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Review

Freezing of Gait and Falls in Parkinson's Disease

Yasuyuki Okuma*
Department of Neurology, Juntendo University Shizuoka Hospital, Shizuoka, Japan

Abstract. Freezing of gait (FOG) and falls are common and disabling phenomena in Parkinson's disease (PD) and related disorders as they may lead to loss of independence. Both are usually observed in the advanced stage of the disease, although they can also be seen in the early stage. FOG and falls have similar risk factors, such as axial motor disability and cognitive impairment, and FOG is one of the most common causes of falls. The objective of this review is to address recent ideas about the underlying pathophysiology of FOG and falls, and discuss the similarities, differences, and relationships between FOG and falls. Recent advances in studies that elucidate physical and cognitive risk factors to predict future falls are also reviewed. In addition to the history of prior falls and disease severity, the presence of FOG and cognitive dysfunction are associated with falls in PD.

Keywords: Parkinson's disease, freezing of gait, falls, pathophysiology

Both freezing of gait (FOG) and falls are episodic and disturbing phenomena in Parkinson's disease (PD) [1, 2]. They have devastating consequences in affected individuals, often leading to injuries, secondary immobility, and reduced quality of life [3–5]. Because sudden FOG likely disturbs balance, it is one of the most important causes of falls in PD patients [5, 6]. The last review showing the relationship between FOG and falls was published in 2004 [5]. The objective of this article is to discuss the relationship between these two symptoms, mainly by reviewing the literature of the past 10 years. Relevant pioneering works are also mentioned in this review.

*Correspondence to: Yasuyuki Okuma, Department of Neurology, Juntendo University Shizuoka Hospital, 1129 Nagaoka, Izunokuni, Shizuoka 410-2295, Japan. Tel.: +81 55 948 3111; Fax: +81 55 948 5088; E-mail: sgz02202@nifty.ne.jp.

EPIDEMIOLOGY AND FEATURES

Freezing of gait

The definition of FOG accepted at the 2010 FOG workshop held in Washington DC is "a brief, episodic absence or a marked reduction of forward progression of the feet despite the intention to walk" [7]. FOG occurs more often in the advanced stage of PD [2–4, 6–8]. A long-term prospective follow-up of 136 patients with newly diagnosed PD (Sydney multicenter study) showed a high cumulative incidence of FOG (81%) at 20 years [9]. Another prospective study revealed the high prevalence of FOG (87%) at a mean follow-up of 11 years [10]. FOG can also be experienced in a relatively early stage of PD and even in untreated patients [11]. FOG observed in the early stage, however, is mild and short in duration. The DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study showed that the

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absence of tremor, the presence of a gait disorder, and the development of balance and speech problems are associated with the occurrence of FOG [11]. A recent study has shown that nongait freezing, increased dopaminergic drug dose, falls/near falls, and cognitive problems are independent determinants of FOG in PD patients [12]. When a patient shows the wearing-off phenomenon, FOG is more commonly observed in the "off" state. Although FOG can be seen in the "on" state, "true-on" FOG (FOG exclusively appears in the "on" state) is rare [13].

Falls

In the Sydney multicenter study, when patients survive 20 years from the disease onset, 87% of patients experienced falls and 35% suffered from resulting fractures [9]. The incidence of falls increases as patients approach Hoehn and Yahr (H&Y) stage 3, which is when balance becomes impaired but patients are still actively mobile enough to be at risk of falling [14]. A meta-analysis of six prospective studies of falling showed that the risk of falling increased as the unified Parkinson's disease rating scale (UPDRS) increased to about a 60% chance of falling within 3 months for UPDRS motor scores of 40 to 50, and remained at this level thereafter with a tendency to slightly decrease [14]. However, data for fall incidence in patients with H&Y stages 4 and 5 seems very limited. A recent cohort study of late-stage PD (stages 4 and 5) showed that falls occurred in 20 (67%) of 30 patients with stage 4, and in 5 (25%) of 20 patients with stage 5, indicating a decrease in fall risk towards stage 5 [15].

