Movement Disorders
Vol. 23, Suppl. 2, 2008, pp. S426–S430

The Clinical Spectrum of Freezing of Gait in Parkinson's Disease

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Abstract: Freezing of gait (FOG) is a common and very disabling symptom in Parkinson's disease (PD). It is usually observed in the advanced stage of the disease, although a mild form can be seen in the early stage. Although some studies have suggested that longer duration of dopaminergic treatment is associated with FOG, the disease progression alone may be responsible for the development of FOG. FOG can be experienced on turning, in narrow spaces, while reaching a destination, and in stressful situations. In PD, FOG is strongly associated with motor fluctuation. FOG is commonly observed in the "off" state and is observed less frequently in the "on" state. Dual tasking (cognitive load) aggravates FOG. Visual or auditory cues often resolve FOG. Analysis of gait revealed that the stepping rhythm suddenly jumps into high frequency (4–5 Hz) in FOG (hastening), and that floor reaction forces are disregulated. Since the hastening phenomenon was also reported in patients with lesions in the striatum and/or the frontal lobe, fronto-basal ganglia projections are considered essential for FOG. Careful observation and gait pattern analysis may lead to a successful management of individual PD patients with FOG.

Key words: freezing of gait; Parkinson's disease; rhythm of action; gait analysis.

Freezing of gait (FOG) is a unique and disturbing gait disorder in which parkinsonian patients are unable to initiate or continue locomotion.[1-6] FOG is characterized by a difficulty in stepping forward, which appears either in the initiation of or during gait, with the inability to lift the foot from the floor and trembling of the legs.[1] Patients with FOG may have a disturbance of balance, and sudden FOG is likely to further disturb balance. Therefore, FOG is one of the causes of falls in parkinsonian patients.[6] FOG is common in Parkinson's disease (PD) and may even be more common in atypical parkinsonism, such as pure akinesia by Imai and Narabayashi, progressive supranuclear palsy, vascular parkinsonism, and normal pressure hydrocephalus.[1,7-12] FOG in atypical parkinsonism is discussed in the next chapter; here, we review the clinical features and pathophysiology of FOG in PD.

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Received 13 August 2007; Revised 30 October 2007; accepted 5 December 2007

Published online 25 July 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21934

CLINICAL CHARACTERISTICS OF FOG IN PD

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.[2-4] Some advanced PD patients show foot grasping (marked flexion of the toes on standing or when stroking the sole), and this reaction would likely hinder smooth locomotion.[1]

Situations that can cause FOG are variable. The strongest provocative factor of FOG is turning (turning hesitation).[5,6,13] Most patients have their favorite direction of turning.[4] Usually, PD patients prefer to turn towards more affected side, but there are some exceptions, because each patient has his or her own strategy for turning (Bloem and Okuma, personal experiences). Freezing is also common at the initiation of gait (start hesitation), and when a patient is passing through a narrow space (tight quarters hesitation) or immediately before reaching

a destination (destination hesitation). Time pressure to execute walking also worsens FOG.[2] An example of this is when a patient attempts to cross a busy street before the traffic signal changes or when using an elevator. On the other hand, 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). Stern et al. described individual methods for overcoming FOG in 61 patients.[14] The most frequently used method was providing verbal or auditory stimuli such as giving a marching command similar to that given to a soldier. Providing visual stimuli such as stepping over objects, including inverted walking sticks, another person's foot, and carpet patterns, were also helpful.[15,16] Kinesia paradoxa is well described in the movie "Awakenings" by Oliver Sacks in which an actress played the role of a patient with postencephalitic parkinsonism. Although stressful situations that limit time or space aggravate FOG, moderate emotional stress frequently improves FOG, so that a patient can walk without freezing in a doctor's office. Patients can focus their attention on the act of walking in such situations. This is one of the reasons why the videotaping of FOG is difficult in outpatient clinics. In contrast, many patients have experienced the worst degree of freezing while being at home.[4-6] This may be due to distraction of the attention to walking.[1] To assess FOG in daily life, Giladi et al. constructed a FOG questionnaire for parkinsonian patients.[17]

Cognitive load, such as verbal fluency task and "serial 7 calculation", worsens FOG. Camicioni et al. 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.[18] The authors concluded that patients with FOG may be more dependent on attention that is related to frontal lobe function than patients without FOG. Dual tasking, such as carrying a tray or bags, also aggravates FOG. Besides cognitively challenging situations, the presence of stress, depression, and anxiety is associated with FOG.[19]

Festinating gait is a typical and unique locomotion disorder in PD, which was described by Sir James Parkinson in his essay "The Shaking Palsy": "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."[20] 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.[21,22]

