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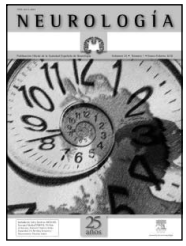

ORIGINAL ARTICLE

# Freezing of gait unresponsive to dopaminergic stimulation in patients with severe Parkinsonism

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**Abstract**
*Introduction:* Freezing of gait unresponsive to dopaminergic stimulation in patients with severe Parkinsonism. The freezing of gait episodes (FOG) normally appear during the "off" period and generally improve with dopaminergic stimulus, at the same time as improving other Parkinsonian symptoms.
*Patients and methods:* We report a group of 10 patients with severe Parkinson's disease. All patients suffered motor fluctuations, dyskinesias and episodes of FOG during the "on" and "off" state. The patients received a subcutaneous apomorphine bolus, without other dopaminergic medication; an effective dose of apomorphine was considered as one that induced a reduction of at least a 60% in the UPDRS motor scale.
*Results:* The baseline motor UPDRS was 61.3 ± 4.7, which dropped to 21 ± 4.3 after the apomorphine injection. The mean dose of apomorphine was 5.5 mg (3-7 mg). The bolus of apomorphine improved the parameters of the gait related to bradykinesia and the tapping tests of the limbs, but the episodes of FOG did not vary significantly between the "off" and "on" state.
*Conclusions:* We present a group of 10 patients with freezing of gait episodes that did not improve with treatment and persisted during the "on" period induced by dopaminergic stimulus with apomorphine.


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**PALABRAS CLAVE**
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**Bloqueos de la marcha sin respuesta al estímulo dopaminérgico con apomorfina en pacientes parkinsonianos grave**

**Resumen**
*Introducción:* Los episodios de congelación de la marcha (CDM) normalmente aparecen durante el *"off"* y en general mejoran con tratamiento dopaminérgico a la par que mejoran otros síntomas parkinsonianos.
*Pacientes y métodos:* Presentamos un grupo de 10 pacientes con enfermedad de Parkinson de larga evolución con episodios de CDM. Todos los pacientes presentaban las complicaciones motrices habituales tras años de enfermedad y tratamiento. En todos los pacientes, el síntoma más incapacitante era la aparición de episodios de CDM *(freezing)* durante el *"on"*. Los pacientes fueron sometidos a un test agudo de apomorfina por vía subcutánea; se consideró dosis eficaz la que inducía la reducción de al menos un 60%en la escala de motricidad de la UPDRS.
*Resultados:* La UPDRS-III basal fue de 61,3 ± 4,7, que se reducía a 21 ± 4,3 tras la inyección de apomorfina s.c. a una dosis media de 5,5 mg (intervalo, 3-7 mg). Durante el *"on"* inducido por la inyección s.c. de apomorfina mejoraron los parámetros de la marcha relacionados con la bradicinesia, así como el *tapping,* también en extremidades inferiores, pero los episodios de CDM no variaron de forma significativa.
*Conclusiones:* Presentamos un grupo de 10 pacientes con enfermedad de Parkinson de larga evolución con episodios de CDM que persistían durante el *"on",* sin respuesta al estímulo dopaminérgico.


## Introduction

Walking and stability are two aspects which influence the quality of life considerably in patients with Parkinson's disease (PD)1. It is generally considered that there are three functional levels involved in motion control that act in an integrated manner: musculoskeletal and neuromuscular system, subcortical structures of the central nervous system and cortical structures (afferent, integrative and efferent systems)2. The central nervous system uses and integrates the information it receives through the afferent system and establishes the motor plans needed to maintain stability and posture and develop a walk with the appropriate motor and speed patterns, for which the subcortical structures such as basal ganglia and cerebellum, as well as the connections between the frontal lobe and subcortical structures, are fundamental3. The alteration of subcortical structures causes walking disorders in PD; thus lack of movement, small steps, diminished or absent arm swing, forward flexion of the trunk, etc., configure the typical PD walk4-6. The alteration of walking in PD that we call freezing, the locking up or freezing of gait (FOG), began to be described more explicitly from 1970, when the motor benefit achieved with levodopa on other PD symptoms was not equally evident for this strange alteration7. Episodes of freezing of gait in which patients have the feeling of "having their feet stuck to the ground", are characterised by their episodic appearance (at the beginning of walking, with obstacles, in turns, etc.) and their brief duration8. They are often, but not always, associated with a hastening of the walk with successively faster and shorter steps, with uncontrolled forward displacement of the centre of gravity9,10. Blocking of gait can occur at the beginning of PD, but always in a mild form; so much so that, if this is not the case (if it is strong in early stages), the diagnosis of idiopathic PD is called into question and other types of Parkinsonism should be considered11,12. We have observed this phenomenon in most patients after years of illness and treatment, when also suffering from motor complications after chronic treatment, such as motor fluctuations and dyskinesias13. Locking of walk usually appears during the "off" period, coinciding with the deterioration of other motor symptoms, but can also occur during the "on" state, when the patient has acceptable mobility14. Interestingly, the severity of other PD symptoms does not correspond to the severity of walk blockages15.

