

Pure akinesia: a kinematic analysis in a case responsive to rotigotine

Roberto Di Fabio, MD^a
Mariano Serrao, MD^a
Francesco Pierelli, MD^b
Gaia Fragiotta, MD^a
Giorgio Sandrini, PhD^c

^a Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

^b IRCCS Neuromed, Pozzilli (IS), Italy

^c Neurorehabilitation Unit, C. Mondino National Institute of Neurology Foundation, IRCCS, Pavia and University of Pavia, Italy

Correspondence to: Roberto Di Fabio
E-mail: rodifa@gmail.com

Summary

A patient with pure akinesia is described. This rare gait disorder, poorly responsive to therapy, is characterized by gait impairment which may be associated with handwriting and speech difficulties, in the absence of further signs of extrapyramidal involvement. Here, we report the improvement in a patient suffering from pure akinesia after low doses of rotigotine, a non-ergolinic dopamine agonist, detailing the kinematic analysis before and after the treatment. After therapy, an improvement in all of the gait parameters, particularly gait speed, was observed with a trend toward normalization. Our case report suggests that rotigotine may be a therapeutic option in cases of pure akinesia.

KEY WORDS: kinematic, pure akinesia, rotigotine, therapy.

Introduction

Pure akinesia (PA) is characterized by akinesia of gait, which may be associated with handwriting and speech impairment, in the absence of rigidity, tremor, or dementia (Yoshikawa et al., 1997; Matsuo et al., 1991). While some patients with PA may develop signs of progressive supranuclear palsy (an atypical parkinsonian syndrome characterized by supranuclear gaze palsy, axial dystonia, bradykinesia, dysarthria, pseudobulbar palsy, postural instability, and cognitive

disturbances), others can have isolated gait impairment without additional extrapyramidal signs over time. PA can be severely disabling since it can be unresponsive to therapy (Rascol et al., 2001).

Rotigotine, a non-ergoline dopamine agonist, is effective in Parkinson's disease, another syndrome associated with freezing of gait, but, to date, it has never been tested in PA.

We report the clinical improvement of gait, evaluated through a quantitative analysis, observed in a patient with PA, after low doses of rotigotine.

Case report

For two years, a 79-year-old otherwise healthy man had been complaining of a tendency to shorten his steps and marked slowness of walking associated with rare episodes of starting and turning hesitation (3-4 episodes per day), resulting in a reduction of walking confidence. He also showed a tendency to micrographia. No additional extrapyramidal features or depression were noted (Hamilton scale 0/66, MMSE 30/30). Brain and cervical MRI were not significant. His UPDRS III score was 11/56, while he scored 10/24 on the Gait and Falls Questionnaire (GFQ) (Giladi et al., 2000).

The patient gave his informed consent to participate in the study. A quantitative gait assessment, before and after one month of therapy with rotigotine patch (4 mg), was performed. A SMART-E motion analysis system (BTS, Milan, Italy) was used according to a validated biomechanical model (Davis et al., 1991). The patient was asked to walk barefoot at self-selected natural speed along an eight-meter walkway. The following time-distance parameters were considered: percentage duration of the stance and swing phases and double support phase, swing velocity, step length, step width, and gait speed. To assess lower limb segmental kinematics in the sagittal plane, we ascertained hip, knee and ankle joint centers of rotation and calculated joint angular displacements.

At the baseline evaluation, compared to age-matched healthy subjects, the patient showed longer stance and double support percentage durations and a marked reduction of gait speed, step length, swing velocity, hip peak extension, knee peak flexion and ankle peaks of dorsal and plantar flexion.

After therapy, an improvement in all of the gait parameters, particularly gait speed, was observed with a trend toward normalization (UPDRS III, 1/56; GFQ, 1/24) (Fig. 1, over).

