Rasagiline Improves Freezing in a Patient with Primary Progressive Freezing Gait

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Video 

Abstract: **We herein report the case of a 84-year-old man with a 4-year history of freezing of gait (FOG) consistent with the diagnosis of primary progressive freezing gait. Single photon emission tomography (SPECT) with a radiolabeled ligand of the dopamine transporter (DAT-SPECT) showed integrity of striatal dopaminergic terminals, whereas brain perfusion SPECT disclosed multiple areas of decreased perfusion in frontal and parietal lobes, as well as in the subcortical gray nuclei of both sides. Treatment with the new irreversible monoamine oxidase B inhibitor rasagiline at standard doses resulted in a rapid, dramatic, and sustained improvement of the frequency and duration of FOG episodes. In addition, brain perfusion SPECT after treatment showed a marked increase of the activity in all cortical areas as well as in the basal ganglia and thalamus. Rasagiline may prove to be an effective and safe treatment for this disabling condition.** © 2007 Movement Disorder Society

Key words: freezing of gait; primary progressive freezing gait; MAOB inhibitors; rasagiline; brain perfusion SPECT.

Freezing of gait (FOG) is a common symptom of advanced Parkinson's disease (PD) and may be the only or the first symptom of a variety of parkinsonian syndromes, such as progressive supranuclear palsy (PSP), vascular parkinsonism, and normal pressure hydrocephalus.[1] Primary progressive freezing gait (PPFG) refers to a gait disorder, in which arrests of gait appear in isolation, without other typical parkinsonian features such as rigidity, bradykinesia, or tremor, and could not be attributed to other neurological conditions.[2-6] This is a progressively incapacitating disorder that does not respond or may even worsen with dopaminergic therapies, and no definite treatment is yet available.[6] We now report that rasagiline, a new selective inhibitor of the monoamine oxidase B (MAOB),[7] provides sustained improvement in a patient with PPFG.

CASE REPORT

A 84-year-old right-handed man, presented with a 4-year history of walking difficulties leading to fear of falling and progressive restriction of outside activities. The patient complained of gait blocking on walking, that was more prominent when attempting to go through doorways, crossing streets, or find obstacles on his way. He was previously treated with several combinations of dopaminergic drugs, including L-dopa, pramipexole, ropinirole, entacapone, and selegiline at standard doses, but the gait disorder continued to worsen to the point that he needed assistance to walk and began to use a wheelchair to get outside. The patient and his wife reported no problems with hand dexterity or difficulties to stand from a chair or the bed and no difficulties to start walking, even after prolonged periods of resting. There was no history of significant systemic diseases.

At examination, the patient showed no signs of dementia as judged by MMSE score of 28. He showed a mild stooped posture and slow short-stepping gait and reduced swing of both arms. There were marked and frequent blocks of gait (Segment 1), which were more apparent on turns or trying to pass through doors or in front of small obstacles placed on the floor. Arrests of walk lasted seconds and were accompanied by marked hesitation. The patient has no apparent difficulties to start walking. The application of the FOG questionnaire[8] gave a score of 18 out of 24, indicating severe disability. He showed no rigidity or tremor, and hand and foot tapping while sitting were both normal. The pull test revealed no impairment of postural reflexes. There were no signs of pyramidal or cerebellar dysfunction or supranuclear gaze palsy.

Routine laboratory investigations were unremarkable. MRI of the brain showed mild diffuse cortical atrophy. Single-photon emission computed tomography (SPECT) with ^{123}I-Ioflupan (DAT-SPECT) before treatment showed normal binding of the radiotracer in the striatum. In contrast, perfusion SPECT of the brain using ^{99m}Tc-ECD disclosed multiple large scattered perfusion defects involving the frontal, parietal, and the right temporal lobes, as well as a marked reduction of activity in the basal ganglia and thalamus of both sides, but more prominent on the right (Fig. 1A).

All dopaminergic agents were then removed with no apparent changes in his clinical status. After a wash-out period of 4 weeks, rasagiline 1 mg once a day was

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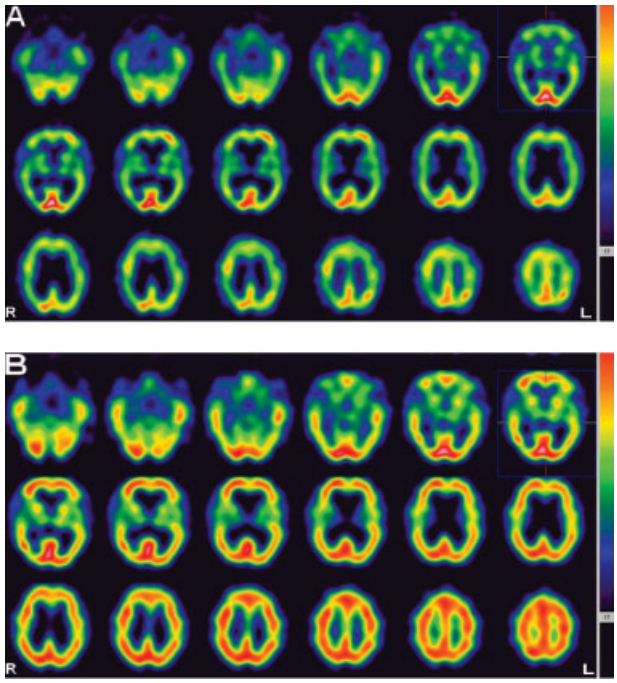

