Original Article

A Comparative Study of Early and Late Onset Freezing of Gait in Parkinson's Disease

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Abstract

Background: Freezing of gait (FOG) is a common and debilitating symptom in Parkinson's disease (PD); the pathogenesis and natural course of which has not been fully understood. **Objectives:** This study was performed to evaluate patients with FOG in PD and ascertain factors contributing to an early onset of FOG in patients with PD. **Methodology:** A chart review of 100 patients with PD (FOG [+] 50, FOG [−]: 50) was performed. FOG (+) patients were subdivided by a median split of time from motor onset to development of FOG (median: 6 years) into early onset FOG (EOFOG [n = 24]) and late onset FOG (n = 26). **Results:** The FOG (+) group had a significantly longer duration of motor symptoms, a higher Hoehn and Yahr stage, and greater severity of disease. Festination, falls, and wearing off were more prevalent in the FOG (+) group. Several nonmotor symptoms (NMS) such as constipation, psychosis, fatigue, weight loss, drooling, excessive sweating, depression, and postural giddiness were significantly higher in the FOG (+) group. The EOFOG group had a later age at onset of motor symptoms. There were no significant differences observed in the NMS, with the exception of fatigue in EOFOG. **Conclusions:** FOG is associated with longer disease duration and higher severity of disease. FOG (+) patients have distinct NMS which are contributory to disease morbidity. EOFOG might be associated with an accelerated disease progression and is linked with older patients and shorter disease duration.

Keywords: Early onset, freezing of gait, Parkinson's disease

Introduction

Freezing of gait (FOG) is a paroxysmal motor phenomenon commonly observed in advanced Parkinson's disease (PD) and other parkinsonian syndromes such as pure akinesia with gait freezing, progressive supranuclear palsy, vascular parkinsonism, and normal pressure hydrocephalus.[1] FOG has been defined as "an episodic inability (lasting seconds) to generate effective stepping in the absence of any known cause other than parkinsonism or high-level gait disorders."[2] It is characteristically described by patients as a feeling of their feet being "glued to the floor," occurring more often during turning, step initiation, stress, and distraction.[3] Due to its unpredictability, FOG is one of the leading causes of falls in patients with PD.[4] Prevalence is reported to vary between as much as 60% in advanced PD to 7% in early PD.[5]

FOG has been frequently associated with longer duration of disease, higher motor severity, and a higher prevalence among the postural instability and gait disturbance (PIGD) variant.[6,7] It has a negligible correlation with bradykinesia[8] and fluctuating response to levodopa therapy. Factors which contribute to and determine the onset of FOG are uncertain. The exact mechanism of FOG persists to be unclear despite adequate awareness and interest in the field. Studies suggest the involvement of the supplementary motor area, striatum, and mesencephalic locomotor region including the pedunculopontine nucleus.[9] Four potential models have been proposed to explain the episodic nature of FOG. These include (1) the threshold model: FOG occurs when various motor deficits accumulate to reach a threshold and produce a motor breakdown; (2) the interference model: there may be an inability to process motor, cognitive, and limbic processes simultaneously; (3) the cognitive model: deterioration in processing of response conflicts may lead to behavioral indecision; and (4) the decoupling model: disconnection between preparatory programming and intended motor

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response induces a motor block.[10] Reports of phenotypic variations in patients with early FOG implicate a frontostriatal dysfunction,[11] which contradicts the popular Braak hypothesis of disease spread in PD.[12] In addition, functional neuroimaging studies have demonstrated a functional decoupling between the basal ganglia network and the cognitive control network, which was associated with paroxysmal motor arrests.[13]

In this study, we evaluated and compared the clinical features of patients with PD and FOG (FOG [+]), and those without FOG (FOG [−]). We also compared patients with early onset FOG (EOFOG) and late-onset FOG (LOFOG) to determine the characteristics of EOFOG and ascertain factors associated with a comparatively early onset of FOG in patients with PD.

