

Worsened postural deformity in multiple-system atrophy patients with excessive dopaminergic treatment

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Abstract

Postural deformities like dropped head, camptocormia, and Pisa syndrome are seen in both Parkinson's disease and multiple-system atrophy (MSA). However, these features are relatively more common in MSA. These deformities may worsen during treatment and cause the patient distress. We report here two MSA patients. The first patient was a 53-year-old woman with severe bradykinesia, rigidity, and orthostatic hypotension developed dropped head after increasing her levodopa dose from 400 to 600 mg/day. This symptom improved when we reduced the levodopa dose back to 400 mg/day. The second was a 59-year-old woman with severe bradykinesia, rigidity, and urinary incontinence who showed putaminal atrophy on magnetic resonance imaging. After Pisa syndrome was observed at her last follow-up visit, we decreased the pramipexole dose from 4.5 to 3 mg, and she improved. In conclusion, postural deformities in MSA patients may worsen with higher doses of dopaminergic treatment, and decreasing the dose may be the treatment of choice in these patients.

INTRODUCTION

Multiple-system atrophy (MSA) is a neurodegenerative disorder characterized by Parkinsonian features, cerebellar ataxia, autonomic failure, urogenital dysfunction, and corticospinal disorders. Pathologically, it is considered an alpha synucleinopathy. Clinically, MSA is subdivided into MSA with parkinsonism (MSA-P) and MSA with cerebellar ataxia (MSA-C).¹ Although MSA-P patients may resemble idiopathic Parkinson's disease (PD) patients at first sight, they have an atypical clinical presentation, with rigorously defined autonomic failure and poor response of the parkinsonism to levodopa. Sometimes, other features are needed to make a diagnosis of MSA, such as postural deformities involving the neck and thoracolumbar spine causing disproportionate antecollis, dropped head, camptocormia, and Pisa syndrome.^{1,2}

These postural deformities can trouble the patient more than other parkinsonian features. Treatment strategies include adjusting the PD medication, botulinum toxin therapy, deep brain stimulation, and spinal deformity surgery.³ Sometimes, however, the PD medication itself may worsen postural deformities. For example, increased antecollis with dopamine agonists

has been reported in PD and MSA patients.^{4,5} We report two MSA patients with postural deformities whose symptoms were alleviated after levodopa dose decrease in the first and pramipexole dose reduction in the second patient.

CASE REPORTS

Patient 1

A 52-year-old woman who had been diagnosed with PD for 2 years consulted our movement disorders clinic complaining of severe bradykinesia, which rendered her unable to perform daily activities. She also complained of postural dizziness, which negatively affected her walking. She had been on 300 mg L-dopa-carbidopa-entacapone, 3 mg pramipexole, and 1 mg rasagiline treatment for one year with minimal benefit. Her neurological examination revealed a hypophonic voice and facial hypomimia. She had minimal antecollis, with severe bradykinesia and moderate rigidity (greater on the right than the left) but no resting tremor. She had no cerebellar or pyramidal signs. She had autonomic dysfunction (orthostatic hypotension with systolic and diastolic drops of 30 and 20 mmHg, respectively). She was cognitively impaired, with a Mini-Mental State Examination



Figure 1. Photographs of a 52 years old woman (Patient 1) with MSA who developed antecollis after levodopa dose increase. A) Prominent antecollis in an upright position. B) Marked improvement in antecollis after levodopa dose decrease.

(MMSE) score of 27. Her laboratory results were normal, and brain magnetic resonance imaging (MRI) did not show any abnormalities. First, we increased the levodopa-carbidopa-entacapone dose to 400 mg/day, but she did not improve, so we increased the dose to 600 mg/day. Fifteen days later, she returned complaining of severe neck flexion, which caused marked discomfort and walking difficulty. She had mild neck extension weakness in the sitting position but normal strength in the supine position (Figure 1). Furthermore, no improvement was seen in her parkinsonian symptoms. Electromyography (EMG) was performed to differentiate concomitant myopathy. During concentric needle EMG evaluation abnormal spontaneous activity or dystonic activity were not detected from the right first dorsal interosseous, right biceps brachii, left deltoid, bilateral cervical paraspinal (C3-5-7), right anterior tibial and left medial vastus muscles. During voluntary contractions of these muscles, myogenic motor unit potential activities were also

not detected. Nerve conduction evaluation of the patient was within normal limits.