FIG. 1. ^{99m}Tc-ECD SPECT of the brain before (**A**) and after (**B**) 1 year of continuous treatment with rasagiline. Notice decreased activity in frontal and parietal areas and temporal cortex before treatment and almost normal activity in all cortical areas after treatment. The subcortical gray nuclei displayed more reduced activity in the right than in the left side. After treatment, the activity in the basal ganglia and thalamic regions was increased in the left side, but the right thalamic region still showed an almost complete absence of activity.

prescribed. During the following days the number and duration of gait blocks were dramatically reduced, so he was able to walk without assistance and regained outside activities. Transient discontinuation of rasagiline resulted in a rapid worsening of gait. After 14 months on rasagiline the patient was still fully ambulant with no need of external aids, and scored 2 on the FOG questionnaire. Brain perfusion SPECT 1 year after continuous treatment with rasagiline demonstrated a marked improvement of perfusion in all affected cortical areas and in the cerebellum (Fig. 1B). Perfusion defects of the subcortical gray nuclei also improved, more in the left than in the right side, where the thalamic region remained with poor perfusion levels (Fig. 1B).

DISCUSSION

This patient has a FOG disorder that fulfils clinical criteria for PPFG,[5] a subtype of the so-called high level gait disorders.[9] In addition, we show that DAT-SPECT before treatment was normal, indicating integrity of dopaminergic terminals in the striatum. This suggests that the gait disorder in this patient is not a symptom of an underlying PD or other parkinsonian syndromes.[10]

Brain perfusion SPECT showed a complex pattern of abnormalities, with asymmetrical reduction of cortical perfusion in the lateral frontal and lateral parietal lobes, and in the subcortical gray nuclei. After sustained clinical improvement with rasagiline, all cortical areas regained nearly normal perfusion levels, and perfusion of subcortical gray nuclei also increased, but to a lesser extent. Decreased perfusion of the basal ganglia should be related to mechanisms other than degeneration of the nigro-estriatal pathway preserved in this case as demonstrated by DAT-SPECT.

Previous brain perfusion studies specifically addressing the pathological anatomy of the FOG phenomenon have provided conflicting results.[11-15] Based on these and other studies, it has been speculated that a bilateral dysfunction of the medial supplementary motor area may underlie this phenomenon.[11] Neuroimaging findings in the present case add little support to this single-localization hypothesis, and suggest that FOG may result from a more widespread alteration of the striato-thalamic-cortical circuit. Further studies on cases with PPFG may contribute to the understanding of the pathophysiology of this phenomenon.

The neurochemical bases of PPFG are also poorly understood. Dopaminergic, noradrenergic, and cholinergic systems have been implicated.[11] The role played by dopaminergic systems in this disorder seems to be minor, since it responds poorly to current dopaminergic therapies[5] and DAT-SPECT was normal 4 years after the onset of FOG in the patient reported here.

PPFG has no definitive treatment to date. Small open studies and case reports have shown beneficial effects with donepezil,[13] methylphenidate,[16] and selegiline.[3,17] Botulinum toxin[18] and deep brain stimulation[19] have provided variable results. On the other hand, double-blind placebo-controlled studies have shown that MAOB inhibitors, selegiline, and rasagiline, have a moderate but significant effect on FOG in patients with advanced PD.[20-23]

Besides a placebo effect, the mechanism by which rasagiline and other selective MAOB inhibitors may improve PPFG is not clear. Rasagiline and selegiline have symptomatic as well as putative neuroprotective effects.[7] The rapid onset of the clinical effect in this and other cases[17] suggests a symptomatic rather than a protective effect.

It is currently held that the benefits of MAOB inhibitors on motor symptoms of PD are mediated by increasing dopamine availability from endogenous and exogenous sources, thus facilitating continuous dopaminergic stimulation. In addition, MAOB inhibitors dramatically increase phenylethylamine, a potent dopamine releaser.[7] Other authors have suggested that the effects of selegi-

line on FOG may also be mediated by its main active metabolite methamphetamine.[17] This is consistent with the beneficial effect observed with other sympathomimetics, such as methylphenidate.[16] Nevertheless, rasagiline does not metabolize to amphetamine derivatives,[7,24] and other sympathomimetic drugs, such as the synthetic norepinephrine precursor, L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS) has been found of limited and transitory usefulness in reducing FOG in patients with PD and pure akinesia.[25]

Other lines of evidence have suggested that FOG may be related with disturbances of psychoaffective functions often associated with parkinsonian syndromes, such as depression, anxiety, panic,[26] and drive.[13] In fact the DATATOP study and other clinical studies showed that depression and anxiety were both associated with an increased risk of FOG.[20] In this context, the beneficial effects of MAOB inhibitors may be related to their potential effects on mood[20,24] and perhaps drive.

