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A prospective study of freezing of gait with early Parkinson disease in Chinese patients

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Abstract

This study investigated the risk factors for freezing of gait (FOG) in the early stage of Parkinson disease in China, using a sample of 248 patients who were followed for 3 years. Part III of the Unified Parkinson Disease Rating Scale and the modified Hoehn-Yahr grading scale were used to evaluate the severity of motor symptoms. Nonmotor symptoms were assessed using the Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale (HAMD), and Non-Motor Symptoms Scale (NMSS). The end-point was the presence of FOG at the end of follow-up; patients with FOG were classified as freezers. The risk factors for FOG were analyzed at the end of the first, second, and third years after baseline. There were 40 freezers (16.13%) 1 year later, 98 (39.52%) 2 years later, and 128 (51.61%) 3 years later. FOG 3 years later was associated with the following variables: depression ($P=0.003$), older age, living in the countryside, lower education, akinetic-rigid style, lower limbs as site of onset, early use of levodopa, higher daily dose of levodopa, and not using amantadine or selegiline and dopamine receptor agonists ($P<0.001$). Early use of amantadine, selegiline, and dopamine receptor agonists was negatively related to FOG ($P<0.001$). Binary logistic regression found that FOG was associated with lower education (odds ratio [OR] = 0.012, $P<0.001$), akinetic-rigid style (OR = 4.881, $P=0.024$), not using dopamine receptor agonists (OR = 4.324, $P=0.035$), cognitive disturbances (OR = 0.331, $P=0.007$), and sleep disorders (OR = 2.418, $P=0.036$). However, the cardiovascular domain of the NMSS (OR = 2.729, $P=0.001$) was the only risk factor for FOG 1 year later. Two years later, FOG was associated with mixed style (OR = 0.189, $P=0.005$), lower limbs as site of onset (OR = 4.772, $P=0.008$), not using dopamine receptor agonists (OR = 0.031, $P<0.001$), and the anxiety/somatic domain of the HAMD (OR = 0.596, $P=0.033$). Scores at baseline, patients with Parkinson disease were more likely to experience FOG if: they were older, or from the countryside; had an akinetic-rigid style, anxiety, or higher NMSS scores; they used levodopa early or did not use amantadine or selegiline; their lower limbs were the site of onset; or they had more severe motor disability or higher HAMD scores at baseline.

Abbreviations: EOPD = Early-onset Parkinson Disease, FOG = freezing of gait, H&Y = Hoehn-Yahr grading, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, LOPD = late-onset Parkinson Disease, NMSS = Non-Motor Symptoms Scale, PD = Parkinson disease, UPDRS-III = Part III of Unified Parkinson Disease Rating Scale.

Keywords: freezing of gait, Parkinson disease, risk factors

1. Introduction

Freezing of gait (FOG) is a common and disabling phenomena in Parkinson disease (PD) that usually is observed in its advanced stage: modified Hoehn–Yahr grading (H&Y) stage more than 2.5.[1] It is a progressive manifestation of PD and it is one of the most common causes of falls.[2] The definition of FOG is "a brief, episodic absence or a marked reduction of forward progression of the feet despite the intention to walk."[3] Patients report their feet seem to be suddenly glued to the floor as they try to initiate or maintain locomotion.[4] FOG often leads to falls, injuries, secondary immobility, and reduced quality of life, thus, it has been investigated by a large number of studies.[5–7]

The pathophysiology of FOG is not well understood, although there are some hypotheses. First, FOG may emerge from changes in neuroanatomical networks in the brainstem, including the pedunculopontine nucleus and locus ceruleus, which are part of the mesencephalic locomotor center and postural control circuits.[8] Second, an abnormality of the basal ganglia-brain stem loop may be a cause of FOG.[9] Third, increasing evidence suggests that nonmotor systems are likely to be involved in its underlying mechanism.[10] However, the relevant risk factors have not been identified. Several cross-sectional studies have analyzed the risk factors for FOG in advanced stages of PD.[10,11] Nevertheless, there are few prospective studies of FOG in patients with early stage PD, even though such research would be very important for preventing FOG in PD. Therefore, exploring the risk factors for FOG has great clinical significance. Our study attempted to investigate the risk factors for FOG in the early stage of PD (http://links.lww.com/MD/B90).

Editor: Li Yong.

HZ and ZO contributed equally to this work and share first authorship.

Conceived and designed study: HZ, ZO, and XY. Performed the experiments: HZ, XY, JC, SZ, CZ, XP, SW, JY, YF, PY, and QZ. Analyzed the data: HZ and ZO. Wrote the manuscript: HZ and XY.

The authors declare no conflict of interest.

Supplemental Digital Content is available for this article.