Owing to the poor levodopa response, severe orthostatic hypotension, and disproportionate antecollis, we diagnosed the patient with probable MSA. We decreased the levodopa dose to 400 mg, and her antecollis improved markedly within few days. Her final treatment was 400 mg levodopa/day, 3.75 mg pramipexole, and 1 mg rasagiline. She had some benefit from this treatment.

Patient 2

In 2008, a 55-year-old woman developed progressive limb bradykinesia beginning on her right side. Her symptoms worsened progressively over one year. Her speech had become softer and dysarthric, and her family members had difficulty understanding her. In 2009, she was diagnosed with PD and started on pramipexole and rasagiline. After a small improvement, her bradykinesia worsened, and levodopa was

added to the treatment gradually. In 2010, she was taking 400 mg levodopa-carbidopa/day, 4.5 mg pramipexole, and 1 mg rasagiline. During this period, she complained of dizziness when standing up and urinary incontinence. An urologist diagnosed unexplained urinary incontinence due to incomplete bladder emptying. In 2011, her walking difficulty and bradykinesia had increased. Consequently, the levodopa dose was increased to 1 g/day for one year, but the initial beneficial effect was lost. In 2012, she was admitted to hospital with severe forward and lateral flexion. The abnormal position of the spine recovered during supine position. The patient was diagnosed as Pisa syndrome. The Pisa syndrome in this patient developed over approximately 3-4 months. During this time, she was unable to walk without assistance. Her neurological examination revealed asymmetric, severe bradykinesia (right more than left side). She also had brisk deep-tendon reflexes and a positive Babinski sign on the right. No cerebellar symptoms were observed. She was normal cognitively, with a MMSE score of 30. Although she complained of postural unsteadiness, her systolic and diastolic pressures did not change from lying to standing position. Cranial MRI showed marked putaminal hypointensity and a hyperintense rim (T2-weighted images, 1.5 T) at the lateral edge of the left putamen (Figure 2). Due to the rapid progression, poor response

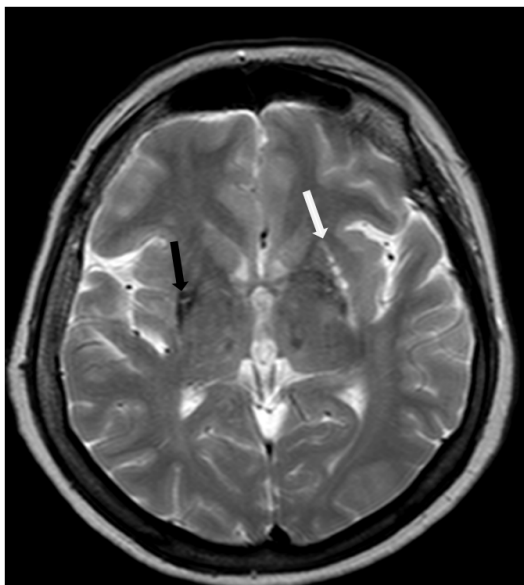


Figure 2. MRI scans (T2 weighted image, 1.5 T), Patient 2. The hypointense putamen (black arrow) with left lateral hyperintense rim (white arrow).

to levodopa, urinary incontinence, severe Pisa syndrome, and atrophy of the putamen on MRI, we diagnosed her with MSA. Because excessive dopaminergic treatment can cause worsening of Pisa syndrome, we decreased the pramipexole from 4.5 to 3 mg. She improved within two weeks.