We present a group of 10 patients with PD of long evolution, with highly disabling episodes of walking locks that were not modified after dopamine stimulation despite evidence of improvement in lower limb akinesia after the stimulus.

## Patients and method

The patient characteristics are listed in Table 1. We studied 10 patients with an average age of 60.2 ± 4.5 years and longstanding PD (13.4 ± 3.2 years) treated with levodopa (LD) for an average of 12.1 ± 2.1 years. Patients were also treated with bromocriptine, pramipexole or ropinirole, combining this with rasagiline in 4 of them. All patients presented common motor complications after years of illness and treatment, in the form of motor fluctuations (8 patients, deterioration at the end of doses and 2 more complex on-off fluctuations) and dyskinesias (the 10 patients

**Table 1** Patient characteristics

| | |
|---|---|
| Patients, n | 10 |
| Age (years) | 60,2 ± 4,5 |
| Duration of illness (years) | 13,4 ± 3,2 |
| Levodopa treatment (years) | 12,1 ± 2,1 |
| Fluctuations | 10 |
| Dyskinesias | |
| Chorea | 10 |
| Dystonia *"off"* | 4 |
| Biphasic | 3 |

**Table 2** Response to treatment

| | *"Off"* | *"On"* |
|---|---|---|
| UPDRS-movement | 61,3 ± 4,7 | 21 ± 4,3 |
| *T*apping, upper limbs(s) | 128 ± 12,6 | 46,3 ± 4,2 |
| Tapping, lower limbs(s) | 83,9 ± 11,7 | 42,8 ± 8,3 |
| Freezing (unchanged) | 3,7 ± 1,6 | 3,2 ± 1,4 |

Tapping: time(s) required to touch 50 times on two points separated by 50 cm the upper limbs and 25 cm in the lower limbs; UPDRS: Unified Parkinson's disease rating scale.

suffered from dose profit chorea, 4 from off dystonia and 3 from biphasic dyskinesias). In all patients the most disabling symptom was the onset of FOG episodes during the on. None of the patients presented significant abnormalities in the cranial MRI.

After the appropriate consent from patients to participate in the study, they underwent an acute test of subcutaneous apomorphine; they received apomorphine doses early in the morning in a state of *off*, after having spent the night without medication, and the dose was considered effective when it induced a reduction of at least 60% on the unified Parkinson's Disease rating scale (UPDRS) motor scale. The test was repeated on successive days to obtain the effective dose for each patient. During the 3 days prior to the study, patients received oral domperidone, 30 mg/day in three doses.

Patients quantified their *on* and *off* time for 1 week before the study by filling in the corresponding daily sheets of *on* and *off* time (better and worse mobility). During the study, the motor part of the UPDRS (scoring left and right limbs, with 108 as the highest score) and a tapping test (time required to touch 50 times two points separated by 50 cm in the upper limbs and 25 cm in the lower limbs) was used for patient assessment. The freezing was quantified from 0 (absent) to 4 (severe interference with walk). This movement assessment was made in the baseline situation and then during the motor benefit induced by the injection of subcutaneous apomorphine.

Student's t-test was used to study the statistical significance of results ($p \leq 0.05$).

