Neurological Sciences (2019) 40:293–298
https://doi.org/10.1007/s10072-018-3625-6

ORIGINAL ARTICLE

Factors associated with freezing of gait in patients with Parkinson's disease

Seong-Min Choi[1,2,3] · Hyun-Jung Jung[1] · Geum-Jin Yoon[1] · Byeong C. Kim[1,2,3]

Received: 29 August 2018 / Accepted: 25 October 2018 / Published online: 1 November 2018

Abstract

Background Freezing of gait (FOG) is a common and debilitating problem in patients with Parkinson's disease (PD). The aim of this study was to estimate the prevalence of FOG, and to identify factors that independently contribute to FOG in patients with PD.
Method We included 157 PD patients. FOG was assessed using the FOG Questionnaire (FOG-Q). Patients with or without FOG were defined as item 3 in the FOG-Q.
Results One hundred eleven (70.7%) out of 157 PD patients presented with FOG. Patients with FOG were older, had long disease duration, were taking higher doses of dopaminergic agents, and had higher motor and non-motor scores than those without FOG. Multivariate linear regression analysis showed that high modified Hoehn and Yahr (mHY) stage, Unified PD Rating Scale (UPDRS) part II score, and non-motor symptom assessment scale for PD (NMSS) total score were significant predictors of a high FOG-Q score. Patients with FOG had significantly higher scores for cardiovascular, gastrointestinal tract, urinary, and miscellaneous NMSS domains than those without FOG.
Conclusions FOG in PD was associated with higher mHY stage, UPDRS part II score, and total NMSS score. Therefore, clinicians should consider non-motor, motor features and activities of daily living states for the proper management of FOG.

Keywords Parkinson's disease · Freezing of gait · Non-motor symptoms

Introduction

The characteristics of Parkinson's disease (PD) include bradykinesia, rest tremors, rigidity, and postural instability [1]. Freezing, also referred to as motor blocks, is a form of akinesia and is one of the most disabling symptoms of PD [2]. Freezing most commonly affects the legs during walking, referred to as freezing of gait (FOG). FOG is common in advanced PD stages and affects approximately 50% of patients [3]. FOG is relatively rare in early stages of PD, and if it is the presenting symptom of parkinsonism, the diagnosis of other parkinsonian syndromes should be suspected, such as progressive supranuclear palsy [4]. FOG affects the quality of life (QoL) of patients with PD [5] and should be considered as a highly important symptom in the management of PD patients.

FOG is characterized by temporal and local variability. Therefore, FOG measurement is quite challenging as objective FOG assessment requires a continuous ambulatory system that can monitor locomotion and FOG episodes. FOG questionnaire (FOG-Q) could be a useful substitute for FOG recordings [3, 6].

FOG was related to many clinical factors in previous studies. Among them, a longer disease duration, a more severe disease severity (Hoehn-Yahr stage) and disability (Unified PD Rating Scale ADL), and wearing off were significant clinical features associated with FOG [7, 8]. Non-motor and motor symptoms were also related to FOG [8]. FOG affects the degree of ambulating ability and is hence associated with loss of independence, falls, and depression [5]. Urinary symptoms and depression were associated with FOG in one study [8], and cardiovascular domain of the NMSS was the only risk factor for FOG in another study [9]. Therefore, FOG-related factors seem various from study to study. The aim of this study is to

✉ Byeong C. Kim
byeong.kim7@gmail.com

[1] Department of Neurology, Chonnam National University Hospital, Gwangju, South Korea

[2] National Research Center for Dementia, Gwangju, South Korea

[3] Department of Neurology, Chonnam National University Medical School, 160, Baekseo-ro, Dong-gu, Gwangju 61469, South Korea

estimate FOG prevalence, and to identify factors that independently contribute to FOG in patients with PD.

