworth Sleepiness Scale, FOG = freezing of gait, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, H-Y = Hoehn and Yahr, LEDD = levodopa equivalent daily dose, MDS-UPDRS III = part III of Movement Disorder Society Unified Parkinson's Disease Rating Scale, MMSE = Mini-Mental State Examination, NFOG-Q = New Freezing of Gait Questionnaire, NMSS = Non-Motor Symptom Scale, PDQ-8 = Parkinson's Disease Questionnaire-8, PDSS = Parkinson's Disease Sleep Scale, PDSS1 = first item of Parkinson's Disease Sleep Scale, PSQI = Pittsburgh Sleep Quality Index, RBD = Rapid Eye Movement Sleep Behavior Disorder Questionnaire, TD = tremor-dominant.

proportion of RBD ($P = .641$) and the use of sleep medication ($P = .125$) between the 2 groups. In addition, the freezers had significantly higher Parkinson's Disease Questionnaire-8 score compared with the nonfreezers (5.0 vs 3.0, $P < .001$).

Clinical characteristics of PD patients with different PDSS1 score

We also categorized the patients into a low PDSS1 score (PDSS1 < 6) group and a high PDSS1 score (PDSS1 ≥ 6) group according to their response to PDSS1 to further identify the clinical characteristics of PD patients with different PDSS1 scores.[24] There were 121 patients with high PDSS1 score (PDSS1 ≥ 6) and 42 patients with low PDSS1 score (PDSS1 < 6). Demographics and clinical characteristics of both groups were presented in **Table 2**. No significant differences in age, sex, age at PD onset, years of education, and body mass index were observed between the 2 groups. The PDSS1 < 6 group had significantly higher total PSQI (12.0 vs 5.0, $P < .001$) and ESS (8.0 vs 6.0, $P = .001$) score and lower total PDSS (113.0 vs 130.0, $P < .001$) score compared with the PDSS1 ≥ 6 group.

Table 3—Baseline and follow-up characteristics of study population in the prospective study (n = 52).

	Baseline			Follow-Up			*P* (change)
	PDSS1 ≥ 6 (n = 41)	PDSS1 < 6 (n = 11)	*P*	PDSS1 ≥ 6 (n = 41)	PDSS1 < 6 (n = 11)	*P*	
Age, y	66.2 ± 5.8	69.09 ± 3.75	.116[a]	67.51 ± 5.70	70.27 ± 3.70	.135[a]	NA
Male, n (%)	54% (22)	73% (8)	.428[b2]	54% (22)	73% (8)	.428[b2]	NA
Onset age, y	61.8 ± 6.0	63.09 ± 3.53	.355[a]	61.76 ± 6.00	63.09 ± 3.53	.355[a]	NA
Education years, y	11.0 (8.5–14.0)	12.0 (8.0–14.0)	.821	11.0 (8.5–14.0)	12.0 (8.0–14.0)	.821	NA
BMI	23.3 ± 2.6	23.31 ± 2.63	.669[a]	22.93 ± 2.05	22.85 ± 2.12	.598[a]	NA
Disease duration, y	4.6 ± 2.7	6.32 ± 2.72	.174[a]	5.96 ± 2.68	7.51 ± 3.65	.213[a]	NA
Hypnotics, n (%)	7% (3)	27% (3)	.191[b1]	10% (4)	27% (3)	.311[b2]	NA
TD, n (%)	78% (32)	30% (11)	.871[b1]	30% (11)	27% (4)	.132[b2]	NA
Motor fluctuation, n (%)	37% (15)	55% (6)	.281[b1]	49% (20)	82% (9)	.106[b2]	NA
Dyskinesias, n (%)	7% (3)	0% (0)	.845[b1]	12% (5)	18% (2)	.985[b2]	NA
RBD, n (%)	51% (21)	36% (4)	.592[b2]	56% (23)	27% (3)	.174[b2]	NA
FOG, n (%)	NA	NA	NA	24% (10)	73% (8)	.008[b2]	NA
NFOG-Q	NA	NA	NA	10.70 ± 3.89	10.75 ± 4.23	.980[a]	NA
H-Y	2.0 (1.5–2.5)	2.0 (1.5–2.5)	.872	2.5 (1.5–3.0)	2.5 (2.5–3.0)	.384	.080
MDS-UPDRS III	23.0 ± 10.0	19.5 ± 5.8	.139[a]	23.0 (16.5–30.0)	25.0 (22.0–30.0)	.004[c]	.001
NMSS	180.0 (90.5–315.0)	480.0 (144.0–946.0)	.022	240.0 (136.0–388.5)	408.0 (280.0–966.0)	.026	.523
HAMA score	6.0 (3.0–9.0)	5.0 (3.0–7.0)	.484	8.0 (4.0–10.0)	9.0 (6.0–13.0)	.036[c]	.017
HAMD score	7.0 (4.0–13.0)	8.0 (5.0–13.0)	.551	9.0 (5.5–14.0)	14.0 (8.0–20.0)	.027[c]	.208
MMSE score	29.0 (28.0–30.0)	29.0(28.0–30.0)	.683	29.0 (28.0–30.0)	30.0 (26.0–30.0)	.981	.711
PDQ-8	2.0 (1.0–4.5)	3.0 (1.0–4.0)	.838	4.0 (2.5–6.5)	5.0 (3.0–7.0)	.388	.150
LEDD	325.0 (218.8–594.0)	350.0 (262.5–450.0)	.388	482.96 ± 214.91	598.86 ± 204.06	.115[a]	.099
PSQI	3.0 (2.0–7.5)	11.0 (9.0–14.0)	< .001	5.78 ± 3.50	11.82 ± 3.49	< .001[a]	.848
PDSS	130.02 ± 9.10	111.82 ± 10.93	< .001[a]	126.32 ± 10.85	105 ± 14.06	< .001[a]	.645
ESS	5.0 (3.0–6.5)	8.0 (4.0–17.0)	< .008	6.0 (4.0–8.5)	9.0 (7.0–19.0)	.013	.909
Sleep quality	1.0 (.0–1.0)	2.0 (2.0–3.0)	< .001	1.0 (1.0–2.0)	2.0 (2.0–3.0)	< .001	.449
Sleep onset latency	.0 (.0–1.0)	1.0 (1.0–2.0)	.006	.0 (.0–1.0)	2.0 (1.0–2.0)	.001	.026
Sleep disturbances	1.0 (.0–1.0)	1.0 (1.0–1.0)	.030	1.0 (.0–1.0)	1.0 (1.0–1.0)	.021	.844
Daytime dysfunction	1.0 (.0–1.0)	2.0 (1.0–3.0)	.032	1.0 (.5–2.0)	2.0 (1.0–3.0)	.019	.517
Sleep duration	1.0 (.0–1.0)	2.0 (1.0–3.0)	< .001	1.0 (.0–1.0)	2.0 (1.0–3.0)	.003	.262