Prospective studies showed that about half of the patients fell within a 6- or 12-month period, although there is substantial variability in the falling rate reported in previous studies, with the proportion of fallers in the range from 35 to 90% [4, 16–27]. This high variability in falling rate may be attributable in part to the inclusion criteria used in different studies. For instance, the study with the highest proportion of fallers included only demented PD patients [16]. The second highest falling rate was found in the study including PD patients with two or more falls in the previous year [17]. Most falls occur when patients are in the "on" state, possibly reflecting their increased mobility [4].

Relationship between FOG and falls

Although both FOG and falls occur in the later stage, their occurrence may be different in the very advanced stage. As long as patients can walk, the incidence of FOG continues to increase, and so does postural instability [9]. However, falling rate may decrease in the very advanced stage [15], although this has not been well substantiated [14]. Further prospective study including a large number of patients with H&Y stages 4 and 5 will conclude this argument. FOG predominantly occurs in the "off" state, whereas falls occur in the "on" state [4]. This may be because "on" state falls have more variable causes than "off" state falls, which are more commonly caused by FOG. Another possibility is that determination of the "on" or "off" state is relative.

PATHOPHYSIOLOGY

FOG

The pathophysiology of FOG is not well understood. Many hypotheses are presented, and they are not mutually exclusive. A better understanding of its mechanisms may lead to the development of effective therapeutic strategies.

In PD, disruption of the basal ganglia (BG) – supplementary motor area (SMA) circuit for self-initiated movements decreases central driving and internal cueing to the motor cortex. Progressive shortening of steps before freezing episodes, which is one of the consequences of decreased motor drive or defective cue production, is called the "sequence effect" [28, 29]. Abnormalities of spatiotemporal characteristics of gait just prior to FOG, such as premature stepping, were also shown [30, 31]. Physiological malfunction in PD also causes a motor set mismatch between the cortically selected step size and that maintained by the BG (hypokinesia) [29]. Skilled movements like gait are automatic and require less attention [32]. Because automaticity is impaired in advanced PD, this puts more stress on voluntary mechanisms, and cognitive resources become increasingly pressured. PD patients without FOG may compensate for deficits in automaticity by switching to increased cognitive control, but PD freezers cannot [33]. Impaired automaticity would explain why FOG frequently occurs during performance of secondary cognitive or motor tasks (dual tasking) [32].

Studies using an ambulatory gait analysis system with pressure-sensitive insoles revealed that increased stride-to-stride variability, bilateral uncoordinated gait, and marked gait asymmetry are associated with FOG [34–36]. Although these abnormalities could be due to abnormal output from the central pattern generators of the spinal cord, supraspinal facilitation (driving) may also be disordered. Plotnik et al. proposed a "thresh-

old model" to explain the transient occurrence of FOG [37]. They suggested that when overall gait performance deteriorates below a certain threshold, FOG occurs.

The most characteristic feature of FOG is knee trembling. Yanagisawa et al. first recorded floor reaction forces of this motion of the knees using a force plate [1]. The frequency of alternating steps (trembling) is very similar to that observed in a hastened response during alternating voluntary movements such as finger tapping in PD [38]. Since the hastening phenomenon was also reported in patients with striatal lesions after stroke [39], the basal ganglia and its frontal projections may be among the essential lesion sites for FOG [8]. Another hypothesis of this phenomenon is impaired postural adjustment in preparation for stepping. Jacobs et al. showed that multiple anticipatory postural adjustments (APAs) produce knee trembling, and that FOG associated with a forward loss of balance is caused by an inability to couple normal APAs to the motor programs for stepping [40].

PD patients have difficulty in passing through narrow spaces such as doorways. Almeida and Lebold examined the performance of PD patients in the "walking through different–sized doorways" task quantitatively [41]. Shortened steps and increased gait variability while approaching a narrow doorway were found only in the PD-with-FOG group. These changes were not evident in non-FOG patients or healthy subjects, indicating that FOG may involve an underlying perceptual mechanism that interferes with online movement planning [41]. Other studies showed that the judgment of just-passable-door width was not significantly different between PD patients and healthy controls [42], and that the estimated just-passable doorway was wider in PD patients than in control subjects, but there was no significant difference in estimation between PD patients with FOG and those without FOG [43]. These results suggest that visuomotor disturbance associated with PD freezers is such that responses to action-relevant, but not resting visual information, are exaggerated.