Patients and methods

Subjects

The study population was based on 157 PD patients who attended the Movement Disorders Clinic of Chonnam National University Hospital, South Korea. The patients were diagnosed with PD according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria [1]. The diagnosis was confirmed by a movement disorder specialist (SM Choi) at the last hospital visit. All PD patients had a positive response to levodopa and did not have clinically significant brain lesions, as seen by magnetic resonance imaging. Exclusion criteria included unclear diagnosis, neurological diseases other than PD, atypical or secondary parkinsonism, dementia, severe comorbidities that interfere with daily functioning, deep brain surgery, and inability to complete clinical assessments.

All participants provided written consent for their participation in this study. The study was approved by the Institutional Review Board of the Chonnam National University Hospital, South Korea, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Clinical evaluation

Patients were interviewed and examined by neurologists (HJ Jung and GJ Yoon) pre-trained for the survey. The clinical evaluations were completed by the neurologists during the patients' last hospital visit and missing historical data were retrieved from hospital charts. The patients were examined in the "on" or best condition. Participants were asked about the age of symptom onset, disease duration, past, and current medications. Weight and height were measured in the standing position, and body mass index (BMI) was calculated as the weight in kilograms divided by the square height in meters. The levodopa equivalent dose (LED) of for all medications taken at the time of the interview was calculated [10]. The parkinsonism states of the patients were assessed using the Unified PD Rating Scale (UPDRS) [11] and modified Hoehn and Yahr (mHY) stage [12]. General cognition was measured with the Korean version of mini-mental status examination (K-MMSE) [13], and depression was assessed using Beck's depression inventory (BDI) [14]. Non-motor symptom assessment scale for PD (NMSS) was used to evaluate non-motor symptoms of the patients [15].

FOG was assessed using FOG-Q [6]. The total FOG-Q score ranges from 0 to 24, with high total scores corresponding to severe FOG. Patients were instructed to answer the FOG-Q (except for item 3) based on their experience over the week prior to the assessment. FOG-Q was completed by the researcher who questioned the patients in all six items. We paid special attention to item 3, regarding the unique experience of the feet getting glued to the floor while walking, making a turn or when trying to initiate walking (freezing) [6]. If the patient was not familiar with the freezing phenomenon or did not understand the question, researchers showed several FOG video cases or demonstrated the phenomenon to the patients [3]. Patients with or without FOG were defined by item 3 of the FOG-Q [3].

Statistical analysis

SPSS, version 20.0 for Windows (IBM, Armonk, NY, USA) was used to perform all statistical analyses. Independent sample Student's t tests for continuous variables and χ^2 test for categorical variables were used to determine the significance of any differences in the clinical variables between PD patients with or without FOG. Pearson's correlation analysis was used to analyze potential factors associated with FOG-Q. Statistically significant variables in the aforementioned analyses were included in the multivariate linear regression model with FOG-Q as the dependent variables. Analysis of covariance (ANCOVA), controlling for age, disease duration, LED, mHY stage, and UPDRS part II score, was used to compare the total and domain NMSS scores. Data with a $p < 0.05$ were considered statistically significant.

Results

The clinical characteristics of PD patients with and without FOG are shown in Table 1. One hundred eleven out of 157 (70.7%) PD patients reported FOG. The mean FOG-Q score was 12.1 in PD patients with FOG, and 2.7 in patients without FOG. PD patients with FOG were older, had long disease duration, and were taking a higher dose of dopaminergic agents than those without FOG. There were no significant differences in sex, age of PD symptom onset, or BMI between the two groups. All motor scores, including mHY stage; UPDRS part II, III, and IV dyskinesia; and motor fluctuation scores, were higher in PD patients with FOG than in those without FOG. All non-motor scores, including MMSE, BDI, and total NMSS scores, were also worse in PD patients with FOG than in those without FOG.

Pearson's correlation analysis was performed to investigate the relationship between FOG-Q score and clinical variables in patients with PD. There were statistically significant associations between FOG-Q score and either of the following: age, disease duration, LED, mHY stage, UPDRS part II–IV scores, MMSE, BDI, and total NMSS scores (Table 2).