FOG IN PD IN RELATION TO DISEASE PROGRESSION AND DOPAMINERGIC TREATMENT

FOG occurs more often in the advanced stage of PD.[23-25] By utilizing a questionnaire, Lamberti et al. reported that 60 of 100 consecutive PD patients had FOG.[24] A significant correlation of FOG with the duration of the disease was found, but not with the duration of L-dopa therapy. Daily fluctuations were observed in 75% of the patients with FOG. Giladi et al. studied 172 consecutive patients with disease durations of 5 years or more, and showed that FOG occurred in 53% (92 patients) of the patients. The severity of the disease was a significant contributing factor for FOG, as was long duration of levodopa (L-dopa) treatment.[23] They also found a significant association between FOG and the presence of dyskinesia or early morning dystonia. Thus, motor complications seem to be a risk factor for FOG.[23,24] FOG can be experienced in a relatively early stage of PD. FOG as observed in the early stage, however, is mild and short in duration. Severe FOG in the early stage of the disease suggests atypical parkinsonism. Giladi et al. 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.[26] The associated factors at the onset of the disease were the absence of tremor and the presence of a gait disorder. The development of FOG during the course of PD was strongly associated with the development of balance and speech problems, was less associated with the worsening of bradykinesia, and was 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.[26] Other studies revealed that FOG occurs more frequently in the subgroup of patients showing the akinetic-rigid form, while an opposite tendency was evident in the tremor predominant type.[24] However, Bartels et al. showed that bradykinesia does not correlate with FOG.[27]

One of the distinctive features of FOG in PD, as compared to atypical parkinsonism, is the patient's response to dopaminergic therapy. When the patient shows the wearing off phenomenon, FOG is more commonly observed in the "off" state. Schaafsma et al. 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.[13] Start hesitation, tight quarters hesitation, and destination hesitation are also less common in the "on" state than in the "off" state. In relation to leg motion, "small steps" and "trembling in place" types of freezing

TABLE 1. *Methodology in study of gait*

Center of foot pressure on standing
Posturography
Record of locomotion
Movie, video
Position sensor
Goniometer
Analysis of Gait
EMG
Floor reaction forces
Ambulatory gait analysis system with pressure sensitive insoles
Foot trace
Treadmill
Brain activity at rest or during walking
PET
SPECT

were manifested in both the "off" and "on" states. In contrast, the total akinesia type of freezing was observed only during the "off" state.[13] The duration of the freezing episode in the "on" state was significantly shorter than that in the "off" state. These observations suggest that L-dopa is effective in reducing FOG in most PD patients. The recently conducted ELLDOPA (Early versus Late LevoDOPA) study showed that a certain amount of L-dopa delayed the development of FOG in early stage PD patients.[28] Furthermore, the development of FOG was less common in the L-dopa treated groups than in the dopamine agonist treated groups in two double-blind prospective studies in early PD.[29,30] However, this could be the result of the milder symptomatic effect of a dopamine agonist on the motor symptoms.

In contrast to the beneficial effects of L-dopa, there have been reports showing that high-level L-dopa therapy induces FOG (hypotonic freezing) within years from the treatment onset.[31,32] This phenomenon may be associated with an excessively high daily L-dopa doses administered in the late 1960s to the early 1970s; moreover, FOG improved with the reduction in L-dopa dose, as shown in Ambani and Van Woert's case.[31] In recent years, this type of FOG has been relatively rare because low-dose L-dopa therapy has been recommended. Concomitant dyskinesia may worsen FOG during the hypotonic "on" state (Okuma, personal experience).

PATHOPHYSIOLOGY OF FOG IN PD

To elucidate the pathophysiology of FOG, various methods have been employed (Table 1). Ueno et al. studied FOG using EMG and a force plate.[1,33] 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 at rates of 4 to 6 Hz during "trembling in place"; therefore, it is reasonable not to attribute a cause of FOG to the disturbance in reciprocity in leg muscle activities.[1,33] Nieuwboer et al. showed that the tibialis anterior swing activity starts prematurely during the preswing phase before freezing, but the activity is significantly shortened during the actual swing phase.[34] 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.[35] 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.[36,37]

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.[1,33] In contrast, 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 extremely smaller than those in 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.[1,33] It is interesting that this frequency is very similar to that observed in a hastened response during alternating voluntary movements such as finger tapping in PD.[38] In contrast, FOG in vascular parkinsonism is associated with slower stepping rhythm of around 2.3 Hz during freezing.[33] Since the hastening phenomenon was also reported in patients with striatal lesions,[39] the basal ganglia and its frontal projections may be one of the essential lesion sites for FOG.[1,40]