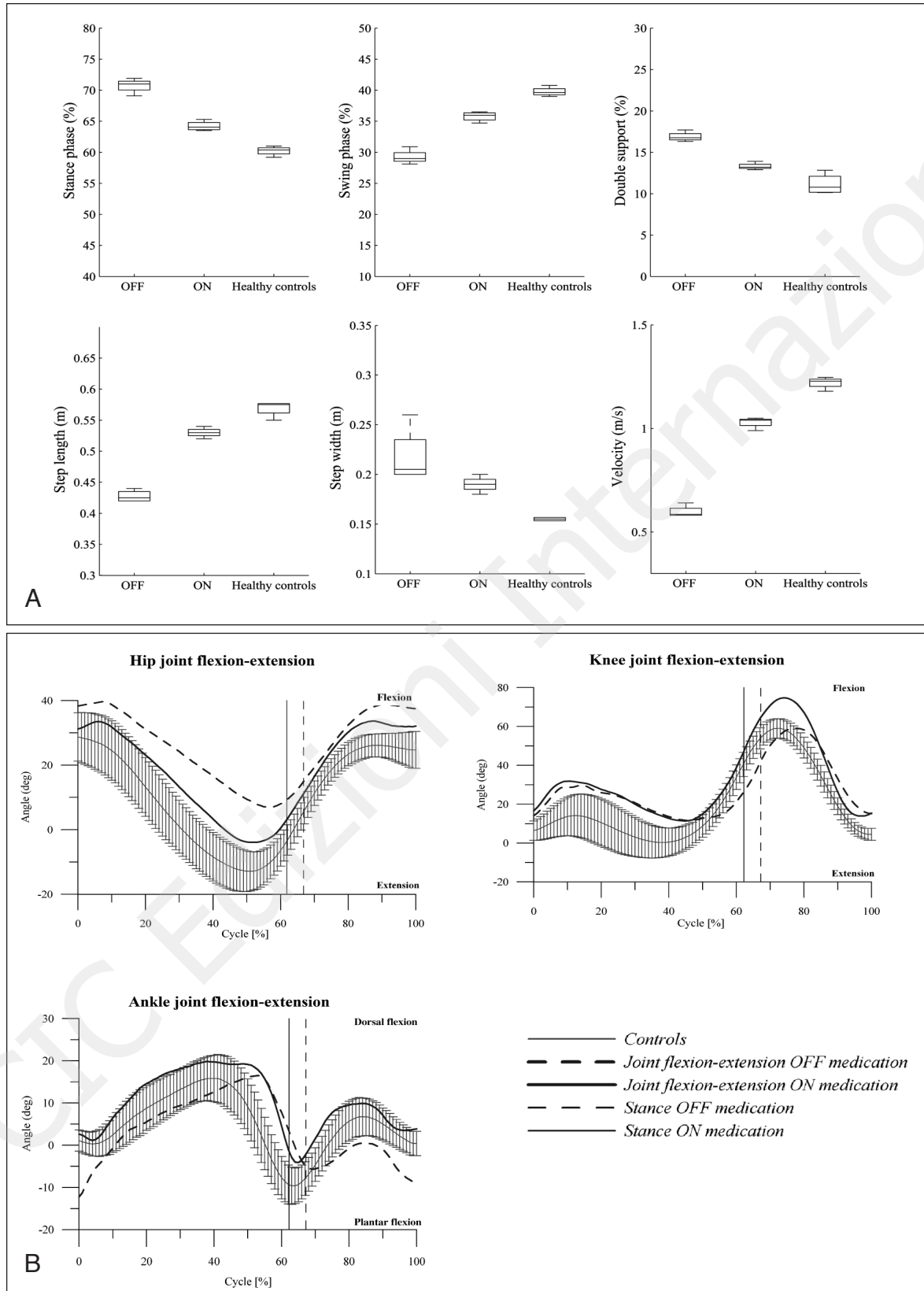


Figure 1 - Time-distance parameter values (A) and kinematic behavior of the hip, knee and ankle joints (B) before and after treatment with rotigotine in a patient with pure akinesia. As no relevant differences between left and right sides were observed, the right side was considered. The gait parameters of a sample of ten age-matched healthy subjects are reported.

Discontinuation of the drug for one week caused a worsening of the clinical picture, while resumption of rotigotine resulted in an improvement of the gait parameters, as had been observed at the first administration of the drug.

Discussion

Pure akinesia may show sub-clinical features, detectable by means of a quantitative study. We described the kinematic analysis of gait in a patient suffering from PA, a neurological disorder poorly responsive to therapy (Williams et al., 2007). In this patient, treatment with rotigotine significantly reduced walking impairment and improved gait performance. The functional improvement in this case consisted of: i) longer step length and increased stance, stride and double support duration; ii) increased range of motion of the hip, knee and ankle joints; iii) greater gait velocity (Fig. 1).