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Table 3—Baseline and follow-up characteristics of study population in the prospective study (n = 52). (continued)

	Baseline			Follow-Up			*P* (change)
	PDSS1 ≥ 6 (n = 41)	PDSS1 < 6 (n = 11)	*P*	PDSS1 ≥ 6 (n = 41)	PDSS1 < 6 (n = 11)	*P*	
Sleep efficiency	.0 (.0–1.0)	2.0 (1.0–3.0)	.002	1.0 (.0–2.0)	2.0 (1.0–3.0)	.027	.118
Sleep medication	.0 (.0–.0)	.0 (.0–3.0)	.013	.0 (.0–.0)	.0 (.0–2.0)	.117	.803

Results expressed as mean scores ± standard deviation (normally distributed data) and median (interquartile range) (not normally distributed data). *P*: comparison of corresponding groups; *P*(change): comparison of change variables between nonsleep disturbance and sleep disturbance. [a]Independent samples *t* test; [b1]Pearson chi-squared test; [b2]Fisher's exact test; [c]Analysis of covariance (ANCOVA) test with adjustment for baseline data. Otherwise Mann-Whitney *U* test used. BMI = body mass index, ESS = Epworth Sleepiness Scale, FOG = freezing of gait, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, H-Y = Hoehn and Yahr, LEDD = levodopa equivalent daily dose, MDS-UPDRS III = part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale, MMSE = Mini-Mental State Examination, NA = no answer, NFOG = nonfreezing of gait, NMSS = Non-Motor Symptom Scale, PDQ-8 = Parkinson's Disease Questionnaire-8, PDSS = Parkinson's Disease Sleep Scale, PSQI = Pittsburgh Sleep Quality Index, RBD = Rapid Eye Movement Sleep Behavior Disorder Questionnaire. PDSS1 = the first item of Parkinson's Disease Sleep Scale, TD = tremor-dominant.

