Neurol Sci (2014) 35:1615–1617
DOI 10.1007/s10072-014-1806-5

LETTER TO THE EDITOR

Insidious onset of Pisa syndrome after rasagiline therapy in a patient with Parkinson's disease

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Received: 3 March 2014 / Accepted: 15 April 2014 / Published online: 27 April 2014

Dear Editor,

Pisa Syndrome (PS) is clinically defined as a pronounced lateral flexion of the trunk (at least 10°), completely alleviated by passive mobilization or on lying supine [1]. PS has been described in patients with Parkinson's disease (PD) and, until now, few studies have pointed out its possible relationship with either clinical evolution of disease and medical treatment. Although pathophysiology of PS still remains largely unexplained a dopaminergic impairment seems to play a major role in its onset. Accordingly, in some PD patients, PS may be triggered by starting of dopamine blocking agents, or by changes in dopaminergic medication (e.g., start of a new drug, and dose increase or decrease of existing medication). In addition, non-dopaminergic medications might also contribute for developing PS such as neuroleptics, lithium carbonate, valproic acid, antidepressants, anti-emetics, and cholinesterase inhibitors [1].

Here we describe the case of a 73-year-old woman with a 5-year PD history, who showed, during an outpatient visit, a lateral flexion of the trunk on the left side (10° on spine X-ray). This abnormal posture was not present at a previous clinical examination performed 6 months before. At current visit, the patient had not awareness of the abnormal posture that was made evident by the physicians. The patient's past medical history was unremarkable and laboratory tests were normal. The patient denied assumption of neuroleptics, antiemetics, or cholinesterase inhibitors in the past years. Current treatment regimen was pramipexole (1.57 mg/day), levodopa (200 mg/day), and rasagiline (1 mg/day). Neurological examination showed a right hand rest tremor, a slight ipsilateral cogwheeling rigidity and bradykinesia, and a lateral flexion of the trunk to the left side (Fig. 1a). The patient underwent conventional EMG recordings in the paravertebral muscles at the thoracic-lumbar level T12-L1 (longissimus thoracis muscle) [2]. Recordings, that were performed with the patient in stance position and during voluntary right and left lateral trunk flexion, showed a pattern of a co-contraction of agonist and antagonist muscles compatible with dystonia of paraspinal muscles (Fig. 2). As PS may be related to dopaminergic therapy [3], and according to recent observations that PS might be reversed after rasagiline withdrawal [4], we hypothesized that the onset of PS in our patient could be linked to the last modification in the antiparkinsonian treatment, that occurred nearly 1 year before when rasagiline was added in order to manage motor worsening and wearing-off phenomena. Based on these considerations, rasagiline was withdrawn and, within 4 weeks, an improvement of posture was observed (Fig. 1b). An EMG examination performed 4 weeks after rasagiline withdrawal showed disappearance of the abnormal dystonic pattern (Fig. 2).

This report may further support the pathogenetic role of the dopaminergic therapy in the development of PS in PD, and its potential reversibility by optimizing the regimen of antiparkinsonian medications. It is noteworthy that, in our patient, the temporal interval between

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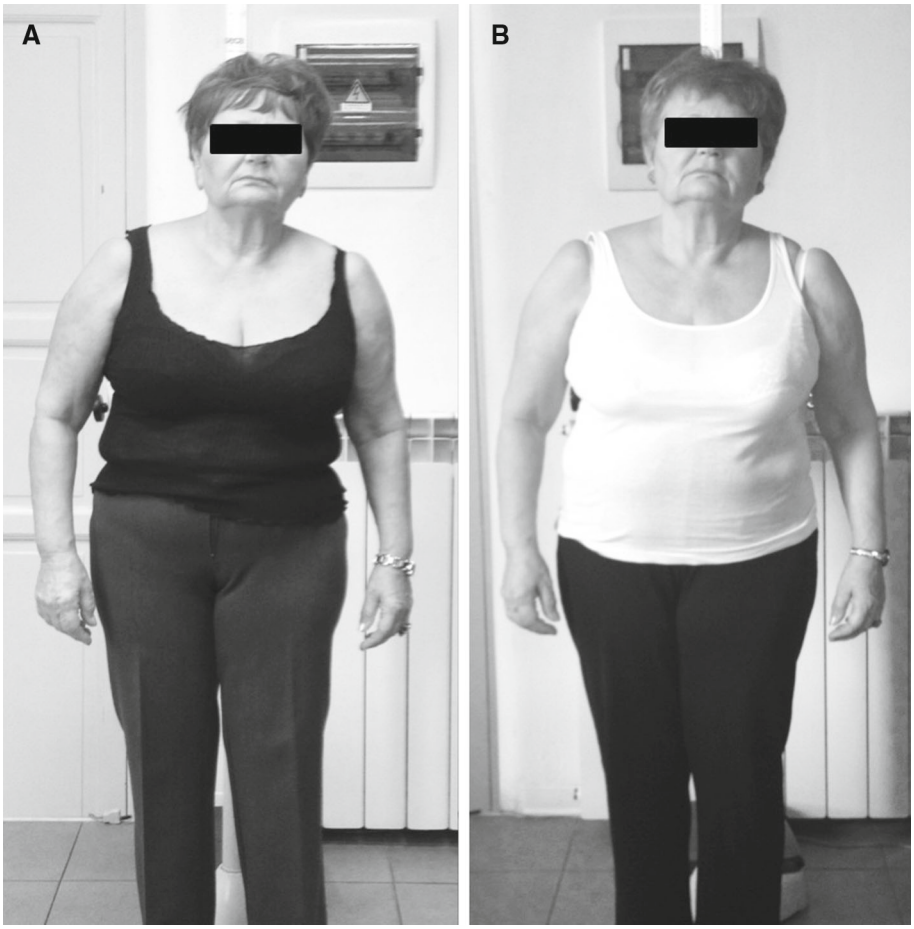