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Medicine (2016) 95:26(e4056)

Received: 26 January 2016 / Received in final form: 7 May 2016 / Accepted: 19 May 2016

http://dx.doi.org/10.1097/MD.0000000000004056

2. Methods

2.1. Participants

The study had got the approval of the ethics committee of the Third People's Hospital of Huzhou, Zhejiang Province, China. Patients were enrolled in the study consecutively. All participants were recruited through the third People's Hospital of Huzhou, Zhejiang Province of China. The study roadmap is shown in Fig. 1. All participants were diagnosed according to the Unified Kingdom PD Society Brain Bank Clinical Diagnostic Criteria for PD[12] and they had never taken anti-Parkinson drugs. Patients with atypical and secondary Parkinsonism were excluded from the study. All patients were in the early-stages of PD and never had FOG. They were regularly treated according to Chinese guidelines for the treatment of PD after receiving their diagnosis.[13] Patients with anxiety or depression were diagnosed by at least one of trained psychiatrists, in addition to completing the Hamilton Anxiety Rating Scale (HAMA) and Hamilton Depression Rating Scale (HAMD). Patients with depression were treated regularly with antidepressants.

Table 1 shows the demographic characteristics and clinical details of the participants at baseline. All clinical items were assessed by an experienced neurologist. The clinical data included disease duration, type of motor symptoms, site of initial motor symptoms, H&Y stage, and scores on Part III of Unified Parkinson Disease Rating Scale (UPDRS-III), the HAMD, and the HAMA. Early-onset PD (EOPD) was defined as onset at an age younger than 50 years old, whereas late-onset PD (LOPD) was defined as onset at 50 years of age or older. Patients were grouped into 3 subtypes, including tremor-dominant, akinetic-rigid, and mixed, according to the criteria described in a previous study.[14] The UPDRS-III and H&Y stage were used to evaluate the severity of the motor symptoms. The degree of depression, anxiety, and nonmotor symptoms were assessed using the HAMA, the HAMD, and the Non-Motor Symptoms Scale (NMSS), respectively.

2.2. Assessment of FOG

FOG was identified by 2 criteria used in a previous study:[15] (i) a convincing subjective report of FOG that was consistent with the characteristics of the phenomenon, especially the typical feeling that the feet were glued to the floor; and (ii) a patient's recognition of the typical FOG phenomenon when it was demonstrated to him or her by an experienced clinician.[16] We mainly determined FOG by patients' responses to the question: "Do you feel that your feet get glued to the floor while walking, making a turn, or when trying to initiate walking?" Patients who answered "yes" were identified as freezers. FOG was also identified when it was observed by an experienced neurologist during a visit, or it was reported by the patients, their family members, or their caregivers when it occurred at home or anywhere outside of the hospital.

