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Reversible Pisa Syndrome (Pleurothotonus) Due to the Cholinesterase Inhibitor Galantamine: Case Report

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Abstract: We report on a case of reversible Pisa syndrome developed after treatment with galantamine in a patient with Alzheimer's disease without previous exposure to neuroleptic or other cholinesterase inhibitors. Complete and persistent resolution of the syndrome was achieved several weeks after botulinum toxin type-A injection. © 2004 Movement Disorder Society

Key words: Pisa syndrome; galantamine; Alzheimer's disease

Pisa syndrome, or pleurothotonus, is a form of dystonia characterized by abnormal, sustained posturing, with flexion of the neck and head to one side, first described in 1972 by Ekbom and coworkers.[1] It has been reported primarily as a side effect of neuroleptic drugs[1–3] but, in some cases, appears to be triggered by anticholinergic medication (donepezil and rivastigmine) in patients with dementia of the Alzheimer's type[4,5] or multiple system atrophy.[6] We report on the development of Pisa syndrome in a patient with Alzheimer's disease taking the cholinesterase inhibitor galantamine.

Case Report

A 72-year-old Sardinian woman, presenting a progressive global intellectual deterioration (with a Mini-Mental State Examination[7] score of 21), was diagnosed with probable Alzheimer's disease according to NINCDS-ADRDA criteria.[8] The symptoms had started approximately 1 year earlier with short-term memory impairment and temporal–spatial disorientation. Heavy wandering was also a prominent clinical feature. The patient's medical history included a cardiomyopathy on a hypertensive basis treated with antihypertensive therapy (furosemide). There was no history of hallucination, depression, extrapyramidal disorders, or neuroleptic, vestibular, or antiemetic medication. Treatment with galantamine 4 mg twice daily was started. After 4 weeks of therapy, the patient slowly developed right laterocollis with slight right axial deviation (see Video, Segment 1). Two weeks later, the symptoms worsened with severe head and trunk right deviation and great difficulty in standing and walking. On examination, there was dystonic spasm of the right sternocleidomastoid, scalenus, trapezius, and paraspinal muscles. Laboratory tests, including complete blood count, serum electrolytes, blood urea nitrogen and creatinine, creatine kinase, liver function test, iron, and total iron binding capacity were within normal limits and a computed tomography scan of the brain and the cervical spinal cord was normal. The electromyographic study was unremarkable. Galantamine was suspended, and local and systemic therapy with muscle relaxant drugs were started without improvement.

The neurological symptoms remained unchanged and, 4 months later, injections of 500 UI of botulinum toxin type-A (BTX-A; Dysport Porton Downs, UK) in the right sternocleidomastoid, scalenus, trapezius, and paraspinal muscles were performed. Two days after the injection, the patient fell and broke her right femur but within a few weeks she showed a complete dissolution of the dystonia. Three months later (see Video, Segment 2), the patient had completely recovered from her leg fracture and no recurrence of truncal and head dystonia was observed. At present (1 year after onset of dystonic symptoms), neurological examination, with the exception of the cognitive problems that remain unchanged, can be considered as normal.

Discussion

We report on a case of reversible Pisa syndrome developed after treatment with galantamine in a patient with Alzheimer's disease without previous exposure to neuroleptic or other cholinesterase inhibitors. Although the pathophysiology of Pisa syndrome has not been completely established, an imbalance in cholinergic–dopaminergic central pathways, which are strategic in the regulation of axial muscle tone, has been claimed as a possible crucial factor in this type of dystonia.[9,10] This finding is supported mainly by the coexistence of a dopaminergic disorder in many patients with Pisa syndrome taking cholinesterase inhibitors and by the evidence of a clinical improvement when the cholinergic–dopaminergic balance has been restored.[9,10] Of interest, our patient pre-

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sented heavy wandering as a prominent clinical feature. Meguro and coworkers[11] demonstrated that, in Alzheimer's disease patients, the presence of wandering behaviour correlates with abnormalities of striatal dopamine metabolism. In our patient we can easily hypothesize a dopaminergic–cholinergic vulnerability as a predisposing factor.

In some cases of Pisa syndrome,[12,13] as in ours, the symptoms persist for a long time and the mere interruption of the cholinesterase inhibitor may not be effective for clinical recovery. In our patient, because of cognitive impairment that contraindicates the use of anticholinergic systemic drugs, we decided to perform local therapy with BTX-A. We observed the complete and persistent resolution of the syndrome some weeks after BTX-A injection.

We have no experimental evidence to exclude that our patient's improvement was coincidental and the natural history of the illness was a spontaneous improvement of symptoms. Nevertheless, we consider this possibility unlikely because in our case dystonia persisted for 4 months after galantamine had been stopped. We are not certain of the exact modality, but the BTX-A administration probably played a role by contributing to the restoration of the patient's cholinergic–dopaminergic balance. This reasoning is suggested by the patient's clinical features, the temporal profile of symptom resolution, and by the absence of recurrence.

Previous reports of Pisa syndrome induced by cholinesterase inhibitor medication relate symptoms to donepezil and rivastigmine.[4,5] To our knowledge, this is the first report after treatment with galantamine. In such patients, if dystonia persists after cholinesterase inhibitor has been withdrawn, and if anticholinergic drugs are not suitable owing to pre-existing cognitive impairment, the use of BTX-A might be considered.

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Legends to the Video

Segment 1. Before treatment, right laterocollis and mild trunk right deviation are seen. (Two weeks later, the symptoms worsened with severe head and trunk right deviation and great difficulty in standing and walking.)

Segment 2. After treatment, a clear improvement in head and trunk deviation is observed.

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Dominantly-Inherited Adult-Onset Leukodystrophy With Palatal Tremor Caused by a Mutation in the Glial Fibrillary Acidic Protein Gene

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Abstract: We report on a pedigree of dominantly-inherited, adult-onset Alexander disease caused by the glial fibrillary acidic protein (GFAP) gene mutation, R416W. This pedigree highlights the importance of genetic analysis of the GFAP gene in leukodystrophy with palatal tremor.

Key words: Alexander disease; GFAP; leukodystrophy; palatal tremor

Palatal tremor is usually symptomatic (SPT) and the lesion considered to lie within the dentato-olivary pathway, part of the Guillain-Mollaret triangle.[1] Less commonly, palatal tremor is idiopathic (essential palatal tremor; EPT); there is no evidence

A videotape accompanies this article.

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