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Freezing of gait in patients with Parkinson's disease: Provoking conditions and risk factors

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Abstract

Background & Objective: Freezing of gait (FOG) in Parkinson's disease (PD) significantly impacts patients' quality of life. Determining whether a patient has FOG is a clinical challenge. We aimed to investigate an improved rapid clinical assessment method to detect FOG and its risk factors in PD patients. *Methods*: This cross-sectional study involved 103 PD patients performing a walking trial designed to provoke FOG, which included tasks like 180-degree turns, navigating narrow corridors with obstacles, and 360-degree turns, both with and without a dual cognitive task of counting down from 100. Video recordings were examined to document freezers and non-freezers. Univariate analysis and multivariate logistic regression were used to determine risk factors. Receiver operating characteristic (ROC) curves were computed to obtain sensitivity and specificity of predictors of FOG. *Results:* Turning 360 degrees counterclockwise while counting down from 100 provoked FOG in all patients with FOG. Freezers (26.2%) had significantly longer disease duration, higher disability, and greater use of levodopa (LEDD). Independent risk factors included Hoehn & Yahr stage >2.5 (OR=4.32; 95% CI: 1.16-16.09), motor fluctuation (OR=5.93; 95% CI: 1.86-18.88), and MDS-UPDRS part II (OR=1.10; 95% CI: 1.00-1.20). MDS-UPDRS part II cut off of 17 can predict FOG with a sensitivity of 55.6 % and specificity of 86.8 %.
Conclusions: A rapid clinical assessment involving a 360-degree counterclockwise turn with a cognitive task is effective for FOG detection. This method provides a quick, reliable screening tool in clinical practice, especially for patients with Hoehn & Yahr stage >2.5 and motor fluctuations.

Keywords: Freezing of gait, Parkinson's disease, video recordings assessment, provoking conditions, risk factors.

INTRODUCTION

Freezing of gait (FOG) is a common gait abnormality that severely affects patients with Parkinson's disease (PD), occurring even in the early stages of the condition.[1] FOG was defined as "a brief episodic absence or marked reduction of forward movements of the feet despite the intention to walk".[1,2] The freezing state can last a few seconds but sometimes may prolong up to 30 seconds or even minutes. Because of this, patients may occasionally be unable to move independently and may experience some serious health problems.[3] FOG has a detrimental effect on the patient's quality of life as well as increases the risk of falls and depression.[4,5]

According to numerous earlier studies, the prevalence of FOG varies, but overall ranges from 5% to 85.9%.[6] The wide variability is mostly driven by the methods that were used to evaluate the phenomenon. To establish the diagnosis of FOG, both subjective clinical inquiry and questionnaires as well as objective gait observation (live or via video) and wearable sensors can be used. Among them, the objective method is considered the most accurate method to determine whether a patient actually has FOG. However, due to the sudden and unpredictable

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character of FOG, it is challenging to consistently assess this phenomenon, especially during short visits.[7] There are certain conditions that have been identified as triggers of FOG episodes, such as turning or changing direction, narrow spaces, crowded areas, distractions, and dual tasking (performing a cognitive or motor task while walking).[8] Some previous studies have shown that full turns in combination with a dual task elicited most FOG episodes.[9,10]

Clinical features associated with the occurrence of FOG including longer disease duration, severe motor symptoms, high levodopa equivalent daily dose (LEDD), motor fluctuations, predominance of postural instability and gait abnormalities (PIGD) hallucinations and cognitive impairment were matters of concern.[11-14] However, these predictors vary across different studies due to method of assessment, characteristics of participants, disease duration, quality of evidence as well as geographical and racial factors. Additionally, the limited number and small sample sizes of research on these parameters, combined with the lack of well-designed prospective studies, means that it is uncertain whether these characteristics are truly risk factors of FOG.[15,16]

To identify the settings that most consistently prompted FOG during clinical evaluation, and discover the clinical risk factors of FOG, we conducted this cross-sectional study in Vietnamese patients with PD.