For PSQI subitems, sleep quality ($P < .001$), sleep duration ($P < .001$), sleep efficiency ($P < .001$), sleep onset latency ($P < .001$), sleep disturbances ($P = .009$), and daytime dysfunction ($P < .001$) were significantly more abnormal in the PDSS1 < 6 group than those in the PDSS1 ≥ 6 group. Moreover, the proportion of freezers in the PDSS1 < 6 group was significantly higher than that in the PDSS1 ≥ 6 group (52% vs 35%, $P = .043$).

In addition, the proportion of motor fluctuation in the patients with low PDSS1 score was significantly higher than that in the patients with high PDSS1 score (57% vs 31%, $P = .002$). The patients in the PDSS1 < 6 group had significantly higher total score of NMSS (608.0 vs 253.0, $P < .001$), HAMA (8.5 vs 6.0, $P < .001$), and HAMD (13.0 vs 7.0, $P < .001$) compared with the patients in the PDSS1 ≥ 6 group.

Association of PDSS1 score with incident FOG

Demographics and clinical characteristics of the 52 nonfreezers at baseline and during the follow-up were shown in **Table 3.** As expected, the patients in the PDSS1 < 6 group had significantly higher total PSQI and ESS score and lower total PDSS score compared with the patients in the PDSS1 ≥ 6 group at baseline and follow-up. During the 18-month follow-up, a total of 18 (35%) patients developed FOG, 8 (73%) in the PDSS1 < 6 group and 10 (24%) in the PDSS1 ≥ 6 group. The FOG incidence was significantly different between the 2 groups ($P = .008$). In addition, annual Δ MDS-UPDRS III ($P = .001$), annual Δ HAMA ($P = .017$), and annual Δ sleep onset latency ($P = .026$) in the PDSS1 < 6 group were significantly higher than those in the PDSS1 ≥ 6 group.

The assumption of proportional hazards was assessed by using the Schoenfeld residuals test ($P = .855$). The results of Cox proportional hazards regression analysis are shown in **Table 4**. According to the univariable Cox regression results, age, disease duration of PD, motor fluctuation, NMSS, HAMD, LEDD, PSQI, and PDSS1 were selected into the final multivariable Cox regression model (**Table 4**). We observed that PDSS1 (hazard ratio = 4.23, 95% confidence interval 1.64–10.92, $P = .003$) and LEDD (hazard ratio = 4.18, 95% confidence interval 1.62–10.75, $P = .003$) were significantly associated with FOG incidence by the forward stepwise variable selection. The hazard curve showed that incidence rate of FOG in the PDSS1 < 6 group was significantly higher than that in the PDSS1 ≥ 6 group during the follow-up (**Figure 2**). We also observed that the patients with low PDSS1 score tended to have an earlier onset of FOG compared with the patients with high PDSS1 score (**Figure 2**).

DISCUSSION

A large number of studies reported that approximately 80% patients with PD ultimately developed FOG.[4,29] Previous studies have described some predictors for FOG, including motor and nonmotor factors.[16,17,30] Some studies have suggested that PD patients usually experience worse sleep, characterized by long periods spent in bed while not asleep and difficulty remaining asleep.[17,25] However, clinical characteristics of freezers and nonfreezers in PD remain unclear. Clinical characteristics of PD patients with different PDSS1 scores also

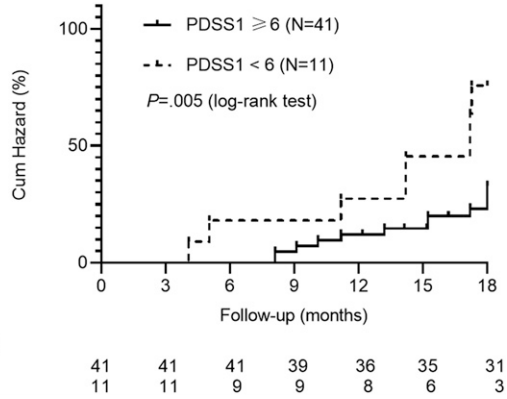
Table 4—Cox regression analyses for potential risk indicators of future fog in nonfreezers at baseline (n = 52).