## Results

Patients had an average of 4.5 ± 1.3 h off time between 8.00 and 22.00 with their usual medication. Study results are listed in Table 2. Baseline UPDRS-III was 61.3 ± 4.7, which was reduced to 21 ± 4.3 after injection of subcutaneous apomorphine in an average dose of 5.5 (range 3-7) mg. Tapping also improved significantly ($p < 0.001$) in the upper extremities (128 ± 12.6 to 46.3 ± 4.2 s) and the lower extremities (83.9 ± 11.7 to 42.8 ± 8.3 s). During the on state induced by the subcutaneous injection of apomorphine, the walk parameters related to bradykinesia (incorporation from a chair, amplitude of steps, arm movement, etc.) improved, but the episodes of FOG did not vary significantly between the off and on (3.2 ± 1.4 in the off; 3.7 ± 1.6 in the on).

## Discussion

We present a group of 10 patients with longstanding PD and FOG episodes that persisted during the *on* state, without response to dopaminergic stimulation. FOG episodes are common in patients with longstanding PD. Lamberti et al.[13] observed this phenomenon in 60 patients out of 100 evaluated PD patients, and the duration of the disease was the main determining factor for their appearance. Similarly, Giladi et al.[16] consecutively studied 172 patients with PD, all with a progression time of disease over 5 years, and 53% showed evident FOG episodes. Chronic levodopa therapy and the existence of other motor complications (fluctuations and dyskinesias) are also risk factors for its appearance. Episodes of FOG that occur during the *off* may improve with dopaminergic therapy, as other PD symptoms improve, but there are patients (such as the group referred to in this study) in whom the improvement of bradykinesia is not accompanied by an improvement of the episodes of freezing of gait. Some authors point out the discrepancy between the severity of bradykinesia and FOG episodes[15]; in fact, in our patients the improvement of akinesia after dopaminergic stimulation with subcutaneous apomorphine was not accompanied by an improvement in FOG episodes. Years ago, when high doses of L-dopa were used in patients with advanced PD, there was an improvement in blocking episodes during the *on* state when the dosage of L-dopa was reduced, and it was considered that dopaminergic overstimulation was a main cause of FOG during the *on* in these patients[7,17]. This is not the case with the patients described in this study, who received a dose of L-dopa which was never >750 mg/day and in whom the study was carried out after more than 12 hours from the last dose of L-dopa.

FOG physiopathology is not well understood. Although it is associated to PD, striatonigral degeneration is not an essential condition for its appearance; thus, there is a primary form of FOG in which no other symptoms or PD signs are added[18,19]. Some authors indicate that PD patients who present FOG have a background of general alteration in terms of sequence, rhythm and symmetry of movements during walking, which is much more severe than in PD patients without this problem, and that blocking episodes

are an exacerbation of this phenomenon as a response to certain stimuli (initiation of walk, obstacles, turns, etc.)[20]; the frontal lobe would be very involved in its appearance[21]. Functional neuroimaging studies (positron emission tomography [PET], functional magnetic resonance imaging [MRI]), seem to point to an affectation of the fronto-caudal pathway, predominantly in the right hemisphere[22]; some studies also implicate the parietal lobe. It can be deduced from this that sensory motor integration is a part of the genesis of the problem[22,23].

In recent years, the possible involvement of the degeneration of cholinergic and glutamatergic neurons from the pedunculopontine nucleus, in advanced PD stages, is being studied as at least partial cause of postural and gait disorders that are observed in advanced PD stages and that do not respond to dopaminergic treatment[24]. Kuo et al.[25] have recently described a patient with infarctions in both pedunculopontine nuclei with FOG as a predominant symptom.

Peripheral level studies have also objectified an abnormal pattern in the sequence of contraction of agonist and antagonist muscles in the lower limbs[26].

A fascinating phenomenon is the improvement experienced by patients if they use external cues, usually visual or auditory, to control the FOG episodes. In this sense, Stern et al.[27] recorded the motor tricks used by 61 PD patients with FOG. The most frequent were of verbal or auditory type (such as military marches) or of visual type (such as reaching the foot of another person placed in front). One of our patients was able to walk around the house thanks to having placed coloured lines on the floor to walk on. Hallet[28] indicates a loss in motor automatisms and an alteration in internally-induced movements in PD in general and in the phenomenon of FOG in particular, which would explain the improvement with external keys or signs[27,29]. Moreover, this loss of automatisms would also explain the worsening of locking of gait when the patient is asked to perform another task simultaneously, such as counting by sevens. Camicioni et al.[30] explored the gait (time required to walk a certain distance) while performing verbal tasks in PD patients with and without FOG, and the worsening of gait was much sharper in PD patients with FOG.