METHODS

Study design and participants

We conducted a cross-sectional study at the University Medical center, University of Medicine and Pharmacy at Ho Chi Minh City from January 2021 through June 2021. Opportunity sampling method was used in this study. Inclusion criteria consisted of the patients (1) aged 18 years and older, (2) diagnosed definitely with PD based on the International Parkinson's Disease and Movement Disorder Society 2015 Diagnostic Criteria, and (3) consented to participate in the study. Exclusion criteria included (1) patients with visual or hearing impairments; (2) patients with other comorbidities affecting gait such as stroke, myopathy, peripheral neuropathy, or bone and joint diseases; (3) patients with serious medical conditions such as respiratory failure, heart failure, liver failure, or kidney failure; (4) patients who have had ablation or deep brain stimulation surgery, and (5) those who cannot complete the walking trial for videotaping for any reason (advanced stages of PD with severe motor complications or cognitive decline, etc.). The flow of participants is illustrated in Figure 1.

A hundred and ten patients who satisfied the requirements for inclusion were recruited and received walking trials recordings. However, seven of them failed to finish the designed trial

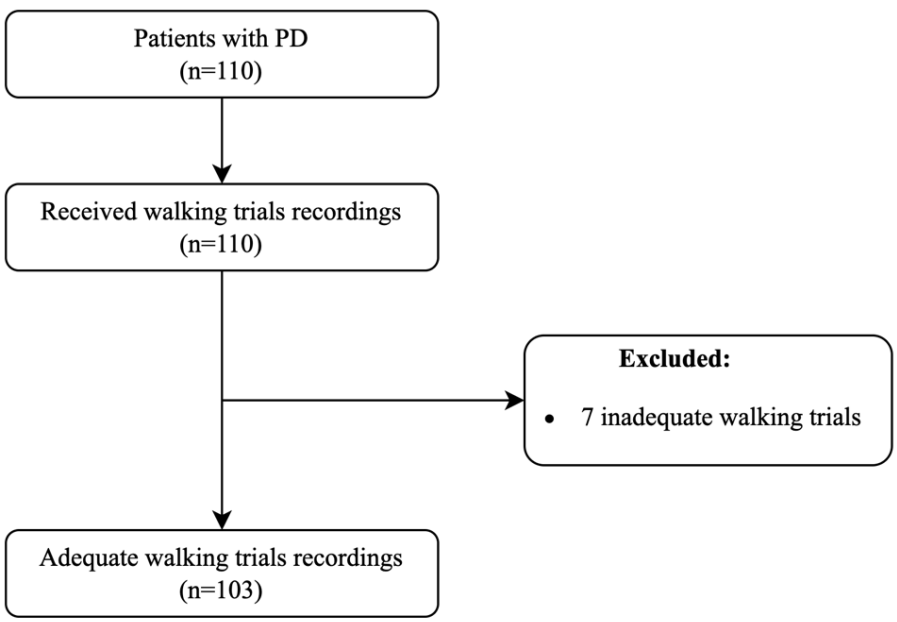

Figure 1. Flow of participants in the study. PD: Parkinson's disease

due to being unable to wait for the study's two phases on and off to analyze the walking lead. Thus, a total of one hundred and three participants were enrolled.

Baseline characteristic assessments

All participants were collected demographic and disease-related characteristics including age, gender, onset age, disease duration, family history, and current treatment. Patients were then assessed with MDS-UPDRS and Hoehn and Yahr Scale. To determine whether patients have motor fluctuations or dyskinesias, we rely on part 4 of the MDS-UPDRS scale. Patients have motor fluctuations if they answer to question 1 part IV of the MDS-UPDRS scale ≥1. The patient has dyskinesia if the answer to question 3, part IV of the MDS-UPDRS scale is ≥1.[17] By using Stebblin's method, motor subtype was classified as tremor domain (TD), posture instability and gait difficulty domain (PIGD), or intermediate domain (IND). To calculate the MDS-UPDRS TD/PIGD score, the mean of MDS-UPDRS items 2.10, 3.15a, 3.15b, 3.16a, 3.16b, 3.17a, 3.17b, 3.17c, 3.17d, 3.17e, and 3.18 is divided by the mean of MDS-UPDRS items 2.12, 2.13, 3.10, 3.11, and 3.12. If the resultant ratio is ≥1.15, then the patient is classified with TD. If the ratio is ≤0.90, then the patient is classified with PIGD. If the ratio is between 0.90 and 1.15, then the patient is classified as IND.[18] The scales were assessed at "ON" state of medication. LEDD was calculated by a conversion factor to sum L-dopa dose. In fact, we assessed the "OFF" state in the morning, after the patient had discontinued dopaminergic drugs for > 12 hours. In the "ON" state, we let the patient take current dopaminergic drugs and wait until the patient feels the symptoms respond best to the drug.

