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Freezing of gait in Parkinson's disease

Abstract Freezing of Gait (FOG) is one of the most disabling and least understood symptoms in Parkinson's disease (PD), and is usually observed in the advanced stage of the disease. FOG can be experienced on turning, in narrow spaces, whilst reaching a destination, and in stressful situations. FOG is commonly observed in the "off" state, but it can also be observed in the "on" state. Dual tasking (cognitive load) aggravates FOG. Visual or auditory cues often resolve FOG. Analysis of gait revealed that the rhythm of stepping suddenly jumps into high frequency (4–5 Hz) in FOG (hastening), and that floor reaction forces are disregulated. Stride-to-stride variability is increased in FOG. Hastening phenomenon was reported not only in PD patients but also in patients with striatal lesions. The basal ganglia and its frontal projections may be one of the essential lesion sites for FOG. A recent study using single-photon emission tomography (SPECT) revealed enhanced lateral premotor cortex (PMC) activity during paradoxical gait in PD, suggesting that PMC can compensate for the impaired function of the medial frontal cortex when cued by visual input. Treatment of FOG includes behavioural, medical, and surgical approaches. Tricks of all kinds (including external cues) are effective therapeutic approaches. If FOG occurs predominantly in the "off" state, dopaminergic therapy can be increased. For "on" freezing or if "on" response is otherwise optimised, the dose of the dopaminergic agent may be manipulated, but it could lead to the deterioration of parkinsonism. Deep brain stimulation of the STN often alleviates FOG in the "off" state.

Key words Freezing of gait · Parkinson's disease

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Introduction

Freezing of gait (FOG), one of the most disturbing and least understood symptoms in Parkinson's disease (PD), is a unique gait disorder in which patients are unable to initiate or continue locomotion [17, 21, 25]. When a patient attempts to lift a foot to step forward, the foot is "stuck" to the ground, making the patient feel as if his or her foot is glued to the ground. FOG is likely to disturb balance, therefore, it is one of the causes of falls in PD [8]. Among parkinsonism, FOG was most commonly reported in pure akinesia of Imai and Narabayashi or pure freezing syndromes, progressive supranuclear palsy (PSP) and vascular parkinsonism [2, 3, 16, 22, 33, 34]. FOG is also common in normal pressure hydrocephalus, PD and multiple system atrophy [22, 29, 41]. In this article, I review the clinical features, pathophysiology, and treatment of FOG in parkinsonism, particularly in PD.

Clinical characteristics of FOG

FOG occurs in various situations. Freezing on turning and start hesitation are the most common types of freezing phenomenon [17, 21, 25, 53]. Freezing is also common when a patient is passing through a narrow space (tight quarters hesitation) or just before reaching destination (destination hesitation). The limitation of time to execute walking also makes FOG worse [17]. An example of this is when a patient attempts to cross a busy street before the traffic light changes or when using an elevator.

On the contrary, if a line is drawn on the ground in front of the foot of a patient, the patient can usually step over it (kinesia paradoxa). This kind of trick is often taken advantage of by the patient [55]. Kinesia paradoxa is well described in the movie "Awakenings" in which an actress imitates a patient with postencephalitic parkinsonism. Although stressful situations that limit time or space aggravate FOG, moderate emotional stress frequently improves FOG, such that a patient can walk without freezing in the doctor's office. In contrast, many patients have experienced the worst degree of freezing while being at home. This is one of the reasons why videotaping of FOG is not easy in outpatient clinics. To assess FOG in daily life, Giladi and colleagues constructed a FOG questionnaire for parkinsonian patients [23].

Cognitive load or dual tasking, such as verbal fluency task and "serial 7 calculation" worsens FOG. Camicioni and colleagues showed that a simultaneous cognitively demanding verbal fluency task increases the number of steps taken to walk 30 feet in PD patients with FOG, but not in patients without FOG [10]. The authors conclude that patients with FOG may be more dependent on attention that is related to frontal lobe function than patients without FOG.