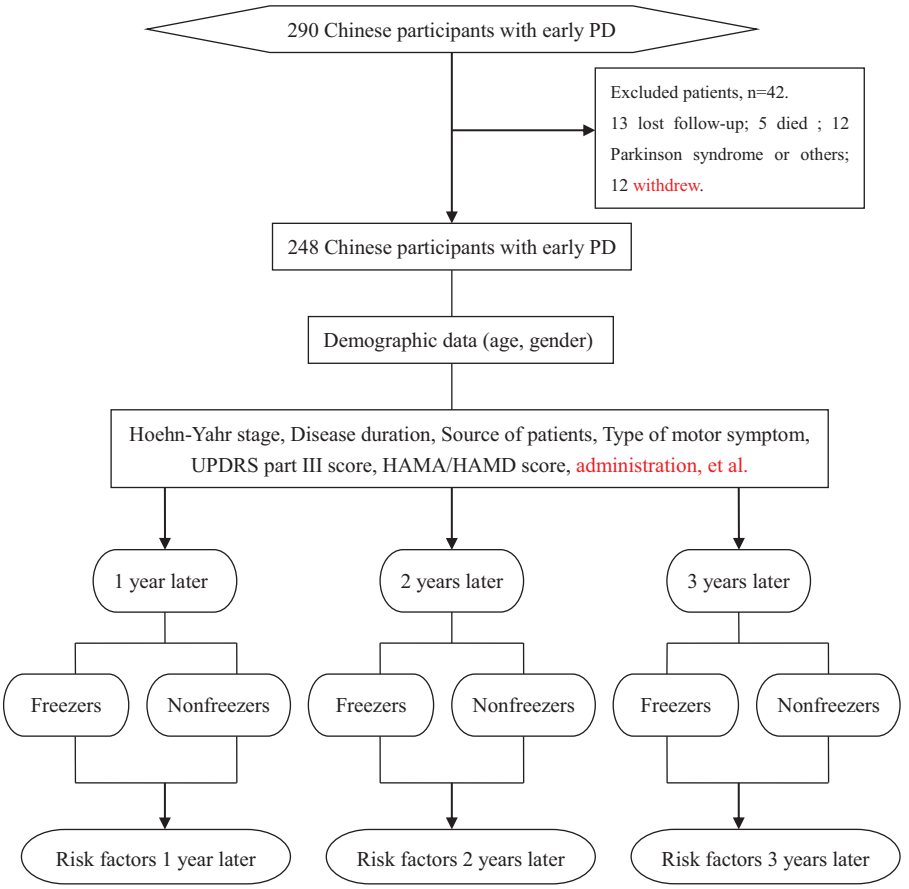

Figure 1. Study Roadmap. HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, PD = Parkinson disease, UPDRS-III = Part III of Unified Parkinson Disease Rating Scale.

Table 1

The demographic characteristics and clinical details of 248 participants at baseline.

Baseline	Groups	Number	Percentage/mean and its standard deviation
Gender	Male	112	45.16%
	Female	136	54.84%
Age, y	<65 years old	78	31.45%/58.22 ± 5.43
	≥65 years old	170	68.55%/69.42 ± 3.41
Disease duration, mo	Na	248	100%/12.21 ± 1.92
Onset age, y	Early-onset	12	4.84%
	Late-onset	236	95.16%
Source of patients	From countryside	141	56.85%
	From city	107	43.15%
Education years, y	≤9 years	162	65.32%
	>9 years	86	34.68%
Lower limbs as site of onset	Yes	99	39.92%
	No	149	60.08%
Type of motor symptom	Tremor-dominant	16	6.45%
	Akinetic-rigid	102	41.13%
	Mixed	130	52.42%
Drug administration			
Use of levodopa	Yes	136	54.84%
	No	112	45.16%
Daily dose of levodopa, mg/day	Na	136	54.84%/443.47 ± 107.55
Use of amantadine	Yes	106	42.74%
	No	142	57.26%
Use of Selegiline	Yes	99	39.92%
	No	149	60.08%
Use of dopamine receptor agonist	Yes	87	35.08%
	No	161	64.92%
Motor severity			
H&Y stage	1	56	22.58%
	1.5	135	54.44%
	2	55	22.18%
	2.5	2	0.81%
UPDRS part III score	Na	248	100%/19.22 ± 2.61
HAMA/HAMD score	Without anxiety and depression	150	60.48%/(6.34 ± 2.72/5.32 ± 2.63)
	With anxiety	51	20.57%/(23.91 ± 3.16/12.37 ± 2.19)
	With depression	47	18.95%/(11.03 ± 2.14/23.83 ± 3.72)
NMSS	Na	248	100%/10.13 ± 3.52

H&Y = Hoehn–Yahr grading, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, NMSS = Non-Motor Symptoms Scale, UPDRS-III = Part III of Unified Parkinson Disease Rating Scale.

2.3. Procedure

The patients were followed for 3 years. The first patient was enrolled on March 2, 2010 and the last patient was enrolled on September 4, 2012. We completed the 3-year follow-up on September 4, 2015. We evaluated the patients at baseline, 1 year later, 2 years later, and 3 years later. The data collected at baseline included age, gender, onset age, disease duration, type of motor symptoms, site of initial motor symptoms, H&Y stage, scores on the HAMA, HAMD, and UPDRS-III, and other information shown in Table 1. We observed changes in prescriptions and mood status at the 3-year follow-up (Table 6). The patients were divided into freezers and non-freezers based on the presence of FOG.

2.4. Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences version 19.0 for Windows. All continuous data, such age, disease duration, daily levodopa dose, and HAMA, HAMD, and UPDRS-III scores are presented as the mean ± the standard deviation. Student *t*-tests were used to compare continuous variables between patients with and without FOG. The chi-square test was used to evaluate differences in categorical variables between patients with and without FOG. Analysis of covariance, adjusting for age, was performed to compare the total scores and the domain scores for the HAMD, HAMA, and NMSS between patients with and without FOG. A binary logistic regression model was used to explore potential factors related to FOG. The presence or absence of FOG was used as the dependent variable, and independent variables included: age, source of patients, years of education, lower limbs as the site of onset, type of motor symptom, drug administration, the NMSS scores for the cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, and urinary domains as well as the HAMD domain scores for anxiety/somatic, weight, cognitive disturbance, block, sleep disorder, and feelings of despair. All statistical tests were 2-tailed, and $P < 0.05$ was considered to be statistically significant (for multiple comparisons of the chi-square test, $P < 0.025$ was considered to be statistically significant).