Variables	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.09 (1.00–1.18)	.056	NA	NA
Male	.70 (.26–1.86)	.470	NA	NA
Disease duration	1.84 (1.01–3.35)	.048	NA	NA
TD	.99 (.56–1.78)	.995	NA	NA
Motor fluctuation	2.57 (1.00–6.64)	.051	NA	NA
Dyskinesias	1.02 (.14–7.69)	.983	NA	NA
RBD	.74 (.29–1.87)	.517	NA	NA
H-Y	1.33 (.44–4.03)	.619	NA	NA
MDS-UPDRS III	1.41 (.56–3.59)	.468	NA	NA
NMSS	3.31 (1.17–9.33)	.024	NA	NA
HAMA	1.09 (.43–2.76)	.859	NA	NA
HAMD	2.56 (.91–7.18)	.075	NA	NA
MMSE	1.30 (.17–9.79)	.799	NA	NA
LEDD	3.64 (1.43–9.26)	.009	4.18 (1.62–10.75)	.003
PSQI	2.43 (.91–6.48)	.076	NA	NA
PDSS1	3.61 (1.42–9.19)	.007	4.23 (1.64–10.92)	.003
ESS	.89 (.20–3.89)	.877	NA	NA

CI = confidence interval, ESS = Epworth Sleepiness Scale, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, HR = hazard ratio, H-Y = Hoehn and Yahr, LEDD = levodopa equivalent daily dose, MDS-UPDRS III = part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale, MMSE = Mini-Mental State Examination, NA = no answer, NMSS = Non-Motor Symptom Scale, PDSS1 = first item of the Parkinson's Disease Sleep Scale, PSQI = Pittsburgh Sleep Quality Index, RBD = Rapid Eye Movement Sleep Behavior Disorder Questionnaire, TD = tremor-dominant.

remains unclear. In addition, we are unclear about the relationship between sleep disturbance and FOG in PD. In our baseline analysis, we observed that the freezers had significantly worse night-time sleep and excessive daytime sleepiness compared with the nonfreezers. More serious excessive daytime sleepiness in freezers may have been due to impaired night sleep and, more importantly, to the disease itself and its treatment. It has been suggested that degeneration of the locus coeruleus and the ascending reticular-activating system may be responsible for the development of excessive daytime sleepiness.[31] Also, in this study, we observed that the freezers were characterized with poorer sleep quality, shorter sleep duration, lower sleep efficiency, increased sleep onset latency, more serious sleep disturbances, and daytime dysfunction compared with the nonfreezers. Meanwhile, our results showed that the proportion of freezers in the PDSS1 < 6 group was significantly higher than that in the PDSS1 ≥ 6 group, indicating that low PDSS1 score was likely associated with the presence of FOG. Although the relationship between sleep disturbance and FOG in PD remains unclear, these results provide important clues for further investigation of the potential risk indicators for FOG. In disagreement with a previous study,[32] there was no significant difference in RBD proportion between the freezers and nonfreezers in our study. In fact, there were some studies[16] showing that RBD was not related to FOG in advanced PD and might not be a predictor of FOG, although the association between increased REM sleep and FOG was observed in the early stages of PD.[33] In addition, in the baseline analysis, the freezers had significantly more severe motor disability with non–tremor-dominant phenotype and had received a higher dose of levodopa medication compared with the nonfreezers. The freezers performed significantly worse on the HAMA, HAMD, and Mini-Mental State Examination score, suggesting that freezers experience worse anxiety, depression, and cognitive dysfunction. Correspondingly, the freezers had significantly poorer quality of life compared with the nonfreezers. Therefore, these results indicate that

Figure 2—Cumulative hazard of FOG in the PDSS1 < 6 and PDSS1 ≥ 6 groups during the follow-up.



FOG = freezing of gait, PDSS1 = the first item of the Parkinson's Disease Sleep Scale.

freezers may have more severe motor and nonmotor symptoms compared with nonfreezers in PD.