Because a frontal lobe dysfunction or a disconnection between the frontal lobe and the basal ganglia has been implicated in FOG, Amboni et al. studied frontal executive function in early-stage, nondemented PD patients and found that the frontal assessment battery (FAB), verbal fluency, and ten-point clock test scores were significantly lower in FOG patients than in non-FOG patients [44]. Another study by Naismith et al. demonstrated that FOG selectively correlated with poorer performance in tasks of set-shifting, but not with a range of other executive tasks [45]. These findings support the hypothesis that the frontostriatal function to keep different tasks online is disrupted in PD patients with FOG.

Postural instability and falls

Until recently, prediction of future falls has been considered difficult, except for the history of prior falls [4]. However, there is an increasing awareness that FOG is one of the leading predictive factors for falls [18, 19]. A study of 113 patients showed that a fall in the past year, abnormal axial posture, cognitive impairment, and freezing of gait were independent risk factors for falls and predicted 75% of future falls within a year [18]. Another prospective study of 101 patients revealed that the best prediction was reached by combining disease-specific measures, such as PD severity, freezing of gait severity, and occurrence of symptomatic orthostatic hypotension, with balance measures, such as the Tinetti total score and the extent of postural anterior-posterior sway [19]. A more recent study including 205 community-dwelling PD people without cognitive impairment showed that three simple clinical tests, that is, falling in the previous year, FOG in the past month, and slow gait, accurately predicted falls [20]. Factors predicting falls are summarized in Table 1 [18–27]. Fear of falling, determined by either just asking about being "worried about falls" or measured by an activity-specific balance confidence scale, was also associated with falls [22, 23].

Recent works have revealed the additional importance of cognitive impairment as a key factor contributing to falls [18, 24, 25]. Cognitive ability is necessary to monitor the environment, choose flexible response patterns to emerging threats, and make appropriate motor responses to maintain balance. Recklessness, decreased ability to learn cues, and decreased cognitive capacity may explain why patients with frontal executive dysfunction are more prone to falls [46]. Allcock et al. prospectively studied 164 PD patients to determine whether motor and cognitive functions are predictive for future falls and demonstrated an association between fall frequency and impaired power of attention [26]. Deficits in attention may exacerbate the difficulties with multitasking and contribute to falls. At least two studies suggest that both FOG and cognitive impairment are significant variables [16, 25]. This indicates strong relationships between cognitive impairment, FOG, and falls.

Recently, the association between falls and degeneration of central cholinergic circuits has been proposed

Table 1
Factors predicting future falls in PD (prospective studies)

1st author Year, [Ref]	No.	Dur	Method	FR %	His	Sev	PoI	Pos	Fog	Cog	Atn	Fof
Bloem et al. 2001 [4]	59	6m	F-Diary, phone	51	+	+						
Ashburn et al. 2001 [22]	57	3m	Phone	39	+							+
Wood et al. 2002 [24]	101	12m	Postcard, phone	68	+					+		
Allcock et al. 2009 [26]	164	12m	F-Diary	63	+	+				+	+	
Latt et al. 2009 [18]	113	12m	Calendar, phone	45	+		+	+	+	+		
Mak et al. 2009 [23]	70	12m	Phone	21*	+	+						+
Kerr et al. 2010 [19]	101	6m	Calendar	48		+	+		+			
Camicioli et al. 2010 [25]	52	12m	Phone	40	+	+			+	+		
Mantinolli et al. 2011 [27]	125	24m	F-Diary, phone	63	+	+			+			
Paul et al. 2013 [20, 21]	205	6m	F-Diary	59	+		(+)		+	(+)		

No., Number of patients studied; Dur, Duration (months) of prospective follow-up; Method, Methods of reporting falls; F-Diary, Falls diary; FR, Fall rate (percentage of patients who fell within the follow-up period); His, History of past falls; Sev, Severity of the disease; PoI, Postural instability; Pos, Abnormality of posture; Fog, Freezing of gait; Cog, Cognitive impairment; Attn, Attention impairment; Fof, Fear of falling; *, Rate of recurrent falls, +: factors showing significant associations with falls in each study, (+): factors showing significant associations with falls in the study by Paul et al. [21].