3. Results

3.1. Participants' demographic characteristics and clinical details

A total of 290 Chinese patients with early PD (H&Y stage ≤ 2.5) were consecutively recruited to examine changes in the

prevalence of FOG and its related risk factors through a 3-year follow-up. There were 13 patients lost in the follow-up, 5 patients died, and 12 patients eventually proved to have Parkinson syndrome or other nervous system degeneration diseases, and 12 patients withdrew because of serious fractures, cardiovascular events, or stoke. Finally, 248 participants with early PD completed the 3-year follow-up and were included in the analyses. Of the 248 patients, 112 cases were male (45.16%) and 136 cases were female (54.84%). There were 78 patients who were less than 65 years old (31.45%) and 170 patients who were more than or equal to 65 years old (68.55%). The EOPD and LOPD patients accounted for 4.84% and 95.16% of the sample, respectively. Table 1 shows the details of the variables.

3.2. Association between variables at baseline and FOG after 3 years

Forty PD patients (16.13%) reported FOG one year later (ie, 1 year after baseline), 98 (39.52%) reported FOG after 2 years, and 128 (51.61%) reported FOG 3 years later. Table 2 shows the relationship between FOG 3 years later and related variables at baseline. There was no significant difference in the prevalence of

Table 2

Association between variables at baseline and FOG after 3 years.

Baseline	Total (n = 248)	Freezers (n = 128)	Nonfreezers (n = 120)	Test	*P* value
Gender					
Male	112	55	57	a	0.474
Female	136	73	63		
Age, y					
<65 years old	78	18	60	a	<0.001*
≥65 years old	170	110	60		
Onset age, y					
Early-onset	12	3	9	a	0.059
Late-onset	236	125	111		
Source of patients					
From countryside	141	114	27	a	<0.001*
From city	107	14	93		
Education years					
≤9 years	162	126	36	a	<0.001*
>9 years	86	2	84		
Lower limbs as site of onset					
Yes	99	80	19	a	<0.001*
No	149	48	101		
Type of motor symptom					
Tremor dominant	16	4	12	b[1]	<0.001*
Akinetic rigid	102	86	16	b[2]	0.724
Mixed	130	38	92	b[3]	<0.001*
Drug administration					
Use of levodopa					
Yes	136	97	39	a	<0.001*
No	112	31	81		
Daily dose of levodopa, mg/day	136	97 (471.65 ± 79.68)	39 (373.40 ± 134.11)	c	<0.001*
Use of amantadine					
Yes	106	27	79		
No	142	101	41	a	<0.001*
Use of selegiline					
Yes	99	21	78		
No	149	107	42	a	<0.001*
Use of dopamine receptor agonist					
Yes	87	14	73	a	<0.001*
No	161	114	47		
Mood					
Without anxiety and depression	150	68	82	d[1]	0.347
With anxiety	51	27	24	d[2]	0.003*
With depression	47	33	14	d[3]	0.08
UPDRS part III score	248	128 (20.00 ± 2.47)	120 (18.37 ± 2.51)	c	0.905

EOPD = early-onset PD, FOG = freezing of gait, freezers = PD patients with FOG, LOPD = late-onset PD, nonfreezers = PD patients without FOG, PD = Parkinson disease, UPDRS-III = Part III of Unified Parkinson Disease Rating Scale.

Test a: chi-square test.

Test b[1]: comparison between patients with tremor-dominant style and patients with akinetic-rigid style using a chi-square test.

Test b[2]: comparison between patients with tremor-dominant style and patients with mixed style using a chi-square.

Test b[3]: comparison between patients with akinetic-rigid style and patients with mixed style using a chi-square.

Test c: compare daily dose of levodopa and UPDRS part III score between patients with and without FOG using a Student *t* test.

Test d[1]: comparison between patients without anxiety/depression and patients with anxiety using a chi-square test.

Test d[2]: comparison between patients without anxiety/depression and patients with depression using a chi-square test.

Test d[3]: comparison between patients with anxiety and patients with depression using a chi-square test.

* Significant difference (for test a and c, *P* values < 0.05 are considered statistically significant; for tests b and d, *P* values < 0.025 are considered statistically significant).

Table 3

Associations between factors in NMSS at baseline and FOG 3 years later in PD patients.