Objective gait assessments

FOG was carefully assessed via walking videotaping. The trial involved walking on a flat concrete pathway that was covered, outdoors, and 10 meters long. The pathway did not have any markings that could be used as external cues. The patient was asked to stand up from a back-supporting chair (point A) before walking forward to point B. There, the patient turned 180-degree (within a circle of 0.5 m diameter) and returned to point A. On the way back, the patient passed through a narrow corridor 0.5 m wide designed with two obstacles on each side (point C and D). The patient then traveled straight forth between the two objects to point A before halting within a circle that also had a diameter of 0.5 m. Finally, the patient rotated two 360-degree turns in place (one 360-degree clockwise rotation and one 360-degree counter-clockwise rotation) inside that area. The patient was instructed to walk at the fastest feasible rate while completing two walking trials, one spontaneous walk, and one dual-task combination counting down from 100. Counting from 100 was repeated if the patient had reached 1 but had not finished the trial yet (Figure 2).

Videos were recorded using Canon EOS-1D X Mark III DSLR; frame rate of 50 Hz. Videos were recorded during two walking trials and assessed independently by two movement disorder neurologists. Both discussed with each other to conclude a unified result whether the patients were freezers or non-freezers.

Patients with motor fluctuation underwent the procedure in both ON and OFF medication states; those who did not experience this motor complication underwent the procedure while continuing to take their regular medication. Patients who were at a high risk of falling were accompanied during the walk trial by a healthcare staff to reduce the risk of falls.

In those with FOG, we also described the conditions which provoked the phenomenon in each patient. These included gait at initiation, narrow space, open space (walking straight without narrow space and reaching destination) and reaching destination (within two meters near the end point (point A), turning 180-degree, turning 360-degree clockwise, and turning 360-degree counter-clockwise).

Subjective gait assessment

The New Freezing of Gait Questionnaire (NFOG-Q) developed by Nieuwboer *et al*.[19] was used to assess subjective FOG. We used part I for classifying freezers or non-freezers. Part I was used to detect FOG (patients and/or their caregivers recall if patients feel/present feet get glued to the floor while walking, making a turn, or start walking during the past month).

Statistical analysis

All data were processed by IBM SPSS Statistics for Macintosh version 28.0. Continuous variables with normal distribution were displayed as the means ± standard deviation (SD). Continuous variables with skewed distributions were presented as the medians (M_{25}–M_{75}). Shapiro-Wilk's test of normality was used to determine

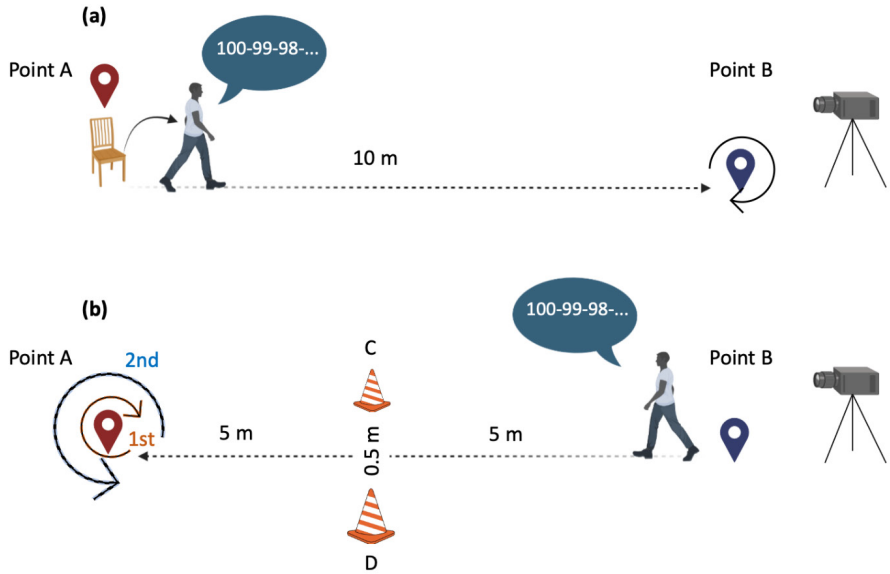

Figure 2. FOG assessment set-up. (a) first the patient is instructed to stand up from a back-supporting chair, then walk toward point B with a total distance of 10 m. The patient makes a return to point A after arriving at point B. (b) On the way back to point A, two obstacles (C and D) are placed simultaneously to form a narrow space of 0.5 m at the walking midpoint. When reaching point A, the patient makes two 360° turns: the first turn is clockwised and the latter is counterclockwised. The cognitive task is counting down from 100. Camera is set at point B to record patient's walking trials.

whether normal distribution of data.