Gait festination is a unique disorder of locomotion, which was described by Sir James Parkinson in his essay "The Shaking Palsy"; stating that "The propensity to lean forward becomes invincible, and the patient is thereby forced to step on the toes and forepart of the feet, ... irresistibly impelled to make much quicker and short steps, and thereby to adopt unwillingly a running pace" [51]. Gait festination is highly associated with FOG, suggesting that there may be a common pathophysiology between the two conditions, such as disturbance of the central timing mechanism [24, 35].

Freezing of gait in Parkinson's disease

FOG is usually observed in the advanced stage of PD [25, 39, 46]. In our series (unpublished data of 228 patients), most of the FOG was reported in patients with Hoehn – Yahr stages 3 and 4. More than half of the patients with disease duration longer than 10 years experienced freezing episodes. Wearing off phenomenon was reported in 67 % of the freezers, and dyskinesia was observed in 45 % of the freezers in the study. Motor fluctuation seems to be a risk factor of FOG. Other studies suggested that longer duration of levodopa or dopamine agonist treatment is associated with FOG [26, 39], but this association was difficult to assess in our patients because of the retrospective nature of our study. FOG can be experienced in a relatively early stage of PD without levodopa therapy. However, FOG observed in the early stage of PD is mild and transient. Severe FOG in the early stage of the disease suggests other diagnosis, such as pure freezing syndrome or PSP. Giladi and coworkers examined the natural course and risk factors of FOG in the early stage of PD using the data of the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study [28]. The risk factors at the onset of the disease are the absence of tremor and the beginning of a gait disorder. The development of FOG in the course of PD is strongly associated with the development of balance and speech problems, is less associated with the worsening of bradykinesia, and is not associated with the progression of rigidity. This prospective cohort showed that disease progression alone could be responsible, at least in part, for the development of FOG [28]. Other studies revealed that FOG occurs more frequently in the subgroup of patients with the akinetic form, whilst an opposite tendency was evident in the tremor predominant type [39]. However, Bartels et al. showed that bradykinesia is not correlated with FOG [6].

Table 1 Freezing of gait in parkinsonism

Name of disease	Frequency
Pure akinesia or pure freezing syndromes	Always present
Progressive supranuclear palsy	Very common
Vascular parkinsonism	Very common
Normal pressure hydrocephalus	Common
Parkinson's disease	Common
Multiple system atrophy	Relatively common

When the patient shows the wearing off phenomenon, FOG is more commonly observed in the "off" state. Schaafsma and colleagues studied 19 patients with FOG and showed that 95 % of the patients experienced freezing on turning in the "off" state, but only 32 % experienced freezing on turning in the "on" state [53]. Start hesitation, tight quarters hesitation, and destination hesitation are also less common in the "on" state than in the "off" state. Turning is a strong provocative factor for FOG. In relation to leg motion, "small steps" and "trembling in place" types of freezing were manifested in both the "off" and "on" states. In contrast, the total akinesia type of freezing was observed only during the "off" state [53]. The duration of the freezing episode in the "on" state was significantly shorter than that in the "off" state. These observations suggest that levodopa is effective in reducing FOG in most PD patients. However, there have been reports showing that high-level levodopa therapy induces FOG (hypotonic freezing) within years from treatment onset [1, 5]. This phenomenon may be associated with excessive daily dose of levodopa in the late 60's to the early 70's; moreover, FOG improved with reduction in levodopa dose in Ambani and Van Woert's case [1]. In recent years, this kind of FOG has been relatively rare because low-dose levodopa therapy has been recommended.