Table 1 Clinical characteristics of Parkinson's disease patients with and without FOG

Characteristics	All patients ($n = 157$)	With FOG* ($n = 111$)	Without FOG* ($n = 46$)	p value
Demographic and clinical				
Age (years)	69.6 ± 7.5	71.1 ± 7.0	66.2 ± 7.4	< 0.001
Sex (female:male)	92: 65	61: 50	31: 15	0.160
Age of PD symptom onset (years)	62.7 ± 8.3	63.6 ± 8.3	60.7 ± 8.1	0.051
Disease duration (years)	6.8 ± 4.0	7.4 ± 4.4	5.4 ± 2.8	0.007
BMI	23.1 ± 3.1	22.9 ± 3.2	23.6 ± 2.7	0.228
Levodopa equivalent dose (mg)	510.2 ± 250.2	564.0 ± 259.0	380.4 ± 169.2	< 0.001
Motor				
mHY stage	2.3 ± 0.8	2.5 ± 0.8	1.9 ± 0.5	< 0.001
UPDRS part II score	13.4 ± 8.5	15.9 ± 8.5	7.3 ± 4.4	< 0.001
UPDRS part III score	26.6 ± 12.2	29.7 ± 12.6	19.1 ± 8.4	< 0.001
UPDRS part IV dyskinesia	0.69 ± 1.20	0.87 ± 1.33	0.22 ± 0.59	0.002
UPDRS part IV motor fluctuation	1.28 ± 0.88	1.40 ± 0.87	0.98 ± 0.88	0.007
Non-motor				
MMSE score	25.2 ± 4.7	23.9 ± 4.9	25.7 ± 3.9	0.014
BDI score	16.5 ± 12.1	19.0 ± 12.2	10.3 ± 9.6	< 0.001
Total NMSS score	86.4 ± 58.5	100.1 ± 60.6	54.0 ± 37.0	< 0.001
FOG-Q score	9.3 ± 6.0	12.1 ± 4.9	2.7 ± 2.1	< 0.001

Values are mean ± standard deviation. *Defined by FOG-Q item 3

FOG, freezing of gait; *PD*, Parkinson's disease; *BMI*, body mass index; *mHY stage*, modified Hoehn and Yahr stage; *UPDRS*, Unified PD Rating Scale; *MMSE*, mini-mental state examination; *BDI*, Beck's depression inventory; *NMSS*, non-motor symptoms assessment scale for PD; *FOG-Q*, FOG-Questionnaire

Multivariate linear regression analysis was performed to explore factors related to FOG-Q. The significant factors associated with FOG-Q were mHY stage, UPDRS part II score, and total NMSS score (Table 3).

The differences in score in the total and domain NMSS scores between PD patients with or without FOG are shown in Table 4. After adjustment for age, disease duration, LED, mHY stage, and UPDRS part II score, PD patients with FOG had significantly higher total NMSS and domain scores, regarding cardiovascular, gastrointestinal tract, urinary, and miscellaneous domains, than in those without FOG.

Discussion

In this cross-sectional study on the clinical features associated with FOG in PD, we observed that patients with FOG were older, had longer disease duration, were taking higher doses of dopaminergic agents, and had worse motor and non-motor scores, than those without FOG. Similar associations were also observed in the correlation analysis between FOG-Q and clinical variables. Modified HY stage, UPDRS part II score, and total NMSS score were significant predictors of FOG in multivariate analysis. Among the various non-motor symptoms, cardiovascular, gastrointestinal, and urinary symptoms were more frequent in patients with FOG than in those without.

FOG is a common disabling symptom in patients with PD. PD patients with FOG have impaired step length and increased variability of step duration, resulting to gait disturbance. This consequently, might be associated with postural instability, fear of falling, physical fatigue, cognitive impairment, and depressive symptoms [16]. A patient with FOG is characterized by the loss of control of some of the most essential motor tasks, gait, and locomotion. Therefore, a study on FOG is very important in PD patients in regard to QoL [5].