Methodology

Subject recruitment and clinical evaluation

This study was conducted at the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. A chart review was conducted for 100 patients with PD, which included 50 FOG (+) and 50 FOG (−) patients, who were matched for gender and age at onset (AAO) of motor symptoms to avoid confounding. Diagnosis of idiopathic PD was based on the United Kingdom PD Society Brain Bank criteria[14] and confirmed by a trained movement disorder specialist. Exclusion criteria included the presence of other neurological diseases or conditions producing gait impairment. FOG (+) was identified by asking item 1.3 of the FOG questionnaire "do you feel that your feet get glued to the floor while walking, making a turn, or when trying to initiate walking?"[15] or if FOG was identified after the phenomenon was demonstrated to them during the evaluation. Patients included in this study have also been part of other studies on PD which were performed at NIMHANS.[16,17]

Several demographic and clinical details such as gender, age, AAO of motor symptoms, disease duration, initial predominant symptom, presence of motor fluctuations, history of falls, nonmotor symptoms (NMS), family history of parkinsonism, and treatment history were recorded. Details of clinical examination were also recorded. Disease severity was assessed by the Unified PD Rating Scale (UPDRS-III) and Hoehn and Yahr (HandY) scale. The details of FOG-AAO of FOG, motor to FOG latency, frequency of FOG, and "OFF" or "ON" state freezing was recorded from the FOG Questionnaire.[15]

All patients had provided informed consent before enrollment into the original projects.

Statistical analysis

Descriptive statistical analysis was performed for the demographic and clinical features of the FOG (+) and FOG (−) group. The FOG (+) group was divided based on a median split of latency between motor onset and onset of FOG (Motor to FOG (MF) latency), into EOFOG (MF latency <6), and LOFOG (MF latency ≥6). The Kolmogorov–Smirnov test was used as a test for normality. Following which, parametric variables were analyzed using the *t*-test and nonparametric variables were analyzed using the Mann–Whitney U-test. The Chi-square test was used for categorical variables. Correlations between parameters of FOG were evaluated by performing Spearman's correlation.

Statistical significance was set at $P < 0.05$. Data were collected using Microsoft Excel and statistical analysis was performed using R statistical software version 3.3.1.

Results

Comparison of patients with and without freezing of gait

Men outnumbered women in both groups. The mean AAO of motor symptoms was not significantly different owing to the two groups being matched based on the AAO of motor symptoms. The FOG (+) group presented significantly later (58.58 ± 7.75 years vs. 54.18 ± 8.92 years, $P < 0.01$) and had a longer duration of illness (8.16 ± 3.86 years vs. 3.90 ± 3.22 years, $P < 0.01$) in comparison to the FOG (−) group. The FOG (+) group was found to have a higher stage of disease as evidenced by the HandY stage compared to the FOG (−) group (2.29 ± 0.43 vs. 2.02 ± 0.47, $P < 0.05$). They also had higher disease severity as measured by the UPDRS-III OFF state score (44.59 ± 13.97 vs. 30.51 ± 12.09, $P < 0.05$). UPDRS-III ON state scores were not significantly different among the groups. Details of demographic and motor features provided in Table 1.

Tremor was the predominant initial symptom across both the groups, followed by bradykinesia and gait disturbances. FOG (+) had significantly higher prevalence of festination in comparison to FOG (−) (38% vs. 10%, $P < 0.05$). Although nonsignificant, the prevalence of falls was higher in FOG (+) (14% vs. 2%, $P = 0.059$). Dyskinesia (64% vs. 10%, $P < 0.01$) and wearing off (84% vs. 24%, $P < 0.01$) were also found to be more prevalent among FOG (+).

Analysis of NMS revealed a significantly higher prevalence of most symptoms in the FOG (+) group. They reported higher rates of constipation (56% vs. 24%, $P < 0.05$), psychosis (50% vs. 10%, $P < 0.01$), fatigue (48% vs. 16%, $P < 0.01$), weight loss (46% vs. 10%, $P < 0.01$), drooling (36% vs. 2%, $P < 0.01$), excessive sweating (24% vs. 8%, $P = 0.053$), depression (24% vs. 6%, $P < 0.05$), and postural giddiness (16% vs. 4%, $P < 0.05$). No significant differences were observed in the other NMS. Details are provided in Table 2.

Details of freezing of gait

The mean AAO of FOG was 56.71 ± 7.60 years and the MF latency was 6.47 ± 3.97 years. Freezing only during the OFF-state was reported in 88% freezers and daily episodes of freezing were reported in 88%. Approximately 78% of FOG (+) reported freezing episodes lasting 3–10 s. The mean FOGQ score was 11.88 ± 1.85. Details are provided in Table 3.