Whatever the mechanisms involved, this and other reports[3,17] suggest that marketed MAOB inhibitors are promising alternatives for the treatment of PPFG. Nevertheless, rasagiline has a better pharmacokinetic and pharmacodynamic profile and fewer potential side-effects than high dose-selegiline,[24] and therefore it would represent a better therapeutic option for these patients.

To our knowledge, this is the first documented case of PPFG with long-lasting clinical and functional imaging improvement with rasagiline. This encourages further studies to demonstrate the efficacy of this drug in this incapacitating disorder.

LEGENDS TO THE VIDEO

Segment 1. Patient before rasagiline treatment. Numerous FOG episodes are present with marked hesitation on turns.

Segment 2: Patient after continuous treatment with rasagiline for 10 months. Notice complete absence of FOG episodes.

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REFERENCES

1. Giladi N. Freezing of gait. Clinical overview. Adv Neurol 2001; 87:191–197.
2. Achiron A, Ziv I, Goren M, et al. Primary progressive freezing gait. Mov Disord 1993;8:293–297.
3. Atchison PR, Thompson PD, Frackowiak RS, Marsden CD. The syndrome of gait ignition failure: a report of six cases. Mov Disord 1993;8:285–292.
4. Nicaretta DH, Pereira JS, Pimentel ML. Primary progressive freezing gait. Case report. Arq Neuropsiquiatr 1997;55:496–498.
5. Factor SA, Jennings DL, Molho ES, Marck KL. The natural history of the syndrome of primary progressive freezing gait. Arch Neurol 2002;59:1778–1783.
6. Factor SA, Higgins DS, Qian J. Primary progressive freezing gait: a syndrome with many causes. Neurology 2006;66:411–414.
7. Youdim MBH, Edmonson D, Tripton KF. The therapeutic potential of monoamine oxidase inhibitors. Nat Rev Neurosci 2006;7: 295–309.
8. 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.
9. Nutt JG, Marsden CD, Thompson PD. Human walking and higher level gait disorders, particularly in the elderly. Neurology 1993; 43:268–279.
10. Scherfler C, Schwarz J, Antonini A, et al. Role of DAT-SPECT in the diagnostic work up of Parkinsonism. Mov Disord 2007;22: 1229–1238.
11. Hashimoto T. Speculation on the responsible sites and pathophysiology of freezing of gait. Parkinsonism Relat Disord 2006;Suppl 2:S55–S62.
12. Fabre N, Brefel C, Sabatini U, et al. Normal frontal perfusion in patients with frozen gait. Mov Disord 1998;13:677–683.
13. Yener GG, Kaya GC, Ozturk V, Akdal G. Improvement in Tc-99m HMPAO brain SPECT findings during donepezil therapy in a patient with pure akinesia. Ann Nucl Med 2005;19:607–609.
14. 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.
15. Bartels AL, de Jong BM, Giladi N, et al. Striatal dopa and glucose metabolism in PD patients with freezing of gait. Mov Disord 2006;21:1326–1332.
16. 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.
17. Zuniga C, Lester J, Cersosimo MG, Diaz S, Micheli FE. Treatment of primary progressive freezing of gait with high doses of selegiline. Clin Neuropharmacol 2006;29:20–21.
18. 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.
19. Davis JT, Lyons KE, Pahwa R. Freezing of gait after bilateral subthalamic nucleus stimulation for Parkinson's disease. Clin Neurol Neurosurg 2006;108:461–484.
20. Giladi N, McDermott MP, Fahn S, et al. Freezing of gait in PD. Prospective assessment in the DATATOP cohort. Neurology 2001; 56:1712–1721.
21. Parkinson Study Group. A randomized, placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson's disease and motor fluctuations. The PRESTO study. Arch Neurol 2005; 62:241–248.
22. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with PD and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily study): a randomized, double-blind, parallel-group trial. Lancet 2005;365:947–954.
23. Giladi N, Rascol O, Brooks DJ, et al. Rasagiline treatment can improve freezing of gait in advanced Parkinson's disease: a prospective, randomized, double-blind and entacapone controlled study. Neurology 2004;62 (Suppl. 5):A329–A330.
24. Rascol O. Rasagiline in the pharmacotherapy of Parkinson's disease. A review. Expert Opin Pharmacother 2005;6:2061–2075.
25. Kondo T. Drug intervention for freezing of gait resistant to dopaminergic therapy: a pilot study. Parkinsonism Relat Disord 2006; Suppl 2:S63–S66.
26. 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.