[47, 48]. Bohnen et al. reported that patients with a history of falls showed a lower acetylcholinergic (Ach) activity, as measured by PET in the pedunculopontine nucleus (PPN)-thalamic pathway and cortical areas than patients without such history [47]. In addition, Karachi et al. showed a decreased number of Ach neurons in the PPN in PD patients with balance deficit as compared with patients without postural instability [48].

In the 2004 review, Bloem et al. summarized results of studies on postural instability using static or dynamic posturography [5]. They discussed postural instability caused by primary disease processes and secondary, or compensatory strategies such as stooped posture and trunk stiffness. What have not been discussed well are the effects of interventions on postural instability. Postural sway abnormalities measured by posturography are worsened by levodopa therapy, and the increase in the extent of sway may be attributed in part to levodopa-induced dyskinesia [49, 50]. Deep brain stimulation of the subthalamic nucleus (STN-DBS) either improved postural sway [51], or provided less postural abnormality induced by levodopa [52], but different effects on postural stability depending on patients' status were also reported [53]. DBS of the globus pallidus interna (GPi-DBS) demonstrated a more constant reduction in the extent of postural sway [54]. Recently, automatic postural responses (APRs) have been recorded by forward translations of the standing surface after STN-DBS and GPi-DBS. Turning on the DBS current improved APR stability for both STN and GPi sites, but there was a detrimental effect of the DBS procedure on the STN group, making overall APR stability functionally worse after surgery for the STN group [55]. Levodopa can only minimally improve APR [55]. Using multidirectional dynamic posturography, Visser et al. showed that instability in PD results from a reduced flexibility of the trunk and pelvis that is largely resistant to STN stimulation combined with optimal drug treatment [56]. Inconsistency of the results of interventions may be explained by different inclusion criteria of patients, different experimental procedures and evaluation methods, and different sites of electrode placement. In addition, balance is mediated by circuits other than dopaminergic motor pathways.

Which specific postural instability problems are FOG-related?

When FOG occurs, the center of gravity (COG) continues to move forward while the feet stop moving. This can lead to imbalance, which cannot be compensated by protective steps [5, 8, 57]. A similar forward loss of balance can be triggered by backward platform translation, as studied by Jacobs et al.; they attributed this to disturbance of APAs [40]. Vervoort et al. studied which aspects of postural control are associated with FOG, and found that freezers showed poor directional control during voluntary rhythmic weight shifting [57]. The impaired voluntary COG control may be a factor contributing to loss of balance during a freezing episode. Falls with backward loss of balance such as retropulsion may also be related to FOG. Whether the inability to make backward corrective steps is FOG or not remains controversial, and evidence on this is sparse. In addition, some of the lateral or backward falls during turning, which seem simply due to a sudden loss of balance, may be FOG-related. A wearable accelerometer recording may help detect body inclination and elucidate the causes of sudden falls [58]. In contrast, the most distinct feature of FOG from falls is

that FOG never occurs at rest but at "the wish to move" [59], whereas falls may happen spontaneously.

CONCLUSIONS

FOG and falls are common and disabling phenomena in PD and are interconnected. FOG and falls have similar risk factors, and FOG is one of the most common causes of falls. Many hypotheses on the pathophysiology of FOG have been presented; dysfunctions in central drive and automaticity, abnormal gait pattern generation, abnormality of rhythm formation and APAs, perceptual malfunction, and frontal executive dysfunction are proposed. Prospective studies on the prediction of future falls showed that previous falls, FOG, poor balance, disease severity, and cognitive dysfunction are risk factors for falls. Postural instability caused by a primary disease process and effects of interventions have been studied using static or dynamic posturography; levodopa and DBS improve some measures of balance but worsen others. A better understanding of the pathomechanisms underlying FOG and falls will improve strategies for their prevention and treatment.

CONFLICT OF INTEREST

The author has no conflict of interest to report.

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