DISCUSSION

Postural deformities affecting the spine are seen in PD and atypical parkinsonism. When the cervical spine is affected, it is called antecollis or dropped head; whereas if the thoracolumbar spine is affected, the term bent spine, Pisa syndrome, or camptocormia is used.^{3,6} Although these postural deformities may be seen in up to one third of PD patients, they are supporting features of MSA¹ and help in making the diagnosis of MSA when they are combined with other criteria for MSA. Both our patients met the criteria of probable MSA, with the spine deformities as supporting features. The pathogenesis of postural deformities in extrapyramidal disorders is heterogeneous. Doherty *et al.* suggest that pathological changes in the basal ganglia or affiliated pathways, proprioceptive disintegration, loss of postural reflexes, rigidity, and dystonia are important in the pathogenesis. Dystonic and myopathic mechanisms are also thought to be important.⁷ Some authors attribute these postural deformities to dystonic contractions of the paraspinal and cervical muscles.^{2,7} Dystonia in MSA has been discussed in many case reports and clinical studies.⁸⁻¹⁰ One study found that dystonia may be seen more in untreated MSA-P as compared with PD; and levodopa-induced dystonia, especially in the craniocervical region, was associated with putaminal pathology.⁸ Putamen is thought to be the site most affected in dystonia, and atrophy and hypometabolism of the putamen are seen in MSA, which may be related to these deformities seen in the illness. Our second patient showed putaminal atrophy on MRI (Figure 2).

The treatment approaches in patients with postural deformities are difficult, and commonly discussed separately according to the affected site. Levodopa has been tried in the treatment of dropped head or antecollis, but the results are inconsistent. Muscle relaxants, botulinum toxin, and physiotherapy are possible treatments.^{3,11} Camptocormia is generally thought to be unresponsive to levodopa. Anticholinergic drugs, botulinum toxin injection, deep brain stimulation (DBS), and spinal surgery may be considered.

Pisa syndrome, especially in its early phases, is a form of axial dyskinesia. Dopaminergic modulation may be tried. Anticholinergic drugs, clozapine, and botulinum toxin are other treatment approaches. DBS and spinal surgery have also been reported to be beneficial in some patients.³ However, the treatment itself may cause these symptoms to worsen. For example, dopamine agonists, especially pramipexole, have been reported to worsen antecollis.^{5,12} Our first patient developed a dropped head after increasing her levodopa dosage, and the symptoms improved after decreasing the dose (Figure 1). Some studies have reported worsening caused by dopamine agonists^{5,12,13} but not with levodopa. Most studies have found levodopa to be effective for treating antecollis.³ However, this benefit is not uniform, as some patients benefit from levodopa, whereas others do not.¹³ Additionally, most of these studies were in PD patients, and the worsening seen in our patient may indicate that MSA patients are more prone to dystonic complications with levodopa treatment.⁸ Additionally, our second patient developed Pisa syndrome on high-dose dopaminergic treatment, and her symptoms improved after we decreased the pramipexole dose from 4.5 to 3 mg. Some reports have identified worsening Pisa syndrome with different dopaminergic treatments, including rasagiline, pergolide, and levodopa carbidopa-entacapone.^{7,14} Cannas *et al.* also reported that 7 out of 8 patients developed Pisa syndrome after increasing the dopaminergic dose, while decreasing the dose caused the same phenomenon in one patient.¹⁵ These authors suggested that adjusting the dopaminergic treatment may avoid a chronic irreversible variant in patients with Pisa syndrome.¹⁵ These studies suggest that worsening of this postural deformity is related to excessive dopaminergic treatment. The improvement in our patients' symptoms on reducing the dopamine agonist dose supports this hypothesis.

In conclusion, postural deformities such as antecollis, camptocormia, and Pisa syndrome are common in MSA patients. These symptoms may be related to the disease itself, although sometimes medications may worsen the postural deformities, especially the dopaminergic drugs.

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