SPECT has been used for assessing dysfunction of certain brain regions. Matsui et al. have reported the hypoperfusion of the frontal lobe Brodmann area 11 in PD patients with FOG.[41] Hanakawa et al. have examined the effects of visual cues by measuring rCBF changes during gait on a treadmill. During paradoxical gait, PD patients showed enhanced activation in the right lateral premotor cortex (PMC) to a significantly greater degree than control subjects.[42] 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.[42]

FOG TREATMENTS OTHER THAN DOPAMINERGIC MEDICATION

The effects of dopaminergic medication on FOG have already been discussed. Recently, two reports have

shown the effects of methylphenidate on FOG in PD.[43,44] Methylphenidate also improved excessive daytime sleepiness and attention significantly. Effects of caffeine, which is an adenosine A2A antagonist, on FOG in PD were also reported.[45] Total akinesia type FOG is more likely improved by caffeine. Although the beneficial effect of injecting botulinum toxin into the calf muscles has been observed in a open-labeled study, recent double-blind placebo-controlled studies have shown no satisfactory positive effect on FOG in PD.[46,47] In "The Rehabilitation in Parkinson's disease: Strategies for Cueing" (RESCUE) trial, the effects of a home physiotherapy program based on rhythmical cueing on gait were investigated.[48] Most patients chose auditory cueing, and significant improvements were found on their posture, gait, and FOG scores. Deep brain stimulation of the subthalamic nucleus (STN-DBS) alleviates "off" state FOG, but FOG in the "on" state is less improved.[49] Recently, preliminary results of DBS in the pedunculopontine nucleus have been reported.[50]

In conclusion, although the analysis of FOG has been extensively carried out recently, FOG is not yet fully understood. A careful observation of individual patients, particularly in relation to motor fluctuation, may lead to the development of an effective therapeutic approach.

REFERENCES

1. Yanagisawa N, Ueno E, Takami M. Frozen gait of Parkinson's disease and parkinsonism. A study with floor reaction forces and EMG. In: Shimamura M, Grillner S, Edgerton VR, editors. Neurophysiological basis of human locomotion. Tokyo: Japan Scientific Societies Press; 1991. p 291–304.
2. Fahn S. The freezing phenomenon in parkinsonism. Adv Neurol 1995;67:53–63.
3. Giladi N, McMahon D, Przedborski, et al. Motor blocks in Parkinson's disease. Neurology 1992;42:333–339.
4. Giladi N. Freezing of gait. Clinical overview. Adv Neurol 2001; 87:191–197.
5. Okuma Y. Freezing of gait in Parkinson's disease. J Neurol 2006; 253 (Suppl 7):27–32.
6. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. Mov Disord 2004;19:871–884.
7. Factor S, Jennings DL, Molho ES, Marek KL. The natural history of the syndrome of primary progressive freezing gait. Arch Neurol 2002;59:1778–1783.
8. Giladi N, Kao R, Fahn S. Freezing phenomenon in patients with parkinsonian syndromes. Mov Disord 1997;12:302–305.
9. Gurevich T, Giladi N. Freezing of gait in multiple system atrophy (MSA). Parkinsonism Relat Disord 2003;9:169–174.
10. Imai H. Syndrome of pure akinesia or freezing phenomenon without rigidity and tremor and with no effect by L-Dopa therapy. Adv Neurol Res (Tokyo) 1980;24:838–848.
11. Imai H, Narabayashi H, Sakata E. "Pure akinesia" and the later added supranuclear ophthalmoplegia. Adv Neurol 1986;45:207–212.
12. Muller J, Seppi K, Stefanova N, Poewe W, Litvan I, Wenning GK. Freezing of gait in postmortem-confirmed atypical parkinsonism. Mov Disord 2002;17:1041–1045.
13. Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. Eur J Neurol 2003;10:391–398.
14. Stern G, Lander C, Lees A. Akinetic freezing and trick movements in Parkinson's disease. J Neural Transm 1980;16 (Suppl):137–141.
15. Dietz MA, Goetz CG, Stebbins GT. Evaluation of a modified inverted walking stick as a treatment for parkinsonian freezing episodes. Mov Disord 1990;5:243–247.
16. Nieuwboer A, Feys P, DeWeerdt W, Dom R. Is using a cue the clue to the treatment of freezing in Parkinson's disease? Physiotherapy Res Int 1997;2:125–134.
17. Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD. Construction of freezing of gait questionnaire for patients with parkinsonism. Parkinsonism Relat Disord 2000;6:165–170.
18. Camicioli R, Oken BS, Sexton G, et al. Verbal fluency task affects gait in Parkinson's disease with motor freezing. J Geriatr Psychiatry Neurol 1998;11:181–185.
19. Giladi N, Hausdorff JM. The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease. J Neurol Sci 2006;248:173–176.
20. Parkinson J. An essay on the shaking palsy. London: Sherwood, Neerby and Jones; 1817
21. Giladi N, Shabtai H, Rozenberg E, Shabtai E. Gait festination in Parkinson's disease. Parkinsonism Relat Disord 2001;7:135–138.
22. Imai H. Festination and freezing. Rinsho Shinkeigaku 1993;33: 1307–1309.
23. Giladi N, Treves TA, Simon ES, et al. Freezing of gait in patients with advanced Parkinson's disease. J Neural Transm 2001;108:53–61.
24. Lamberti P, Armenise S, Castaldo V, et al. Freezing gait in Parkinson's disease. Eur Neurol 1997;38:297–301.
25. Narabayashi H. Three types of akinesia in the progressive course of Parkinson's disease. Adv Neurol 1993;60:18–24.
26. Giladi N, McDermott MP, Fahn S, et al. Freezing of gait in Parkinson's disease; prospective assessment in the DATATOP cohort. Neurology 2001;56:1712–1721.
27. Bartels AL, Balash Y, Gurevich T, et al. Relationships between freezing of gait (FOG) and other features of Parkinson's disease. FOG is not correlated with bradykinesia. J Clin Neurosci 2003;10: 584–588.
28. Fahn S, and the Parkinson Study Group. Does levodopa slow or hasten the rate of progression of Parkinson's disease. J Neurol 2005;252:IV37–IV42.
29. Rascol O, Brooks DJ, Korczyn AD, DeDeyn PP, Clarke CE, Lang AE, for The 056 Study Group. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med 2000;342:1484–1491.
30. The Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson's disease. A 4-year randomized controlled trial. Arch Neurol 2004;61:1044–1053.
31. Ambani L, Van Woert M. Start hesitation—a side effect of long-term levodopa therapy. N Eng J Med 1973;288:1113–1115.
32. Barbeau A. Six years of high-level levodopa therapy in severely akinetic parkinsonian patients. Arch Neurol 1976;33:333–338.
33. Ueno E, Yanagisawa N, Takami M. Gait disorders in parkinsonism. A study with floor reaction forces and EMG. In: Narabayashi H, Nagatsu T, Yanagisawa N, Mizuno V. editors. Parkinson's disease. From basic research to treatment. New York: Raven Pres; 1993. p 414–418.
34. Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fiuws S, Broens-Kaucsik E. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Mov Disord 2001;16:1066–1075.
35. Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Janssens L, Stijn V. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. Brain 2004;127: 1650–1660.

36. Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. Exp Brain Res 2003;149: 187–194.
37. Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor functions? Ann Neurol 2006;57:656–663.
38. Nakamura R, Nagasaki H, Narabayashi H. Arrhythmokinesia in parkinsonism. In: Birkmayer W, Hornykievicz O, editors. Advances in Parkinsonism. Basel: Roche; 1976. p 258–268.
39. Nagasaki H, Kosaka K, Nakamura R. Disturbance of rhythm formation in patients with hemispheric lesion. Tohoku J Exp Med 1981;135:231–236.
40. Yanagisawa N. Natural history of Parkinson's disease: from dopamine to multiple system involvement. Parkinsonism Relat Disord 2006;12:S40–S46.
41. Matsui H, Udaka F, Miyoshi T, et al. Three-dimensional stereotactic surface projection study of freezing of gait and brain perfusion image in Parkinson's disease. Mov Disord 2005;20:1272–1277.
42. Hanakawa T, Fukuyama H, Katsumi Y, et al. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. Ann Neurol 1999;45:329–336.
43. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease. A pilot study. Clin Neuropharmacol 2006;29: 15–17.
44. Devos D, Krystkowiak P, Clement F, et al. Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:470–475.
45. Kitagawa M, Houzen H, Tashiro K. Effects of caffeine on the freezing of gait in Parkinson's disease. Mov Disord 2007;22:710–712.
46. Wieler M, Camicioli R, Jones CA, Martin WR. Botulinum toxin injections do not improve freezing of gait in Parkinson's disease. Neurology 2005;65:626–628.
47. Gurevich T, Peretz C, Moore O, Weizmann N, Giladi N. The effect of injecting botulinum toxin type A into the calf muscles on freezing of gait in Parkinson's disease: a double blind placebo-controlled pilot study. Mov Disord 2007;22:880–883.
48. Nieuwboer A, Kwakkel G, Rochester L, et al. Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. J Neurol Neurosurg Psychiatry 2007;78:134–140.
49. Krack P, Batir A, Blercom NV, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–1934.
50. Stefani A, Lozano AM, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;130:1596–1607.