Categorical variables including sex, family history of PD, levodopa drugs, dopamine agonist drugs, complications of motor fluctuations, dyskinesia, and PD subtypes would be presented by percentage (%) and compared using Chi-squared test or Fisher's exact test.

For continuous variables, we compared the mean values of the two groups by Student's *t*-test. In the case of a non-normal distribution, a Mann-Whitney non-parametric test was computed. The comparison was considered statistically significant when p-value is < 0.05.

Univariate logistic regression analyses were included to ascertain risk factors in relation to FOG. Those with 2-tailed p-value < 0.05 would be concluded in a multivariate logistic regression model and a stepwise approach was used to identify the independent risk factors.

Receiver operating characteristic (ROC) curve analysis was conducted using the predictor FOG to evaluate the performance of the prediction for FOG in patients with PD. Sensitivity and specificity were calculated at an optimal cut-off point derived from Youden's J-index.

RESULTS

One hundred and three people with idiopathic PD aged between 39 and 89 years, with a disease duration ranging from 1 to 25 years completed the assessments. Data on demographic and clinical manifestations of PD of study populations classified by FOG situation were detailed in Table 1.

Baseline characteristics

The FOG classification was satisfied by 27 out of the 103 participants. As a result, this study's observed prevalence of FOG was 26.2%. The FOG's prevalence as assessed by the NFOG-Q was 32% (33/103).

Comparison between freezers and non-freezers showed that on average, freezers had longer disease duration (8.0 [6.0;12.0] vs 3.0 [2.0;5.0], $p < 0.001$), greater disability as reflected by MDS-UPDRS part I (10.6 ± 5.7 vs 8.2 ± 4.7, $p = 0.034$), MDS-UPDRS part II (17.4 ± 7.5 vs 11.3 ± 5.8, $p < 0.001$), MDS-UPDRS part III (33.8 ± 13.2 vs 20.3 ± 12.8, $p < 0.001$), MDS-UPDRS part IV (5.1 ± 3.7 vs 1.3 ± 2.6, $p < 0.001$), motor fluctuation (20% vs 15%, $p < 0.001$), and dyskinesias (48.5% vs 10.0%, $p < 0.001$). Among freezers, the PIGD phenotype was identified in 21 patients (83.6%) and the TD phenotype in 8 participants (24.2%), whereas among non-freezers, 46 (65.7%) were identified as TD and 18 (25.7%) as PIGD. In

Table 1: Baseline features of 103 participants with PD

Parameter		Patients with PD			P-value
		Total (n=103)	Freezers (n=27)	Non-freezers (n=76)	
Age (mean ± SD)		62.9 ± 10.3	64.3 ± 10.4	62.3 ± 10.2	0.405[a]
Gender	Female (n (%))	55 (53.4)	17 (62.9)	38 (50)	0.246
PD's family history (n (%))		8 (7.8)	3 (11.1)	5 (6.5)	0.450[c]
Onset age (mean ± SD)		57.1 ± 11.4	54.6 ± 12.3	57.9 ± 11.0	0.198[a]
Disease duration	<5 years (n (%))	54 (52.4)	6 (22.2)	48 (63.1)	**< 0.001**[d]
	5-9 years (n (%))	31 (30.1)	11 (40.7)	20 (26.3)	
	10-14 years (n (%))	12 (11.6)	5 (18.5)	7 (9.2)	
	≥15 years (n (%))	6 (5.8)	5 (18.5)	1 (1.3)	
PD subtypes	TD (n (%))	54 (52.4)	7 (25.9)	47 (61.8)	**0.006**[b]
	PIGD (n (%))	39 (37.9)	16 (59.2)	23 (30.3)	
	ID (n (%))	10 (9.7)	4 (14.8)	6 (7.9)	
MDS-UPDRS I (mean ± SD)		8.9 ± 5.0	10.6 ± 5.7	8.2 ± 4.7	**0.034**[a]
MDS-UPDRS II (mean ± SD)		12.9 ± 6.8	17.4 ± 7.5	11.3 ± 5.8	**< 0.001**[a]
MDS-UPDRS III (mean ± SD)		23.8 ± 14.2	33.8 ± 13.2	20.3 ± 12.8	**< 0.001**[a]
MDS-UPDRS IV (mean ± SD)		2.8 ± 3.4	5.1 ± 3.7	1.3 ± 2.6	**< 0.001**[a]
Hoehn & Yahr stage	1-2 (n (%))	56 (54.4)	4 (14.8)	52 (68.4)	**< 0.001**[b]
	>2.5 (n (%))	47 (45.6)	23 (85.2)	24 (31.6)	
Motor fluctuation (n (%))		35 (34)	20 (74.1)	15 (19.7)	**< 0.001**[b]
Dyskinesias (n (%))		23 (22.3)	11 (40.7)	12 (15.8)	**0.007**[b]
LD monotherapy (n (%))		41 (39.8)	13 (48.1)	28 (36.8)	0.303[b]
DA monotherapy (n (%))		3 (2.9)	1 (3.7)	2 (2.7)	0.776[b]
LEDD (mean ± SD)		609.7 ± 478.5	936.6 ± 539.9	493.5 ± 397.8	**< 0.001**[a]