Table 1: Demographic and motor features in patient of Parkinson's disease with freezing of gait, patient of Parkinson's disease without freezing of gait, early onset freezing of gait, and late-onset freezing of gait groups

	FOG (+) (*n*=50)	FOG (−) (*n*=50)	*P* (FOG (+) vs. FOG(−))	EOFOG (*n*=24)	LOFOG (*n*=26)	*P* (EOFOG vs. LOFOG)
Male:female	35:15	37:13	NS	16:8	19:7	NS
Age at presentation	58.58±7.75	54.18±8.92	<0.01	56.58±7.93	60.42±7.10	NS
AAO motor symptoms	50.24±8.22	50.22±8.12	NS	51.83±8.84	48.76±7.30	NS
Duration of PD (years)	8.16±3.86	3.90±3.22	<0.01	4.83±1.70	11.23±2.53	<0.01
Family history of PD	6% (3)	10% (5)	NS	8.33%(2)	3.85% (1)	NS
H and Y stage	2.29±0.43	2.02±0.47	<0.01	2.22±0.40	2.34±0.45	NS
UPDRS-III OFF state	44.59±13.97 (37)	30.51±12.09 (30)	<0.05	43.38±12.05 (18)	45.73±15.48 (19)	NS
UPDRS-III ON state	18.71±14.09 (39)	15.31±10.45 (16)	NS	18.95±14.62 (20)	18.47±13.50 (19)	NS
Predominant initial symptom						
Tremor	58% (29)	66% (33)	NS	54.17% (13)	61.54% (16)	NS
Bradykinesia	16% (8)	14% (7)	NS	12.50% (3)	19.23% (5)	NS
Gait disturbance	8% (4)	2% (1)	NS	12.50% (3)	3.85% (1)	NS
Festination	38% (19)	10% (5)	<0.05	50% (12)	26.92%(7)	NS
Falls	14% (7)	2% (1)	=0.059	8.33% (2)	19.23% (5)	NS
Dyskinesia	64% (32)	10% (5)	<0.01	58.33% (14)	69.23% (18)	NS
Wearing off	84% (42)	24% (12)	<0.01	79.17% (19)	88.46% (23)	NS

AAO=Age at onset, EOFOG=Early onset freezing of gait, FOG (+)=Patient of Parkinson's disease with freezing of gait, FOG (−)=Patient of Parkinson's disease without freezing of gait, H and Y=Hoehn and Yahr, LOFOG=Late onset freezing of gait, NS=Nonsignificant, PD=Parkinson's disease, UPDRS=Unified Parkinson's disease rating scale

Comparison between early-onset freezing of gait and late-onset freezing of gait

Men outnumbered women in both the groups. LOFOG had a significantly longer duration of illness in comparison to EOFOG (11.23 ± 2.53 vs. 4.83 ± 1.70, $P < 0.01$). Both groups had similar HandY stages and UPDRS-III OFF and ON scores. There were no significant differences observed in the initial symptoms. Details of the demographic and clinical features are provided in Table 1.

The AAO of FOG was similar in EOFOG and LOFOG (55.20 ± 8.13 vs. 55.09 ± 6.78, $P > 0.05$) despite significant although expected variations in MF latency (3.37 ± 1.29 vs. 9.32 ± 9.45). Both groups reported predominantly OFF-state freezing (91.67% vs. 84.62%) followed by OFF + ON state freezing (8.33% vs. 15.38%). There were no reports of isolated ON-state freezing. Daily episodes of freezing were prevalent in both groups (87.50% vs. 88.00%). Although not statistically significant, only those with LOFOG reported episodes either 2–3 times per week or once a week. Episodes of freezing occurring 2–3/month were reported only in EOFOG (16.67% vs. 0%, $P < 0.05$). Both groups reported freezing lasting 3–10 s (83.3% vs. 73.3%). There was a trend toward significance of the mean FOGQ score in EOFOG (12.37 ± 1.99 vs. 11.42 ± 1.57, $P = 0.06$). Details of FOG are provided in Table 3.

Among the NMS, EOFOG had higher prevalence of fatigue (62.50% vs. 34.62%, $P < 0.05$) and generalized pain (12.50% vs. 3.85%, $P = 0.05$); apart from these, there were no other significantly different NMS. Details are provided in Table 2.

Correlations

A strong positive correlation was observed between the AAO of motor symptoms and AAO of FOG (Spearman's rho (r_S) = 0.884, $P < 0.01$) [Figure 1a]. The MF latency showed a significant correlation with duration of motor symptoms (r_S = 0.948, $P < 0.01$) [Figure 1b]. A negative correlation was found between the AAO of motor symptoms and MF latency ($r_S = -0.330$, $P < 0.05$) [Figure 1c], implying that perhaps those with a later AAO of motor symptoms have an earlier onset of FOG.