NMSS (Baseline)	Freezers (n = 128)	Nonfreezers (n = 120)	*P* value*
Total score	12.49 ± 2.13	7.62 ± 2.92	<0.001b
Cardiovascular	1.45 ± 0.95	1.03 ± 0.86	0.02†
Sleep/fatigue	2.34 ± 0.74	1.88 ± 0.52	<0.001†
Mood/apathy	2.45 ± 0.89	1.61 ± 1.06	<0.001†
Perceptual problems/ hallucinations	0.72 ± 0.90	0.28 ± 0.68	<0.001†
Attention/memory	1.74 ± 1.14	0.77 ± 1.02	<0.001†
Gastrointestinal	1.91 ± 0.65	1.03 ± 0.98	<0.001†
Urinary	0.96 ± 1.00	0.27 ± 0.71	<0.001†
Sexual dysfunction	0.20 ± 0.61	0.18 ± 0.56	0.185
Miscellaneous	0.71 ± 0.92	0.58 ± 0.89	0.515

FOG = freezing of gait, freezers = PD patients with FOG, NMSS = Non-Motor Symptoms Scale, nonfreezers = PD patients without FOG, PD = Parkinson disease.
* *P* value is calculated from an ANCOVA adjusted for age.
† Significant difference.

Table 4

Associations between HAMA/HAMD scores at baseline and FOG 3 years later in PD patients.

Baseline	Freezers (n = 128)	Nonfreezers (n = 120)	*P* value*
HAMA	11.35 ± 7.12	10.23 ± 7.77	0.174
Somatic anxiety	4.81 ± 3.28	4.44 ± 3.50	0.297
Psychic anxiety	6.54 ± 3.96	5.79 ± 4.39	0.115
HAMD	11.25 ± 7.28	8.27 ± 5.74	<0.001†
Anxiety/somatic	2.79 ± 1.75	2.26 ± 1.43	0.002†
Weight	0.33 ± 0.67	0.21 ± 0.55	0.006†
Cognitive disturbance	1.79 ± 1.58	1.46 ± 1.39	0.014
Diurnal variation	0.15 ± 0.42	0.21 ± 0.53	0.652
Block	1.81 ± 1.19	1.48 ± 1.08	<0.001†
Sleep disorder	2.25 ± 1.35	1.61 ± 1.24	<0.001†
Feeling of despair	2.13 ± 2.44	1.04 ± 1.39	<0.001†

FOG = freezing of gait, freezers = PD patients with FOG, HAMD = Hamilton depression scale, nonfreezers = PD patients without FOG, PD = Parkinson disease.
* *P*-value is calculated from an ANCOVA adjusted for age.
† Significant difference.

FOG between male and female patients (45.16% vs 54.84%, $P = 0.474$), or the EOPD and LOPD patients (4.84% vs 95.16%, $P = 0.059$), and there was no difference in UPDRS-III scores between freezers and nonfreezers (20.00 ± 2.47 vs 18.37 ± 2.51, $P = 0.905$).

FOG occurred more frequently in patients older than 65 years old than in patients younger than 65 years old (68.55% vs 31.45%, $P < 0.001$). Patients who were from the countryside (56.85% vs 43.15%, $P < 0.001$), or had a lower education were more prone to have FOG (65.32% vs 34.68%, $P < 0.001$). Patients whose lower limbs were the site of onset were more likely to develop FOG than those whose upper limbs were the site of onset (39.92% vs 60.08%, $P < 0.001$). Patients with an akinetic-rigid style also were more likely to suffer from FOG ($P < 0.001$). With respect to drug use, early use of levodopa seemed to increase FOG (54.84% vs 45.16%, $P < 0.001$). Patients with a higher daily dose of levodopa had a higher incidence of FOG ($P < 0.001$), whereas early use of amantadine (42.74% vs 57.26%, $P < 0.001$), selegiline (39.92% vs 60.08%, $P < 0.001$), and dopamine receptor agonists (35.08% vs 64.92%, $P < 0.001$) appeared to reduce FOG. Patients with depression had a higher rate of FOG ($P = 0.003$).

Table 3 shows the relationship between NMSS scores at baseline and FOG 3 years later. After adjusting for age, patients with FOG (freezers) had a significantly higher NMSS total score and higher scores on the cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, and urinary domains of the NMSS compared with nonfreezers ($P < 0.05$). However, there were no differences in the scores for the sexual dysfunction or miscellaneous domains of the NMSS between the freezers and nonfreezers ($P > 0.05$).

Table 4 shows the relationship between HAMA&HAMD scores at baseline and FOG. After adjusting for age, freezers had higher total HAMD scores as well as higher scores on the anxiety/somatic, weight, cognitive disturbance, block, sleep disorder, and feelings of despair domains of the HAMD compared with nonfreezers ($P < 0.05$). However, there was no group difference in the scores for the somatic anxiety or the psychic anxiety domains of the HAMA or the diurnal variations domain of the HAMD ($P > 0.05$).

The baseline variables potentially related to FOG 3 years later are presented in Table 5. The results indicated that lower

Table 5

Associations between clinical factors at baseline and FOG 3 years later in PD patients.