[a] Student's t test.36.8
[b] Chi-squared test.
[c] Fisher's exact test.
[d] Mann-Whitney U test.

addition, freezers received higher dosage of LEDD than non-freezers (938.7 ± 540.4 vs 454.6 ± 356.2, p < 0.001).

FOG provoking condition

Twenty-two of the 27 patients with FOG experienced it when walking without engaging in a cognitive dual task (counting down from 100); five of them experienced the phenomenon exclusively when engaging in a dual task. Using cognitive dual task, there were five more patients (18.5%) experiencing FOG.

When analyzing the occurrence of FOG when performing the walking trials, we noticed that FOG was seen most frequently while patients turn 360° counterclockwise (27/27 FOG patients). Details were presented in Figure 3.

Risk factors of FOG

As shown in Table 2, univariate analysis was performed on disease duration groups, PD subtypes, MDS-UPDRS part I – IV, Hoehn & Yahr stage groups, motor fluctuation, dyskinesia, and LEDD. Stepwise approach logistic regression revealed motor fluctuation, patients with postural instability with Hoehn & Yahr stage >2.5 and MDS-UPDRS part II as independent and significant determinants of FOG. Table 2 displays the adjusted odds ratios for these factors. Patients with Hoehn & Yahr stage >2.5 had a four times higher risk of FOG (OR=4.32; 95% CI: 1.16 - 16.09). Patients with motor fluctuation had a risk of FOG six times higher (OR = 5.93; 95% CI: 1.86 - 18.88) compared to their counterpart.

Receiver operating characteristic (ROC) curve analysis

Figure 4 reports on the ROC analysis to compare the diagnostic performance of variables that can be used as predictors of FOG. When compared with the non-significant ROC curve value of 0.5, the MDS-UPDRS part II had an AUC value of 0.757 with 95% CI 0.65-0.86. We found the cut-off value of MDS-UPDRS part II of 17 to be the optimal threshold with a sensitivity of 55.6% and specificity of 86.8%. Other ROC analysis values of Hoehn & Yahr stage >2.5 and motor fluctuation are displayed in Table 3.

DISCUSSION

FOG presents in nearly one-third (26.2%) of the research participants. Given the context of the study and the sampling technique, this statistic is not indicative of the prevalence. Yet in cases where findings of previous researches were inconsistent and varied greatly, this result can be used as a reference value for FOG frequency.

Though there are similarities in some aspects of baseline characteristics (gender, age, and PD onset), we discovered significant differences between freezers and non-freezers in all parts of MDS-UPDRS. Freezers were in more advanced stages of disease, had higher LEDD, and experienced more motor complications including motor fluctuation and dyskinesias. Clinically, this seems reasonable given that FOG is more prevalent in late-stage Parkinson's disease and that these motor complications also manifest later in the disease's progression after the patient has