The objective evaluation of FOG is challenging, since it is an intermittent, environmentally sensitive problem which is difficult to elicit during a clinical examination. Furthermore, FOG presents with highly variable manifestations among patient and is affected by numerous parameters, such as disease severity, motor status (i.e., "on" or "off"), visual input, walking environment, and cognitive factors [6]. FOG observed during a visit to the neurology practice might be poorly correlated with FOG reported by patients. Therefore, reliable FOG assessment requires prolonged observation periods in various situations. FOG-Q is a well-validated tool for the assessment of FOG severity and treatment intervention [3, 6]. Among the six items of FOG-Q, item 3 was an effective screening question for the presence of FOG [3]. Therefore, we divided the patients into two groups according to the

Table 2 Association between FOG-Q and clinical variables in patients with Parkinson's disease

Variable	FOG-Q	
	Pearson's correlation (γ)	*p* value
Demographic and clinical		
Age (years)	0.201	0.012
Sex	− 0.059	0.463
Age of PD symptom onset (years)	− 0.005	0.949
Disease duration (years)	0.377	< 0.001
BMI	− 0.090	0.265
Levodopa equivalent dose (mg)	0.480	< 0.001
Motor		
mHY stage	0.618	< 0.001
UPDRS part II score	0.697	< 0.001
UPDRS part III score	0.554	< 0.001
UPDRS part IV dyskinesia	0.389	< 0.001
UPDRS part IV motor fluctuation	0.342	< 0.001
Non-motor		
MMSE score	− 0.253	0.002
BDI score	0.471	< 0.001
Total NMSS score	0.581	< 0.001

FOG-Q, Freezing of Gait Questionnaire; *PD*, Parkinson's disease; *BMI*, body mass index; *mHY stage*, modified Hoehn and Yahr stage; *UPDRS*, Unified PD Rating Scale; *MMSE*, mini-mental state examination; *BDI*, Beck's depression inventory; *NMSS*, non-motor symptoms assessment scale for PD

presence of item 3 FOG-Q to explore the clinical characteristics of patients with FOG, compared with those without.

The prevalence of FOG in our patients (70.7%) was relatively high, which might be related to the long disease duration rates observed in our patients. The FOG prevalence in PD patients increased annually in a previous study, suggesting that older patients or patients with longer PD duration are more likely to experience FOG [9]. On the final multivariate analysis, the FOG-Q score was significantly associated with the mHY stage, UPDRS part II score, and total NMSS score. These findings are consistent with a previous study that showed that FOG in PD was associated with higher HY stage, longer disease duration, and longer duration of levodopa treatment [17].

In our study, the NMSS total score was a significant predictor of FOG and domain scores on cardiovascular, gastrointestinal tract, urinary, and miscellaneous domains of NMSS were significantly higher in patients with FOG than those without. Therefore, non-motor symptoms and motor symptoms should be considered in the management of PD patients with FOG. Several non-motor features, such as fatigue, anxiety, pain, and orthostatic hypotension, have also been reported to be negatively associated with walking difficulties such as FOG in a previous study [16]. In particular, anxiety is common in patients with FOG, both as a trigger and a result of FOG [18, 19]. Anxiety can negatively affect mobility and falls in FOG, and anxiety-lowering strategy can be helpful in FOG reduction [18]. However, in our study, mood/cognition domain scores were not different between PD patients with and without FOG. More comprehensive studies are needed to demonstrate the relationship between non-motor symptoms and FOG in patients with PD.