Baseline	Code	OR	95%CI	*P* value*
Age	<65 years old (R) ≥65 years old	1.401	0.224–8.746	0.718
Source of patients	From city (R) From countryside	1.015	0.216–4.776	0.985
Education years	>9 years (R) ≤9 years	0.012	0.001–0.122	<0.001†
Lower limbs as site of onset	No (R) Yes	0.323	0.097–1.075	0.065
Type of motor symptom				
Tremor dominant	(R)			
Akinetic rigid		4.881	1.236–19.271	0.024†
Mixed		1.083	0.072–16.275	0.954
Drug administration				
Use of levodopa	Yes (R) No	0.255	0.045–1.430	0.120
Use of amantadine	No (R) Yes	1.551	0.390–6.173	0.533
Use of Selegiline	No (R) Yes	0.666	0.131–3.383	0.624
Use of dopamine receptor agonist	No (R) Yes	4.324	1.108–16.877	0.035†
NMSS				
Cardiovascular		1.121	0.526–2.386	0.768
Sleep/fatigue		2.860	0.646–12.655	0.166
Mood/apathy		2.273	0.799–6.470	0.124
Perceptual problems/ hallucinations		0.826	0.434–1.573	0.561
Attention/memory		1.593	0.920–2.759	0.096
Gastrointestinal		1.719	0.670–4.413	0.260
Urinary		1.160	0.628–2.142	0.636
HAMD				
Anxiety/somatic		0.889	0.479–1.651	0.710
Weight		2.278	0.524–9.894	0.272
Cognitive disturbance		0.331	0.149–0.735	0.007†
Block		1.927	0.858–4.327	0.112
Sleep disorder		2.148	1.052–4.385	0.036†
Feeling of despair		1.822	0.849–3.910	0.124

FOG = freezing of gait, HAMD = Hamilton Depression Rating Scale, NMSS = Non-Motor Symptoms Scale, PD = Parkinson disease.
* *P* value is calculated from binary logistic regression analysis.
† Significant difference.

Table 6

Associations between FOG 3 years later and changes in drug administration and mood.

Baseline	Samples	Change 3 years later	Freezers	Nonfreezers	Test	*P* value
No use of levodopa	112	Use	14	51	a	0.088
		No use	17	30		
No use of amantadine	142	Use	41	21	a	0.247
		No use	60	20		
No use of Selegiline	149	Use	33	31	a	<0.001*
		No use	74	11		
No use of dopamine receptor agonist	161	Use	78	26	a	0.114
		No use	36	21		
Without anxiety and depression	150	With anxiety	29	21	b1	0.178
		With depression	28	11	b2	<0.001*
		Without anxiety and depression	11	50	b3	<0.001*

Test a: chi-square test.

Test b[1]: comparison between patients with anxiety and patients with depression using a chi-square test.

Test b[2]: comparison between patients with anxiety and patients without anxiety/depression using a chi-square.

Test b[3]: comparison between patients with depression and patients without anxiety/depression using a chi-square.

* Significant difference (for test a *P* values < 0.05 are considered statistically significant; for tests b and P values < 0.025 are considered statistically significant).

education, akinetic-rigid style, no use of dopamine receptor agonists, higher scores for cognitive disturbances, and higher scores for sleep disorders were associated with FOG ($P < 0.05$). No significant associations were found between the remaining variables and FOG.

3.3. Relationships between the changes in drug use, mood, and FOG

We analyzed the association of FOG: (a) with changes between the baseline and follow-up use of levodopa, amantadine, selegiline, and dopamine receptor agonists; and (b) changes in patient anxiety and depression between baseline and follow-up. The chi-square test was used to compare the difference between freezers and nonfreezers 3 years after baseline (Table 6). The analyses found no differences between use and no use of levodopa, amantadine, and dopamine receptor agonists ($P > 0.05$). In contrast, administering selegiline during the course of the disease appeared to reduce FOG ($P < 0.001$). Patients who developed anxiety or depression during the course of disease were more likely to develop FOG ($P < 0.001$).

3.4. Association between factors at baseline and FOG after 1 and 2 years

We analyzed the association between FOG 1 year after baseline and potential predictor variables 3 years after baseline using binary logistic regression (the same method was used for 2 years after baseline). Table 7 shows that a higher score for the cardiovascular domain on the NMSS was significantly associated ($P = 0.001$) with FOG 1 year later (i.e., 1 year after baseline). The lower limbs as the site of onset ($P = 0.008$), mixed style ($P = 0.005$), no use of dopamine receptor agonists ($P < 0.001$), and a higher score on the anxiety/somatic domain of the HAMD ($P = 0.033$) were significantly associated with FOG 2 years later (ie, 2 years after baseline).