What does seem clear is that FOG episodes are not merely a consequence of akinesia or rigidity; the response to dopaminergic therapy may therefore not be the same. Knowing the physiopathology underlying this disorder, mainly during the *on* state, may help to orient the therapeutic approach, which is very unrewarding at the moment, from a pharmacology point of view[7,8]. In this regard, previous studies suggest that the development of FOG is more common in patients treated with dopaminergic agonists than in those treated with L-dopa[31,32] and that selegiline and rasagiline might have some beneficial effects on the episodes of blocking of gait[33,34]. It was considered that the noradrenergic system might be involved in PD gait disorders, and there are studies indicating that chronic treatment with high doses of methylphenidate would benefit gait parameters, including FOG, in patients with advanced PD[35]. The benefit of caffeine has also been indicated, as it would act as an antagonist of the A2 adenosine receptors[36]. The benefit with injection of botulinum toxin initially reported in an open study in twins was not confirmed later in a double blind study; in fact, there were even more falls in the group of PD patients with FOG treated with toxin, apparently due to adding to the muscular weakness produced by the treatment[37]. Deep brain stimulation of the usual targets does not seem to improve episodes of FOG that occur during the *on*[38]. There are already some encouraging results with deep brain stimulation of the pedunculopontine nucleus[39]. Currently, gait rehabilitation with the search for external cues, with different strategies tailored to the usual environment of each patient, can be a valid therapeutic alternative[40].

## Presentations

This work was partially presented at the annual meeting of the Movement Disorders Society in 2008.

## Conflict of interests

The authors declare no conflict of interests.

## References

1. Giladi N, Hausdorff JM, Balash Y. Episodic and continuous gait disturbances in Parkinson's disease. In: Galvez-Jiménez N, editor. The scientific basis for the treatment of Parkinson's disease. Lancaster: Parthenon; 2004.
2. Nutt JG, Marsden D, Thompson PD. Human walking and higher level gait disorders particularly in the elderly. Neurology. 1993;43:268-79.
3. Marsden CD, Thompson PD. Toward a nosology of gait disorders: descriptive classification. In: Masdeu J, Surdarsky L, Walfson L, editors. Gait disorders of aging. Falls and therapeutic strategies. Philadelphia: Lippincott-Raven; 1997. p. 135-46.
4. Wichmann T, DeLong MR. Functional neuroanatomy of the basal ganglia in Parkinson's disease. Adv Neurol. 2003;91:9-18.
5. Parkinson J. An essay on the shaking palsy. London: Sherwood, Neely and Jones; 1817.
6. Koller WC. An essay on the shaking palsy: James Parkinson's description compared to current concepts. Neurology. 1983;33 Suppl:150.
7. Ambani LM, Van Woert MH. Start hesitation – a side effect of long-term levodopa therapy. N Engl J Med. 1973;288:1113-5.
8. 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;10:391-8.
9. Giladi N, Shabthai H, Rozenberg E, Shabthai E. Gait festination in Parkinson's disease. Parkinsonism Relat Disord. 2001;7:135-8.
10. Bloem B, Van Vuggt J, Beckley D. Postural instability and falls in Parkinson's disease. Adv Neurol. 2001;87:209-23.
11. Selby G. The long term prognosis of Parkinson's disease. Clin Exp Neurol. 1984;20:1-25.
12. Giladi N, Kao R, Fahn S. Freezing phenomenon in patients with parkinsonian syndromes. Mov Disord. 1997;12:302-5.
13. Lamberti P, Armenise S, Castaldo, Vde Mari M, Iliceto G, Tronci P, et al. Freezing gait in Parkinson's disease. Eur Neurol. 1997;38:297-301.