The mechanism of action for FOG in PD remains unclear. A lot of hypotheses, such as motor blocks [17], bilateral dyscoordination of left-right stepping [20], visuomotor disturbance [21], inability to set shift [22], executive, and attentional dysfunction [23] have been proposed. A number of regions,

Table 3 Multivariate regression analysis to explore the factors associated with FOG-Q in patients with Parkinson's disease

Variable	FOG-Q		
	Unstandardized coefficients	Standardized coefficients	*p* value
Age (years)	0.074 (− 0.024–0.172)	0.096	0.136
Disease duration (years)	0.010 (− 0.208–0.228)	0.007	0.927
Levodopa equivalent dose (mg)	0.002 (− 0.001–0.005)	0.086	0.219
mHY stage	1.340 (0.049–2.632)	0.189	0.042
UPDRS part II score	0.265 (0.133–0.397)	0.377	< 0.001
UPDRS part III score	0.007 (− 0.082–0.097)	0.015	0.087
UPDRS part IV dyskinesia	0.526 (− 0.180–1.232)	0.105	0.143
UPDRS part IV motor fluctuation	− 0.028 (− 0.917–0.861)	− 0.004	0.950
MMSE score	− 0.025 (− 0.191–0.140)	− 0.021	0.762
BDI score	− 0.032 (− 0.109–0.045)	− 0.065	0.411
Total NMSS score	0.021 (0.003–0.039)	0.214	0.023

FOG-Q, freezing of gait questionnaire; *mHY stage*, modified Hoehn and Yahr stage; *UPDRS*, Unified PD Rating Scale; *MMSE*, mini-mental state examination; *BDI*, Beck's depression inventory; *NMSS*, non-motor symptoms assessment scale for PD

Table 4 Non-motor symptoms of Parkinson's disease patients with and without FOG

Non-motor symptoms	With FOG ($n = 111$)	Without FOG ($n = 46$)	p value*
Cardiovascular including falls	5.3 ± 6.7	1.9 ± 3.1	0.028
Sleep/fatigue	13.7 ± 10.7	7.3 ± 7.3	0.081
Mood/cognition	17.9 ± 16.0	10.8 ± 13.4	0.142
Perceptual problems/hallucinations	3.8 ± 5.8	0.9 ± 2.3	0.054
Attention/memory	10.0 ± 8.7	7.5 ± 7.7	0.538
Gastrointestinal tract	11.2 ± 9.0	4.4 ± 4.5	0.013
Urinary	17.4 ± 11.8	9.0 ± 9.4	0.031
Sexual function	6.3 ± 6.5	5.2 ± 5.8	0.554
Miscellaneous	14.2 ± 11.1	6.6 ± 6.5	0.003
Total NMSS score	100.1 ± 60.6	54.0 ± 37.0	0.006

Values are mean ± standard deviation

*p value is calculated from ANCOVA adjusted for age, disease duration, LED, mHY stage, and UPDRS part II score

FOG, freezing of gait; *NMSS*, non-motor symptoms assessment scale for PD

such as the midbrain, subthalamic nucleus, globus pallidus, basal ganglia, supplementary motor area, and frontal lobe, have been associated with FOG [24]. From the present findings, anatomical areas or circuits related to non-motor and motor symptoms might be involved in the generation of FOG in patients with PD. A better understanding of FOG is needed to develop effective therapies.

This study has several limitations. First, FOG is more common at home, mainly seen in off time [7], and it is difficult to investigate under a clinical setting. The patients were examined in the "on" or best condition, and therefore, FOG was diagnosed mainly by history. Therefore, it could be affected by uncertain memory, and recall bias may have affected the results of this study. Second, there are potential unmeasured confounders that could affect FOG in patients. Third, the study was cross-sectional; thus, the associations observed herein cannot be considered as definitive evidence of causal associations.

In conclusion, FOG in PD was associated with higher mHY stage, UPDRS part II score, and total NMSS score. Therefore, clinicians should consider the non-motor features, the motor, and activities of daily living states of the patients for the proper management of FOG. Further studies are needed to fully assess the role of non-motor symptoms in the mechanism of action during FOG.

Funding information This work was supported by a grant from the Brain Research Program through the National Research Foundation of Korea, funded by the Ministry of Science, ICT, and Future Planning NRF-2016M3C7A1905469 (to BC Kim).

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of the hospital, and informed consent was obtained from the study participants.

Conflicts of interest The authors declare that they have no conflicts of interest.