4. Discussion

PD is a common disease. When FOG occurs early in PD, it always has a mild form, and early detection of FOG is an alarm signal that may cast doubt on a diagnosis of PD.[17] The prevalence of FOG is higher in older patients, many of whom have osteoporosis and other multisystem diseases. FOG is one of the major disabling symptoms of advanced PD, as severe FOG can lead to falls, pain, skin contusions, fractures, and activity limitations.[18–20] Hence, early identification, treatment, and control of risk factors for FOG are very important. To our knowledge, this is the first prospective study to investigate the prevalence and clinical correlates of FOG in Chinese patients with early PD.

We found FOG was very common in the Chinese population of PD patients; it was 16.13% one year later—that is, 1 year after baseline—39.52% 2 years later, and 51.61% 3 years later. These findings are consistent with previous studies of non-Asian populations (prevalence ranging from 32% to 72%).[21–26] The year-by-year increase in the incidence of FOG suggests that older patients or patients with longer durations of PD are more likely to experience FOG.

We found that patients who had a lower education or were from the countryside were more likely to suffer from FOG. This could be because patients with a higher education had a better understanding of PD and had better compliance, whereas patients from cities were closer to hospitals where they could be treated. Additionally, the results showed that patients whose lower limbs were the site of onset and patients with an akinetic-rigid style were more likely to suffer from FOG. Several studies have reported that patients with onset in the lower limbs were prone to experience FOG.[11,27,28] Our study suggests that early use of levodopa and a higher daily dose of levodopa at baseline were associated with a higher incidence of FOG, which is in accordance with studies by Ou and Macht.[11,25] Furthermore, the result indicated that early use of amantadine, selegiline, and dopamine receptor agonists can reduce FOG, which is consistent with some previous studies.[11,25,29,30] The results also showed that patients with depression were more likely to suffer from FOG, which is consistent with a previous study that found patients with anxiety or depression were more likely to experience FOG.[10] Our study found no difference in FOG between male and female patients, which is consistent with a previous study on English patients.[26] Nor was there any difference in FOG between early-onset and late-onset patients. This could be due to the fact that there were very few early-onset patients enrolled in the study, which might have introduced a statistical bias. Furthermore, patients who had both anxiety and

Table 7

Associations between risk factors at baseline and FOG one or 2 years later in PD patients.

		One year later (40 freezers/208 nonfreezers)			Two years later (98 freezers/150 nonfreezers)		
Baseline	**Code**	**OR**	**95%CI**	***P* value***	**OR**	**95%CI**	***P* value***
Age	<65 years old (R) ≥65 years old	0.086	0.006–1.131	0.062	1.326	0.212–8.278	0.763
Source of patients	From city (R) From countryside	1.082	0.175–6.706	0.932	2.345	0.353–15.577	0.378
Education years	>9 years (R) ≤9 years	–	–	–	2.690	0.161–44.822	0.490
Lower limbs as site of onset	No (R) Yes	0.643	0.204–2.023	0.450	4.772	1.515–15.029	0.008†
Type of motor symptom							
Tremor dominant	(R)						
Akinetic rigid		–	–	–	7.013	0.193–255.216	0.288
Mixed		0.651	0.212–1.994	0.452	0.189	0.060–0.596	0.005†
Drug administration							
Use of levodopa	Yes (R) No	4.295	0.975–18.917	0.054	2.936	0.603–14.300	0.182
Use of amantadine	No (R) Yes	0.658	0.170–2.545	0.544	0.430	0.120–1.548	0.197
Use of Selegiline	No (R) Yes	0.815	0.216–3.074	0.762	2.046	0.433–9.668	0.366
Use of dopamine receptor agonist	No (R) Yes	–	–	0.995	0.031	0.005–0.208	<0.001†
NMSS							
Cardiovascular		2.729	1.473–5.055	0.001†	0.922	0.509–1.670	0.788
Sleep/fatigue		0.524	0.255–1.078	0.079	0.423	0.161–1.111	0.081
Mood/apathy		1.204	0.620–2.338	0.124	0.675	0.288–1.582	0.366
Perceptual problems/hallucinations		1.614	0.901–2.893	0.108	1.037	0.576–1.868	0.904
Attention/memory		0.866	0.567–1.321	0.503	0.858	0.533–1.383	0.531
Gastrointestinal		0.510	0.217–1.198	0.122	0.466	0.206–1.055	0.067
Urinary		1.406	0.876–2.258	0.158	0.643	0.360–1.149	0.136
HAMD							
Anxiety/somatic		0.783	0.531–1.154	0.217	0.596	0.370–0.959	0.033†
Weight		1.498	0.596–3.770	0.390	1.437	0.503–4.107	0.498
Cognitive disturbance		1.302	0.718–2.358	0.385	1.179	0.598–2.324	0.635
Block		0.573	0.304–1.080	0.085	1.283	0.639–2.576	0.484
Sleep disorder		1.163	0.664–2.035	0.597	1.192	0.628–2.264	0.591
Feeling of despair		1.002	0.665–1.512	0.991	0.729	0.405–1.312	0.292

FOG = freezing of gait, HAMD = Hamilton Depression Rating Scale, NMSS = Non-Motor Symptoms Scale, PD = Parkinson disease.