Discussion

The FOG (+) group in our cohort developed initial motor symptoms much earlier than reported in literature.[6] The duration of illness and disease severity observed are in concurrence with several other studies.[18,19] The age of presentation of patients in our cohort is highly influenced by socioeconomic and cultural factors. FOG is frequently reported in the advanced stages of PD. A higher disease severity seen in FOG (+) may be attributable to the correlation of disease severity with disease duration. Furthermore, the

Table 2: Nonmotor symptoms in patients of patient of Parkinson's disease with freezing of gait, patient of Parkinson's disease without freezing of gait, early onset freezing of gait, and late onset freezing of gait

	FOG (+) (*n*=50)	FOG (−) (*n*=50)	*P* (FOG (+) vs. FOG (−))	EOFOG (*n*=24)	LOFOG (*n*=26)	*P* (EOFOG vs. LOFOG)
Postural giddiness	16% (8)	0% (0)	<0.05	20.83% (5)	11.54% (3)	NS
RBD	24% (12)	18% (9)	NS	29.17% (7)	19.23% (5)	NS
EDS	4% (2)	0% (0)	NS	0.00% (0)	7.69% (2)	NS
Apathy	6% (3)	0% (0)	NS	4.17% (1)	7.69% (2)	NS
Depression	24% (12)	6% (3)	<0.05	25% (6)	23.08% (6)	NS
Psychosis	50% (25)	10% (5)	<0.01	54.17% (13)	46.15% (12)	NS
Double vision	2% (1)	2% (1)	NS	4.17% (1)	0.00% (0)	NS
Memory disturbances	12% (3)	6% (3)	NS	20.83% (5)	3.85% (1)	=0.09
ICD	2% (1)	2% (1)	NS	4.17%(1)	0.00% (0)	NS
Drooling	36% (18)	2% (1)	<0.01	33.33% (8)	38.46% (10)	NS
Dysphagia	8% (4)	2% (1)	NS	0.00% (0)	15.38% (4)	NS
Constipation	56% (28)	24% (12)	<0.05	41.67% (10)	69.23% (18)	=0.08
Urinary disturbances	34% (17)	18% (7)	NS	37.50% (9)	30.77% (8)	NS
Sexual dysfunction	14% (7)	4% (2)	NS	20.83% (5)	7.69% (2)	NS
Hyposmia	16% (8)	4% (2)	NS	16.67% (4)	15.38% (4)	NS
Weight loss	46% (23)	10% (5)	<0.01	41.67% (10)	50.00% (13)	NS
Fatigue	48% (24)	16% (8)	<0.01	62.50% (15)	34.62% (9)	<0.05
Generalized pain	8% (4)	4% (2)	NS	12.50% (3)	3.85% (10)	=0.053
Excessive sweating	24% (12)	8% (4)	=0.053	20.83% (5)	26.92% (7)	NS

EDS=Excessive daytime sleepiness, EOFOG=Early onset freezing of gait, FOG (+)=Patient of Parkinson's disease with freezing of gait, FOG (−)=Patient of Parkinson's disease without freezing of gait, ICD=Impulse control disorder, NS=Nonsignificant, PD=Parkinson's disease, RBD=REM behaviour disorder, LOFOG=Late onset freezing of gait, REM=Rapid eye movement

Table 3: Features of freezing in patients with freezing of gait, early onset freezing of gait, and late-onset freezing of gait

	FOG (+) (*n*=50)	EOFOG (*n*=24)	LOFOG (*n*=26)	*P* (EOFOG vs. LOFOG)
AAO of FOG (years)	56.71±7.60	55.20±8.13	55.09±6.78	NS
Motor to FOG latency (years)	6.47±3.97	3.37±1.29	9.32±3.45	<0.01
Occurrence of FOG				
OFF state	88% (44)	91.67% (22)	84.62% (22)	NS
ON state	0% (0)	0% (0)	0% (0)	-
OFF + ON state	12% (6)	8.33% (2)	15.38% (4)	NS
Frequency of FOG				
Daily	88% (44)	87.50% (21)	88.00% (23)	NS
2-3 week	4% (2)	0%(0)	7.69% (2)	NS
1 week	2% (1)	0%(0)	3.85% (1)	NS
2-3 month	1.5%(3)	16.67%(4)	0% (0)	<0.05
Duration of FOG				
1s-2 s	22% (11)	16.66% (4)	26.92% (7)	NS
3s-10 s	78% (39)	83.33% (20)	73.07% (19)	NS
FOGQ score	11.88±1.85	12.37±1.99	11.42±1.57	NS

AAO=Age at onset, EOFOG=Early onset freezing of gait, EOFOG=Early onset FOG, FOG=Freezing of gait, FOGQ=Freezing of gait questionnaire, LOFOG=Late onset FOG. NS=Nonsignificant

scoring systems used have significant weightage for gait disturbance and instability.