To further investigate the association of PDSS1 score with incident FOG, we prospectively followed a cohort of PD patients for 18 months and found a significant association of PDSS1 score with incident FOG, indicating that low PDSS1 score might be related to FOG occurrence. It also showed that the PD patients in the PDSS1 < 6 group exhibited significantly more severe motor symptoms and anxiety compared with patients in the PDSS1 ≥ 6 group during the follow-up. Additionally, unlike a study that used ESS to assess daytime sleepiness,[17] we used PDSS1 as a standard, on the basis of a different study,[24] to divide PD patients into 2 groups based on their responses. The PDSS1 measure could represent overall quality of sleep in the night, shows robust reliability, is easy to use, and therefore fits well with the holistic assessment of nocturnal sleep problems that are common and important in PD.[24,34] Our results suggest that PDSS1 score might be a predictive marker of neurodegeneration, which eventually shows up as FOG. Increasing evidence suggests that a neural circuitry deficit may be associated with FOG. The pedunculopontine nucleus (PPN) appears to be a complex gait generator of the brainstem, linking cortex, basal ganglia, and spinal cord. Its cholinergic neurons partially degenerate in advanced PD. Clinical observations have shown that activating the remaining PPN neurons can restore locomotor function.[35–37] In the meantime, a striking example of the nonmotor role of the PPN is its involvement in modulating wakefulness and sleep.[38] The PPN plays an important role in activating the cerebral cortex to maintain wakefulness.[38] It is also a relay station of gait and posture control.[35,39] Sleep deprivation may increase PPN toxic products such as β-amyloid, tau, and α-synuclein, which cause progressive neural circuitry deficit. These toxic products may also be the predictors of FOG.[40–43] Accumulating studies have shown that activity of the brainstem neuromodulatory system varies with the state of arousal and therefore may be negatively affected by disrupted sleep.[15] Some studies suggest that the neurodegeneration of the thalamic cholinergic afferent projections, which could lead to sleep disturbance, might contribute to disease-specific motor and cognitive abnormalities.[44] Two other studies found that sleep disturbance might be a risk factor for some motor symptoms.[17,45] Neuromodulatory inputs of serotonin and norepinephrine, released by axons originating in the brainstem, exert a powerful effect on motoneuron excitability.[46] Therefore, sleep disturbance may be responsible for impaired gait, motor disability, and mood disorders by negatively regulating the brainstem and thalamic neuromodulatory system. However, the pathogenesis of FOG is intricate and needs further investigation.

Finally, in line with a previous research,[47] we found that a higher dosage of levodopa was associated with the development of FOG. Our results are not consistent with a recent study suggesting no significant relationship between levodopa treatment and future freezing episodes.[48] Perhaps the patients in our study had more severe disease at baseline and thus needed more levodopa for symptom management and could develop FOG more easily. Moreover, previous studies also showed that dopamine receptor agonists and monoamine oxidase B inhibitors might reduce FOG.[49,50] The relationship between levodopa treatment and FOG is complicated. More studies are needed to explore whether LEDD is a useful indicator for incident FOG and whether LEDD could be a target of therapeutic interventions for the treatment of FOG in PD.

This study has some limitations. First, the assessments of NFOG-Q and PDSS1 used to categorize patients are both subjective scales. This could have led to subjective assessment bias. However, these scales are validated and are easy for clinicians to administer.[24,34] In the present study, each patient was assessed by 2 evaluators in an assessor-masked and randomized way to minimize errors. Also, the NFOG-Q does not specifically address issues related to freezing that might occur during the overnight hours, so the association between freezing of gait and sleep disturbance could represent a situation in which the latter is directly related to restricted mobility caused by an inability to initiate movement while in bed during the night. Further studies using polysomnography, actigraphy, or wearable FOG detection systems will be needed to obtain objective data. Second, it would have been more helpful to have conducted both "on medication" and "off medication" assessments of the patients in our study. However, it was difficult to conduct "off medication" assessments of PD patients due to their "off medication" symptoms. Therefore, consistent with many studies,[16–18] we did not have "off medication" assessments of the patients in our present study. Studies that conduct both "off medication" and "on medication" assessments of patients should be considered. Third, the sample size of this study is relatively small. Future studies with larger sample sizes are greatly needed to validate our findings.

CONCLUSIONS

In summary, our baseline study showed that sleep disturbance is likely associated with FOG, which was further supported by our longitudinal study indicating that low PDSS1 score might indicate increased risk of developing FOG and experiencing a shortened onset time of FOG in PD. Our results suggest that therapeutic interventions triggered by PDSS1 score may be a promising approach to prevention or delay of the development of FOG in PD.

ABBREVIATIONS

ESS, Epworth Sleepiness Scale
FOG, freezing of gait
HAMA, Hamilton Anxiety Rating Scale
HAMD, Hamilton Depression Rating Scale
LEDD, total levodopa equivalent daily dosage
MDS-UPDRS III, part III of the Movement Disorders Society Unified Parkinson Disease Rating Scale
NFOG-Q, New Freezing of Gait Questionnaire
NMSS, Non-Motor Symptom Scale
PD, Parkinson disease
PDQ-8, Parkinson's Disease Questionnaire-8
PDSS, Parkinson's Disease Sleep Scale

PDSS1, first item of Parkinson's Disease Sleep Scale
PPN, pedunculopontine nuclei
PSQI, Pittsburgh Sleep Quality Index
RBD, rapid eye movement sleep behavior disorder
REM, rapid eye movement
TD, tremor-dominant
WOQ-9, 9-Symptom Wearing-off Questionnaire

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DISCLOSURE STATEMENT

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