Pathophysiology of FOG

Various methods have been employed to elucidate the pathophysiology of FOG. Yanagisawa, Ueno, and Takami studied FOG using EMG and a force plate [57, 59]. The EMGs of the thigh and leg muscles showed rhythmic contractions in normal walking. Reciprocity of muscular contractions between flexors and extensors was well maintained in shuffling gait. During freezing, these muscles contracted either simultaneously or reciprocally. Ankle flexors and extensors contract reciprocally during "trembling in place", but an overlapping of the EMGs between flexors and extensors is sometimes observed. Nieuwboer and colleagues showed that tibialis anterior swing activity starts prematurely during the preswing phase before freezing, but the activity is significantly shortened during the actual swing phase [48]. A similar pattern of premature activation and termination was found in ankle plantar flexors. Accordingly, a progressive decrease in stride length occurs with stable cadence just before freezing [49]. They attributed the phenomenon to the disturbance of central gait cycle timing. Using an ambulatory gait analysis system with pressure sensitive insoles that continuously record walking, Hausdorff and coworkers found that stride-to-stride variability is markedly increased among PD patients with FOG compared with those without FOG [32]. The same study group showed that bilateral uncoordinated gait and marked gait asymmetry are associated with FOG [52]. Floor reaction force during forward locomotion in normal subjects showed two peaks corresponding to the increase in pressure on stepping in and kicking off from the floor [57, 59]. In contrast, the shuffling gait showed a different pattern, in which the two peaks of vertical pressure in one step were replaced by a narrow, single peak. During freezing episodes, changes in foot pressure in alternating stepping behavior were smaller than those in the shuffling gait, and a complete shift of the center of pressure from one foot to the other was not observed. The frequency of this alternating stepping (trembling) ranges from 4 to 5 Hz [57, 59].

Rhythmic movements are often disturbed characteristically in patients with PD. Nakamura and colleagues conducted finger tapping tests in PD patients, and found that synchronized responses to sound signals fail at a critical frequency (usually above 2 Hz) and a desynchronized response with a hastened rate (4–5 Hz) appears [43]. Note that this hastened response rate is similar to the frequency of trembling legs during FOG. This disturbance of rhythm formation is called "hastening phenomenon". Nagasaki and colleagues applied the same method to patients with cerebrovascular disease, and disclosed that the hastening phenomenon was specifically associated with striatal (and frontal) lesions [42]. They concluded that disturbances of rhythm formation are attributed to either organic or functional deficits in the striatum and its frontal projections.

Abnormalities in the resting levels of regional cerebral blood flow (rCBF) can be examined using functional imaging by SPECT. Fabre and colleagues found normal frontal perfusion in PD patients with FOG [15]. Matsui and colleagues used SPECT with three-dimensional stereotactic surface projection analysis (3D-SSP) and showed that bilateral Brodmann area 11 (orbitofrontal cortex) perfusion decreases significantly in PD patients with FOG compared with patients without FOG [40]. Their observation may be related to the disorder of executive and cognitive functions such as motivation, decision making, or judgment of external and internal cues in patients with FOG. By using ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO), CBF images that reflect neural activity over a period of several minutes after tracer administration can be obtained [20]. Hanakawa and coworkers have examined rCBF changes during gait on a treadmill. Patients with PD revealed relative underactivation in their left medial frontal area, right precuneus and left cerebellar hemisphere, whereas they showed relative overactivity in the left cingulate cortex and cerebellar vermis [30]. They further examined the effects of visual cues during walking by presenting two different visual cues, namely, lines that are oriented transversely to the direction of walk (paradoxical kinesia) and lines that are parallel to it. During paradoxical gait, PD patients showed enhanced

Table 2 Types of FOG

Turning hesitation
Start hesitation
Tight quarters hesitation (freezing when walking through narrow spaces)
Destination hesitation (freezing when reaching destination)

Table 3 FOG in Parkinson's disease

Associated with longer disease duration
Associated with longer dopaminergic treatment?
More often seen in the "off" state, but "on" freezing less frequently

Table 4 Pathophysiology of FOG

Rhythm formation disturbance (hastening phenomenon during freezing)
Disturbance of central gait cycle timing (Gait dysrhythmicity)
Increase in stride-to-stride variability
Shortened stride length just before freezing
Abnormal timing of EMG activity just before freezing
Akinesia (Narabayashi's type 3 akinesia)
Decrease in attention to walk
Postural instability (inability to shift body weight to one leg)
Impaired reciprocity in some muscles

activation in the right lateral premotor cortex (PMC) to a significantly greater degree than control subjects [31]. They speculated that the PMC, mainly regulated by cerebellar inputs, compensates for the impaired supplemental motor area (SMA) or pre-SMA function in PD patients [31].