Tremor was the predominant initial symptom in our group of patients with FOG. The PIGD variant has been reported to be associated with FOG rather than the tremor-predominant disease.[7,19,20] In our study, we did not find an association of FOG with PIGD. Tremor being the predominant initial symptom in our study could be secondary to patient bias while reporting symptoms as a tremor is perceived as more bothersome and noticeable.

Festination and falls have been frequently reported in FOG. A higher incidence of falls may be attributable to the unpredictable and sudden nature of FOG. In addition, those with the PIGD variant are at higher risk due to increased axial involvement and instability which contributes to falls.[4,6] The rates of dyskinesia and wearing off observed in this study may be secondary to the higher severity of disease and consequently higher levels of levodopa equivalent dose.[1,6,20]

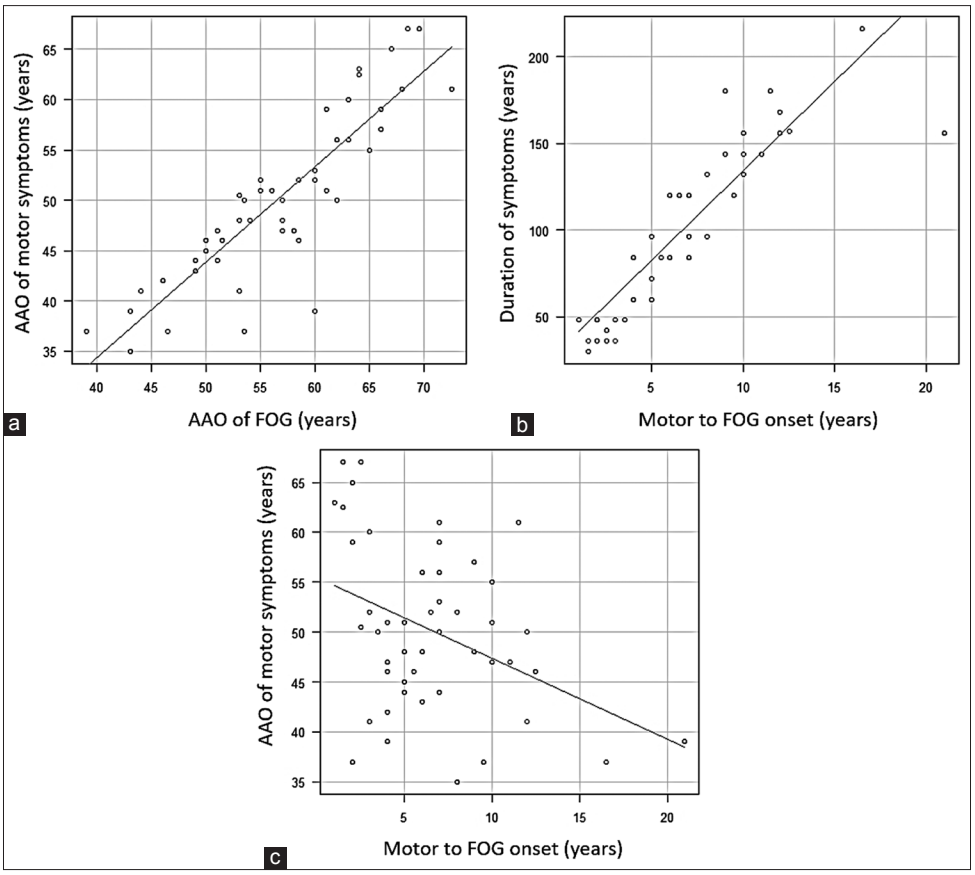

Figure 1: Correlations between (a) age at onset of motor symptom and age at onset of freezing of gait. (b) Duration of symptoms and motor to freezing of gait onset. (c) Age at onset of motor symptoms and motor to freezing of gait onset

The NMS reported in our FOG (+) group have been reported earlier.[11,18] Postural giddiness in FOG may be secondary to the brainstem pathology; however, studies correlating autonomic dysfunction and FOG have not yielded convincing results.[21] A distinct correlation between FOG and psychosis, depression, RBD, and cognitive impairment has been reported.[22] Depression in FOG has been frequently reported and implicated to be secondary to a reduction in noradrenergic and dopaminergic projections.[11,23,24] RBD and FOG have been linked in previous studies;[25] however, no specific pathophysiological alterations have been described.[24] Cognitive impairment has been consistently reported in FOG, specifically executive dysfunction and impaired working memory.[16] Inappropriate gating mechanism in the basal ganglia and frontostriatal dysfunction have been suggested to account for the cognitive impairment.[11,26,27] This is of key significance as it suggests that patients with freezing are unable to adequately recruit the executive domains essential for altering normal gait, which is contributory to the pathogenesis of FOG.