As in Parkinson's disease, an impairment of basal ganglia and frontal circuits has been suggested in PA (Williams et al., 2007; Nutt et al., 2011).

Hence, we decided to administer our patient rotigotine, a molecule which binds both D3/D2/D1 and 5-HT1A receptors. The latter are located mainly in frontal areas and in the dorsal raphe nuclei and contribute to the control of dopamine release from the striatum.

Thus, it is not surprising that antiparkinsonian drugs (Coria and Cozar-Santiago Mdel, 2008), through stimulation of striatal dopamine receptors, and duloxetine (Morgante and Fasano, 2010), which enhances the frontal noradrenergic pathways, have been found to be effective in isolated cases of primary progressive freezing of gait, a syndrome considered to share several similarities with PA.

Interestingly, 5-HT1A stimulation yielded encouraging results in the management of movement disorders and improved motor function in parkinsonian rat models (Dupre et al., 2007; Ohno, 2011).

In this regard, it should be noted that tandospirone, a serotonin 5-HT1A agonist (Miyata et al., 2001), and L-threo-3,4-dihydroxyphenylserine (L-DOPS), a synthetic precursor of noradrenaline (Yamamoto et al., 1997), provided some benefit in isolated PA cases, although the clinical improvement was assessed through non-quantitative methods.

Our hypothesis is that rotigotine, the only dopamine

agonist with relevant binding to 5-HT1A receptors, may contribute to optimizing the release of dopamine through direct action on striatal D2/D3 receptors in the basal ganglia, or by activating 5-HT1A autoreceptors in the frontal areas.

Rotigotine may be an option for the symptomatic treatment of PA, as shown by the quantitative examination of gait in this patient.

Further studies investigating the effect of this drug on a large sample of patients with isolated gait disorder and freezing of gait are warranted.

References

- Coria F, Cozar-Santiago Mdel P (2008). Rasagiline improves freezing in a patient with primary progressive freezing gait. *Mov Disord* 23:449-451.
- Davis RB, Ounpuu S, Tyburski D, et al (1991). A gait analysis data collection and reduction technique. *Hum Mov Sci* 10:575-587.
- Dupre KB, Eskow KL, Negron G, et al (2007). The differential effects of 5-HT(1A) receptor stimulation on dopamine receptor-mediated abnormal involuntary movements and rotations in the primed hemiparkinsonian rat. *Brain Res* 1158:135-143.
- Matsuo H, Takashima H, Kishikawa M, et al (1991). Pure akinesia: an atypical manifestation of progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 54:397-400.
- Miyata S, Hamamura T, Yoshinaga J, et al (2001). Amelioration of frozen gait by tandospirone, a serotonin 1A agonist, in a patient with pure akinesia developing resistance to L-threo-3,4-dihydroxyphenylserine. *Clin Neuropharmacol* 24:232-234.
- Morgante F, Fasano A (2010). Improvement with duloxetine in primary progressive freezing gait. *Neurology* 75:2130-2132.
- Nutt JG, Bloem BR, Giladi N, et al (2011). Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol* 10:734-744.
- Ohno Y (2011). Therapeutic role of 5-HT1A receptors in the treatment of schizophrenia and Parkinson's disease. *CNS Neurosci Ther* 17:58-65.
- Rascol O, Fabre N, Brefel-Courbon C, et al (2001). The pharmacologic treatment of gait ignition failure. *Adv Neurol* 87:255-264.
- Williams DR, Holton JL, Strand K, et al (2007). Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. *Mov Disord* 22:2235-2241.
- Yamamoto M, Fujii S, Hatanaka Y (1997). Result of long-term administration of L-threo-3,4-dihydroxyphenylserine in patients with pure akinesia as an early symptom of progressive supranuclear palsy. *Clin Neuropharmacol* 20:371-373.
- Yoshikawa H, Oda Y, Sakajiri K, et al (1997). Pure akinesia manifested neuroleptic malignant syndrome: a clinical variant of progressive supranuclear palsy. *Acta Neuropathol* 93:306-309.