Treatment of FOG

The freezing phenomenon is often difficult to treat. If FOG appears only in the "off" state or predominantly when patients are in the "off" state, the end of dose deterioration or the " wearing off" phenomenon should be treated by increasing the dose of dopaminergic agents. FOG in the "on" state is more difficult to treat than FOG in the "off" state. Occasionally, patients improve with increased levodopa dosages, even if other signs of parkinsonism appear to be optimally controlled. Drug reduction may be considered, but it is less likely to help patients with "on" period freezing and could lead to the deterioration of parkinsonism. FOG that occurs exclusively in the "on" state is quite rare, but in this condition, the dose of dopaminergic agents should be reduced [25]. In the original DATATOP study and the second randomization study, selegiline has been reported to decrease the risk of freezing in the early stages of PD [28, 54]. However, whether selegiline is useful in the advanced stages of PD needs further controlled examination. Amantadine has been suggested as an effective drug in some PD patients. Giladi and colleagues showed that prolonged amantadine treatment decreases the appearance of FOG [26]. The effect of L-threo-DOPS, a precursor of norepinephrine, has been studied extensively in Japan [44, 50]. Narabayashi and colleagues hypothesized that the loss of noradrenergic projections causes akinesia in the advanced stage of PD, including freezing [44–46]. A significant improvement of FOG has been shown in a nationwide double-blind study, although the effects are mild [45]. Owing to its relatively mild adverse effects, the use of DOPS may be considered in intractable FOG if the drug is available. Tandospirone, a serotonin 1A agonist, was reported to be useful in some PD patients in the advanced stage (Nomoto, personal communication).

Table 5 Treatment of FOG in Parkinson's disease

Pharmacotherapy
Increase dopaminergic treatment for "off" state freezing
Levodopa
Selegiline
Dopamine agonists?
Amantadine?
L-threo-DOPS?
Consider reducing medication for "on" state freezing
Prevent motor fluctuations
Stereotactic neurosurgery
Deep brain stimulation of STN or GPi
Physiotherapy or behavioural approach
Gait and balance training (e.g., use of cues)
Use of walking aids

Different motor and sensory tricks can be effective approaches in overcoming FOG. Stern and coworkers earlier described individual methods for overcoming FOG in 61 patients [55]. The most frequently used methods were verbal or auditory stimuli such as giving a marching command similar to that given to a soldier. Visual stimuli such as stepping over objects, including inverted walking sticks, another person's foot, and carpet patterns, were also helpful. The effectiveness of these tricks has been reported many times by other investigators [11, 12, 14, 19, 36, 38, 47]. The use of physiotherapy seems to be effective, but further evidence is needed [9]. Giladi and colleagues studied the effect of botulinum toxin injections to calf muscles on freezing in 10 patients in an open fashion and 7 patients reported improvement [27]. They suggested that patients with a combination of gait-associated feet dystonia and FOG are appropriate candidates for botulinum toxin treatment. However, two double blind studies conducted later failed to show significant improvement by botulinum toxin injection [18, 58].

Stereotactic deep brain surgery (DBS) can partially alleviate FOG [4, 13, 37, 56, 60, 61]. Both unilateral and bilateral suthalamic nuclei (STN) stimulation can alleviate FOG; however, bilateral surgery was more effective in alleviating FOG than unilateral DBS [4]. Off period FOG is significantly improved by STN DBS; however, on period freezing is not affected much. Careful selection of appropriate patients seems critical. Yokochi showed that the regular rhythm of stepping is maintained when DBS is switched on, whereas the regularity of stepping disappears when DBS is switched off [60]. However, the hastening phenomenon during the finger-tapping test was not improved by DBS in a patient studied. Further studies to clarify the mechanism of improvement of FOG by DBS are necessary.

In conclusion, although knowledge of FOG has been accumulating recently, FOG is not yet well understood and managed. In addition, as the duration of PD is becoming longer, the number of patients with FOG may further increase. Because motor fluctuation seems to be a risk factor for FOG, careful use of levodopa in the early stage of PD would decrease the occurrence of FOG. All kinds of trick (cues) with appropriate physiotherapy should be employed. It is hoped that this review will improve the understanding and clinical management of this debilitating phenomenon.

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