14. Okuma Y, Yanagisawa N. The clinical spectrum of freezing of gait in Parkinson's disease. Mov Disord. 2008;23 Suppl:426-30.
15. Bartels AL, Balash Y, Gurevich T, Schaafsma JD, Hausdorff JM, Giladi N. Relationships between freezing of gait (FOG) and other features of Parkinson's disease. FOG is not correlated with bradykinesia. J Clin Neurosci. 2003;10:584-8.
16. Giladi N, Treves TA, Simon SE, Shabtai H, Orlov Y. Freezing of gait in patients with advanced Parkinson's disease. J Neural Trasm. 2001;108:53-61.
17. Barbeau A. Six years of high-level levodopa therapy in severely akinetic parkinsonian patients. Arch Neurol. 1976;33:333-8.
18. Factor S, Jennings DL, Molho ES, Marek KL. The natural history of the syndrome of primary progressive freezing gait. Arch Neurol. 2002;59:1778-83.
19. Imai H. Syndrome of pure akinesia or freezing phenomenon without rigidity and tremor and with no effect of L-Dopa therapy. Adv Neurol Res (Tokyo). 1980;24:838-48.
20. Plotnik M, Hausdorff JM. The role of gait rhythmicity and bilateral coordination of stepping in the pathophysiology of freezing of gait in Parkinson's disease. Mov Disord. 2008;23 Suppl 2:S444-50.
21. Giladi N, Haussdorff JM. The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease. J Neurol Sci. 2006;248:173-6.
22. Matsui H, Udaka F, Miyoshi T, Hara N, Tamaura A. Three-dimensional stereotactic surgace projection study of freezing of gait and perfusion image in Parkinson's disease. Mov Disord. 2005;20:1272-7.
23. Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. Neuroimage. 2007;34:714-23.
24. Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. Brain. 2000;123:1767-83.
25. Kuo SH, Jankovic KC. Bilateral pedunculopontine nuclei strokes presenting as freezing of gait. Mov Disord. 2008;23:616-9.
26. Nieuwboer A, Domn R, De Weerdt W, Desloovere K, Janssens L, Stijin V. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. Brain. 2004;127:1650-60.
27. Stern GM, Lander CM, Lees AJ. Akinetic freezing and trick movements in Parkinson's disease. J Neural Transm Suppl. 1980;16 Suppl:137-41.
28. Hallet M. The intrinsic and extrinsic aspects of freezing of gait. Mov Disord. 2008;22 Suppl:S439-43.
29. Sacco K, Cauda F, Cerliani L, Mate D, Duca S, Germiniani GC. Motor imagery of walking following training in locomotor attention. The effect of "the tango lesson". Neuroimage. 2006;32:1441-9.
30. Camicioli R, Oken BS, Sexton O, Kaye JA, Nutt JG. Verbal fluency task affects gait in Parkinson's disease with motor freezing. J Geriatr Psychiatry Neurol. 1998;11:181-5.
31. Rascol O, Brooks DJ, Korczyn AD, DeDeyn PP, Clarke CE, Lang AE. 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. 2003;342:1484-91.
32. The Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson's disease. A 4-year randomized controlled trial. Arch Neurol. 2004;61:1044-53.
33. Giladi N, McDermott MP, Fahn S, Przedborski J. Freezing of gait in PD: prospective assessment in the DATATOP cohort. Neurology. 2001;56:1712-21.
34. Elmer LW, Bertoni JM. The increasing role of monoamine oxidase type B inhibitors in Parkinson's disease therapy. Expert Opin Pharmacother. 2008;9:2759-72.
35. 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;29:15-7.
36. Kitagawa M, Houzen H, Tashiro K. Effects of caffeine on the freezing of gait in Parkinson's disease. Mov Disord. 2007;22:710-2.
37. Wieler M, Camicioli R, Jones CA, Martin WR. Botulinum toxin injections do not improve freezing of gait in Parkinson's disease. Neurology. 2005;65:626-8.
38. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003;349:1925-34.
39. Pahapill P, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. Brain. 2000;123:1767-83.
40. Nieuwboer A, Kwakkel G, Rochester L, Jones D, Van Wegen E, Willems AM, et al. Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. J Neurol Neurosurg Psychiatry. 2007;78:134-40.