* *P* value is calculated from binary logistic regression analysis.

† Significant difference.

depression at baseline or later in the study were more likely to suffer from FOG than patients who did not have these combined affective disorders. Giladi study suggested that the use of selegiline later in PD could reduce FOG,[31] and our study found similar results, in addition to the finding that other drugs did not reduce FOG.

We analyzed the association between the risk factors at baseline and FOG 3 years later using a binary logistic regression model. The model only adjusted for age due to the uniformity of early PD patients and the very similar course of disease. The results indicated that FOG was associated with lower education, an akinetic-rigid style, not using dopamine receptor agonists, and higher scores on the cognitive disturbance domain and higher scores on the sleep disorder domain of the HAMD. The longer observation time, the higher the accuracy of the association between risk factors and FOG. Therefore, we also used binary logistic regression to determine whether the risk factors 3 years later were the same risk factors observed at 1 year and 2 years later. The results showed that a higher score on the cardiovascular domain of the NMSS at baseline was associated with FOG 1

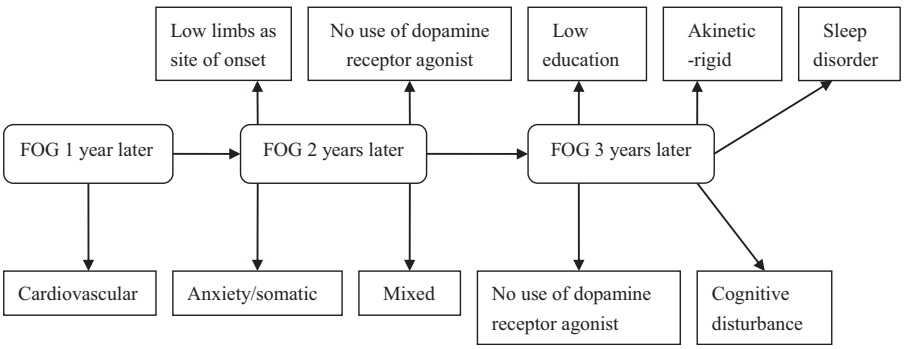

Figure 2. FOG and its risk factors. FOG = freezing of gait.

year later (Fig. 2). Lower limb site of onset, mixed style, not using dopamine receptor agonists, and a higher score on the anxiety/somatic domain of the HAMD were associated with FOG 2 years later (Fig. 2). Though the risk factors changed year by year, we could see that nonmotor symptoms, in addition to movement disorders, had an important role in the occurrence of FOG. Thus, higher scores on the NMSS or HAMA and HAMD in the early stage of PD predicted the early occurrence of FOG. Not using dopamine receptor agonists was a higher risk factor for FOG, which means that early use of dopamine receptor agonists could benefit early PD patients.

Many patients in our study reported falls, skin contusions, and fractures because of severe FOG. Thus, physicians should pay attention not only to the adjustment of drugs, but also to the prevention of FOG. The key way to prevent FOG is to address non-motor symptoms in early PD patients. Doctors should instruct patients and their family members, especially those who have a lower education or live in the countryside, to improve patients' compliance with treatment. Further research is needed to explore the degree to which controlling for some of the controllable risk factors of FOG can delay the occurrence of FOG or reduce FOG.

4.1. Limitations

There were some limitations of our study that should be discussed. First, FOG occurs more commonly at home, which makes it difficult to evaluate by physicians or researchers. Therefore, recall bias might have influenced the results of the study. Second, the results might have been affected by some unpredictable factors, such as the progress of the disease. Third, the drug compliance of each patient was different, and the anti-Parkinson and antianxiety drugs that were used also were different.

5. Conclusions

FOG is a common disabling symptom of PD in Chinese patients. Risk factors for FOG in patients with early PD included: older age, being from the countryside, having an akinetic-rigid style, having anxiety or depression, early use of levodopa, not using amantadine or selegiline and dopamine receptor agonists, the lower limbs as the site of onset, more severe motor disability, and higher scores on the HAMD or NMSS at baseline. Lower education, not using dopamine receptor agonists at baseline, an akinetic-rigid style, and especially, cognitive disturbances and sleep disorders (as measured by the HAMD) are strongly associated with FOG.

Acknowledgments

The authors thank the patients and their families for their participation in the study. We thank Dr Zhigang Chen and Dr Xin He for their assistance with research design and data processing.

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