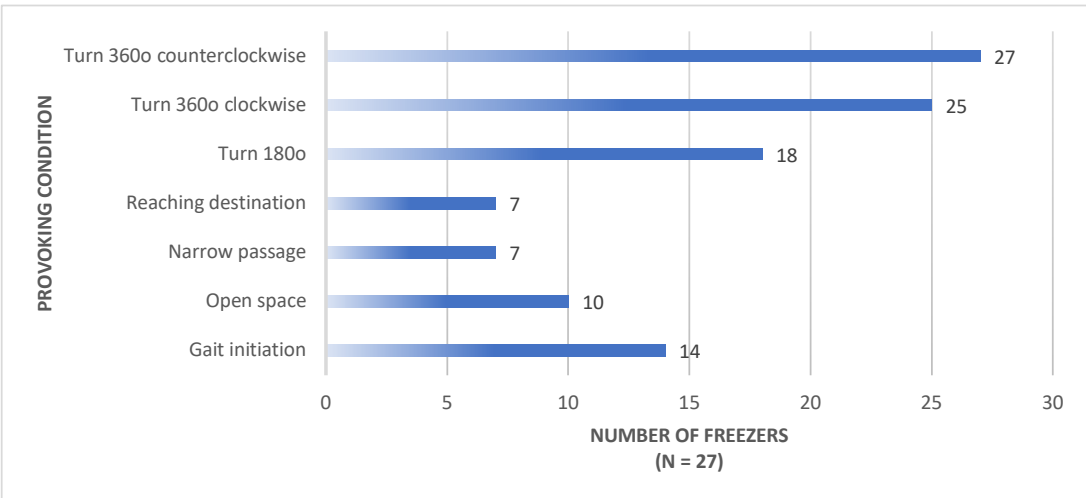

Figure 3: FOG episodes across different provoking conditions in freezers

Table 2: Univariate and multivariate regression analyses

Parameter		Univariate		
		OR	**CI 95%**	**p-value**
Disease duration	< 5 years	1.0		
	5-9 years	4.40	1.43 – 13.52	**0.010**
	10-14 years	5.71	1.37 – 23.81	**0.017**
	≥ 15 years	40.00	3.98 – 402.44	**0.002**
PD subtypes	TD	1.0		
	PGID	4.67	1.69 – 12.93	**0.003**
	ID	4.48	1.00 – 19.93	**0.049**
MDS-UPDRS I		1.09	1.00 – 1.19	**0.041**
MDS-UPDRS II		1.16	1.07 – 1.27	**< 0.001**
MDS-UPDRS III		1.08	1.04 – 1.11	**< 0.001**
MDS-UPDRS IV		1.39	1.20 – 1.60	**< 0.001**
Hoehn & Yahr stage	1-2	1.0		
	>2.5	12.46	3.88 – 40.00	**< 0.001**
Motor fluctuation		11.62	4.15 – 32.52	**< 0.001**
Dyskinesia		3.67	1.37 – 9.81	**0.01**
LEDD		1.002	1.001 – 1.003	**< 0.001**
Parameter		**Multivariate**		
		OR	**CI 95%**	**p-value**
Motor fluctuation		5.93	1.86 – 18.88	**0.003**
Hoehn & Yahr stage >2.5		4.32	1.16 – 16.09	**0.029**
MDS-UPDRS II		1.10	1.00 – 1.20	**0.038**

been receiving treatment for an extended period. Therefore, patients with Parkinson's disease who receive higher equivalent doses of levodopa have more severe motor symptoms and are refractory to lower doses of levodopa. Similar effects were found by Amboni *et al*. and Gan *et al*. as well.[20,21]

In FOG patients, our results revealed that the combination of cognitive task when walking helps detect the additional FOG phenomenon (18.5%). Spilldoren *et al*. reported a 30% additional increase in FOG detection using cognitive task.[22] This result is consistent with the hypothesis that the pathogenesis of FOG is due to disconnection between basal ganglia and accessory motor area leading to FOG that is more likely to occur when performing multiple tasks simultaneously.[23] Several other studies and our study revealed that the most common condition leading to FOG was turning 360 degrees.[3,9,24] Furthermore, we discovered that to detect FOG, turning 360 degrees counterclockwise was preferable to 360 degrees clockwise. These results led us to suggest a rapid clinic-based assessment where patients are asked to rotate 360 degrees counter-clockwise while counting down to quickly screen for freezing state. However, more research was required to confirm this finding. In Vietnam's genuine healthcare system, most patients are older and come from different educational backgrounds. It is difficult to design a cognitive task that everyone can do without producing FOG false positives due to the complexity of the task. This is the reason we decided to use counting down from 100 as a dual task. Contrarily, although being simple to complete, the countdown task could also result in false negatives since it was not challenging enough to cause a pathological asynchrony between movement and cognition.