It is plausible that the higher prevalence of NMS seen in the FOG (+) group may be attributable to the older age at presentation, longer disease duration, and higher disease severity observed in this group.

In our study, the EOFOG had a later AAO of motor symptoms, earlier age at presentation, and shorter disease duration which showed a trend toward significance when compared to the LOFOG group. This perhaps indicates an accelerated disease process in this group. Similar findings have been reported elsewhere.[18,19] Contrary to these findings, Contreras and Grandas reported EOFOG in those with a younger AAO of motor symptoms.[6]

In the present study, disease severity was similar in both groups which is contrary to an expectation of higher disease severity in the LOFOG group which has a longer disease duration. There were no significant differences observed in other demographic or clinical features. No symptoms were found to be specific to EOFOG.

The AAO of FOG was similar in both groups and there was a longer MF latency in LOFOG. The occurrence of FOG in either OFF-state, ON-state, or both was also similar across the groups. Several studies have reported a prevalence of OFF-state freezing.[28] Levodopa has a complex interplay with FOG. Initially, levodopa was thought to be causative of FOG,[29] although with time, this theory was discarded.[28] The ELLDOPA study (Early versus late LevoDOPA) has suggested a protective role of levodopa in delaying FOG.[30] The beneficial effect of FOG with levodopa could be attributed to improvement

in the basal ganglia timing cue amplitude, the reduction of which is directly proportional to the amount of dopamine loss in the striatum.[31] However, the presence of levodopa-resistant FOG and on-state freezing[32] confounds the situation.

Daily episodes of freezing were reported by the majority of patients in both groups. However, a few patients in both groups reported lower frequency of freezing episodes. A high prevalence of daily episodes of freezing in our study could be attributable to patients presenting to the clinic at a later stage of the illness. Similarly, the presence of a few EOFOG cases with freezing 2–3 times/month could perhaps be attributable to better patient awareness rather than different disease pathologies. The FOGQ score was marginally higher among EOFOG; this may be secondary to the higher proportion of EOFOG patients with freezing episodes lasting 3–10 s, which would increase the total score. The duration of freezing episodes was not statistically different.

In our study, NMS such as fatigue, generalized pain, and cognitive impairment had a higher prevalence in EOFOG. The memory disturbances in EOFOG could be indicative of earlier cortical involvement and abnormal frontostriatal networks.[11,18,26] Except for memory disturbances, no distinct correlations have been reported between NMS and EOFOG or LOFOG. Perhaps these results of our study are sporadic findings with no specific implications.

The correlations observed between AAO of motor symptoms and AAO of FOG, and disease duration and MF latency are obvious and expected. The inverse relationship between AAO of motor symptoms and MF latency could be indicative of an accelerated pathophysiology in EOFOG; however, pathological studies have not shown any increase in neuritic or immature plaques.[18] Perhaps a later AAO of motor symptoms may be a predictor for EOFOG.

This study has several limitations owing to its retrospective nature. A standardized questionnaire and individual rating scales were not utilized to record the NMS. Data pertaining to the type of FOG are lacking and the absence of levodopa equivalent dose data restricts the ability to study the relationship between FOG and levodopa. However, since episodes of FOG seldom occur in the clinic, history and questionnaires prove to be better indicators of presence and severity.

Conclusions

FOG is associated with a longer disease duration and higher severity of disease. A higher prevalence of FOG has been reported in patients with the PIGD variant of PD. EOFOG might be associated with an accelerated disease progression and is linked with older patients and shorter disease duration. Patients with FOG have distinct NMS which are contributory to disease morbidity and deserve to be adequately addressed with tailor-made treatment strategies. The lack of significant and specific differences between EOFOG and LOFOG compounds the unpredictability associated with the onset of FOG.

Further studies are required to elucidate the interactions or mechanisms in patients with FOG and freezing involving other activities. A better understanding of these mechanisms may aid in providing targeted therapeutic options and reduce disease morbidity.

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Conflicts of interest

There are no conflicts of interest.

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