References

1. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181–184
2. Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 79:368–376
3. Giladi N, Tal J, Azulay T, Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe WH, Stocchi F, Tolosa E (2009) Validation of the freezing of gait questionnaire in patients with Parkinson's disease. Mov Disord 24:655–661
4. Giladi N, Treves TA, Simon ES, Shabtai H, Orlov Y, Kandinov B, Paleacu D, Korczyn AD (2001) Freezing of gait in patients with advanced Parkinson's disease. J Neural Transm (Vienna) 108:53–61
5. Moore O, Peretz C, Giladi N (2007) Freezing of gait affects quality of life of people with Parkinson's disease beyond its relationships with mobility and gait. Mov Disord 22:2192–2195
6. Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD (2000) Construction of freezing of gait questionnaire for patients with parkinsonism. Parkinsonism Relat Disord 6:165–170
7. Amboni M, Stocchi F, Abbruzzese G, Morgante L, Onofrj M, Ruggieri S, Tinazzi M, Zappia M, Attar M, Colombo D, Simoni L, Ori A, Barone P, Antonini A, DEEP Study Group (2015) Prevalence and associated features of self-reported freezing of gait in Parkinson disease: the DEEP FOG study. Parkinsonism Relat Disord 21:644–649
8. Ou R, Guo X, Song W, Cao B, Yang J, Wei Q, Shao N, Shang H (2014) Freezing of gait in Chinese patients with Parkinson disease. J Neurol Sci 345:56–60

9. Zhang H, Yin X, Ouyang Z, Chen J, Zhou S, Zhang C, Pan X, Wang S, Yang J, Feng Y, Yu P, Zhang Q (2016) A prospective study of freezing of gait with early Parkinson disease in Chinese patients. Medicine (Baltimore) 95:e4056
10. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25:2649–2653
11. Fahn S, Elton R, Marsden C (1987) Unified Parkinson's disease rating scale. In: Fahn S, Marsden C, Goldstein M, Calne D (eds) Recent developments in Parkinson's disease. McMillan Healthcare Information, Florham Park, pp 153–163
12. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427–442
13. Kang Y, Na DL, Hahn S (1997) A validity study on the Korean mini-mental state examination (K-MMSE) in dementia patients. J Korean Neurol Assoc 15:300–308
14. Beck AT, Beamesderfer A (1974) Assessment of depression; the depression inventory. Mod Probl Pharmacopsychiatry 7:151–169
15. Chaudhuri KR, Martinez-Martin P, Brown RG, Sethi K, Stocchi F, Odin P, Ondo W, Abe K, Macphee G, Macmahon D, Barone P, Rabey M, Forbes A, Breen K, Tluk S, Naidu Y, Olanow W, Williams AJ, Thomas S, Rye D, Tsuboi Y, Hand A, Schapira AH (2007) The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. Mov Disord 22:1901–1911
16. Kader M, Ullen S, Iwarsson S, Odin P, Nilsson MH (2017) Factors contribution to perceived walking difficulties in people with Parkinson's disease. J Parkinsons Dis 7:397–407
17. Giladi N, McMahon D, Przedborski S, Flaster E, Guillory S, Kostic V, Fahn S (1992) Motor blocks in Parkinson's disease. Neurology 42:333–339
18. Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N, Bloem BR (2015) Freezing of gait: a practical approach to management. Lancet Neurol 14:768–778
19. Olanow CW, Watts RL, Koller WC (2001) An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 56:S1–S88
20. Plotnik M, Hausdorff JM (2008) The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. Mov Disord 23:S444–S450
21. Cowie D, Limousin P, Peters A, Day BL (2010) Insights into the neural control of locomotion from walking through doorways in Parkinson's disease. Neuropsychologia 48:2750–2757
22. Naismith SL, Shine JM, Lewis SJ (2010) The specific contributions of set-shifting to freezing of gait in Parkinson's disease. Mov Disord 25:1000–1004
23. Yogev G, Plotnik M, Peretz C, Giladi N, Hausdorff JM (2007) Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention? Exp Brain Res 177:336–346
24. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A (2011) Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 10:734–744