Aside from the PIGD phenotype which comprises an evaluation of present FOG, MDS-UPDRS II score 17 or more, Hoehn & Yahr >2.5, and motor complications were the most significant independent risk factors of ongoing FOG. The latest finding is similar to that of

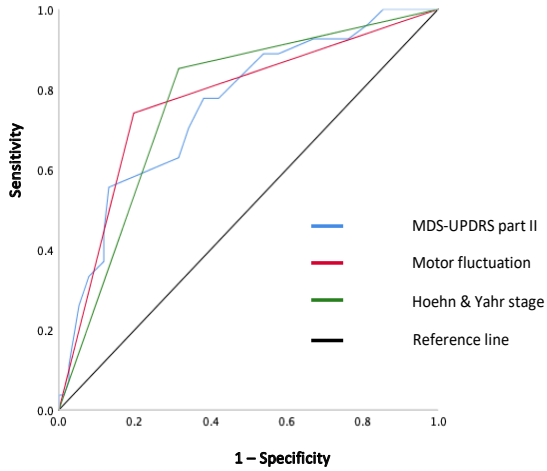

Figure 4. ROC analysis that compares the diagnostic performance of variables used to predict FOG.

Forsaa's study which identified motor variation as an independent risk factor for FOG.[16] On theory, motor fluctuations correlated more closely with the depletion of dopamine in the basal ganglia, which helps partially explain the observation that motor fluctuations may occur before the beginning of FOG. To our knowledge, no research has been done to demonstrate the association between the MDS-UPDRS part II score and FOG. It is probable that the scale's components itself represent the FOG. With an AUC of 0.757 with 95% CI 0.65-0.86, it can be said that MDS-UPDRS part III is fair in indicating FOG in patients who actually have FOG through objective assessment. The result of our study, however, implies that clinicians may use this scale to assess patients and determine if they are likely to have FOG. In the clinic setting, combining particular markers to indicate FOG such as having the patient rotate 360 degrees counterclockwise when doing the walking test, using the MDS-UPDRS part II scale with a 17-point cut-off to quickly recognizing that the patient actually has FOG is a good strategy.

This study has the following strengths and limitations. The walking trial videotaping's objective gait assessment allowed us to devote great attention to each patient, which improved the analysis's accuracy. To better comprehend the nature of this phenomenon, FOG is characterized and categorized in a variety of ways. Individuals with motor fluctuations underwent evaluations when their motor symptoms were at their lowest (ON phase) and greatest (OFF phase). This provides a more thorough description of the freezers group. In this short-term study, we just rely on part I of the MDS-UPDRS scale to provides an overview of the patient's non-motor symptoms, it is less detailed than other non- motor rating scales.

Though frontal function was said to be directly related to the occurrence of FOG, we did not assess it. Any symptoms connected to the frontal lobe should be included in future studies on FOG. Even though this was a cross-sectional study, a longitudinal examination was still necessary to discover more details on the relationship between FOG and additional clinical risk factors. Finally, the walking trial in our study also contained several factors that induced FOG; however, some provoking factors, such as the combination of an obstacle-clearing task with a non-cognitive dual task, were left out due to the short sampling time and conditions that called for rapid office-based assessment. This might make it harder to spot this phenomenon when analyzing the gait disruption in our study.

In conclusion, a rapid clinical assessment involving a 360-degree counterclockwise turn with a cognitive task is effective for FOG detection. This method provides a quick, reliable screening tool in clinical practice, especially for patients with Hoehn & Yahr stage >2.5 and motor fluctuations.

DISCLOSURE

Ethics: All study participants provided informed written consent. The study was approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh city, Vietnam.

Table 3: ROC analysis that compares the diagnostic performance of variables used to predict FOG

Parameter	ROC analysis		
	AUC	Sensitivity (%)	Specificity (%)
Motor fluctuation	77.2	74.1	80.3
Hoehn & Yahr stage >2.5	76.8	85.2	68.4
MDS-UPDRS II	75.7	55.6	86.8

Conflict of interest: Tai Ngoc Tran: has received consultation and/or honoraria/lecture fees from Boehringer-Ingelheim, Ipsen Pharmaceuticals, and Medtronic, and research funding from University Medical Center, University of Medicine and Pharmacy at Ho Chi Minh City. Other authors have no disclosures to report.

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