Fig. 1 The patient posture before (**a**) and 1-month after (**b**) rasagiline withdrawal. The postural bending (10°) observed before rasagiline discontinuation completely remitted 1-month after rasagiline withdrawal. Informed consent was received from the patient for publication of the image

rasagiline supplementation and PS appearance is quite longer than previously reported [4]. Indeed, the trunk deviation was not observed at an outpatient visit performed 6-months after rasagiline introduction, being recognized only 1-year after this therapeutic change. This might lead to consider rasagiline as a possible iatrogenic factor favoring the onset of PS also when patients are on a stable therapeutic regimen for a relatively long time period.

The mechanism by which rasagiline may precipitate PS in PD patients remains to be elucidated. The clinical effect of rasagiline mainly relies on the inhibition of the monoamine oxidase type B, leading to an increase in the dopamine extracellular levels at the striatal synapses. It is to note that although IMAO-B are widely prescribed in PD, only four cases of PS induced by rasagiline have been described in literature until now [4]. This suggests that the drug alone is probably not sufficient to induce the syndrome, but a combination of genetic and clinical PD characteristics might be needed [4]. On this regard, it has been suggested that PS may represent a complication of advanced PD in patients showing marked asymmetry of symptoms, and detectable hyperactivity of the paravertebral muscles on the less affected side, as we observed in our patient [5].

In conclusion, the case we describe supports a previous observation that PS may be related to the rasagiline treatment [4]. In particular, our observation suggests that even in the absence of a close temporal relationship between rasagiline introduction and PS onset, resolution of PS may be observed after rasagiline withdrawal. Finally we emphasize the importance to recognize the initial manifestations of PS in PD, before it evolves into a chronic variant with irreversible changes affecting muscles and bone structures.

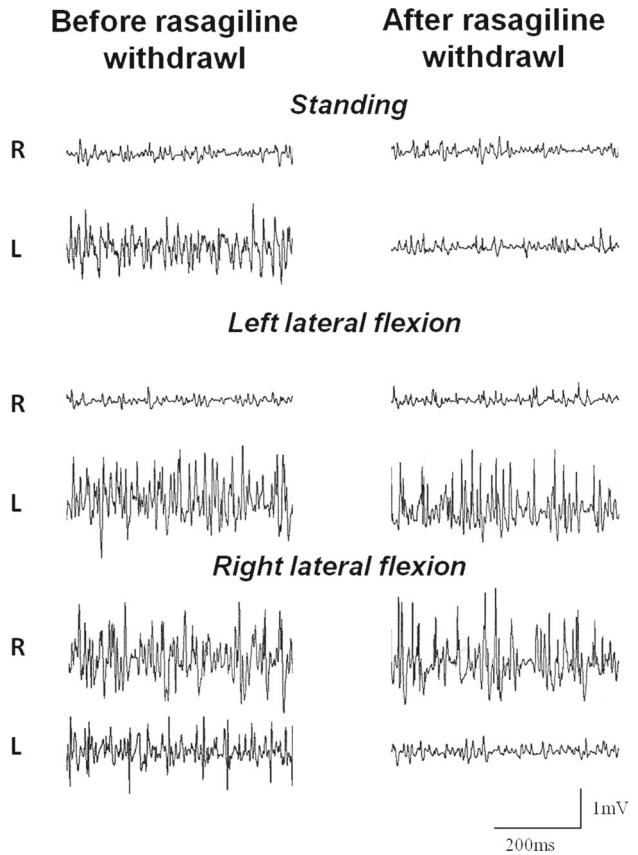

Fig. 2 EMG recordings of the right (*R*) and left (*L*) paravertebral muscles when patient in standing position, and during right and left lateral flexion of the trunk, before and after rasagiline withdrawal. Before rasagiline withdrawal: tonic and persistent bilateral EMG activity of the paraspinal muscles, markedly predominant on the left side, was recorded in the upright standing position. The EMG hyperactivity of the paraspinal muscles on the left side persisted during voluntary right lateral trunk flexion, when an increasing in the activity of the right paraspinal muscles was observed. The pattern of a co-contraction of agonist and antagonist muscles was compatible with dystonia of paraspinal muscles. After rasagiline withdrawal: hyperactivity of the left paravertebral muscles along with abnormal co-activation of left and right paravertebral muscles during right lateral flexion completely remitted 1-month after rasagiline treatment was discontinued. No evidence of myopathic or neuropathic abnormalities was observed

Conflict of interest The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Ethical standards All procedures were conducted according to the ethical standards of studies involving human subjects (declaration of Helsinki).

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