Levodopa-induced Dyskinesias in Spinocerebellar Ataxia Type 2

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Introduction

SCA2 is an inherited, autosomal dominant neurodegenerative disorder caused by an expanded trinucleotide repeat (>35 CAG) in the ATXN2 gene on chromosome 12q24.1. SCA2 typically manifests with progressive gait ataxia and dysarthria—similar to other spinocerebellar ataxias—but additional findings may include ophthalmoplegia, action tremor, dystonia, pyramidal tract signs, fasciculations, peripheral neuropathy, autonomic failure, cognitive dysfunction and parkinsonism.[1]

CASE REPORT

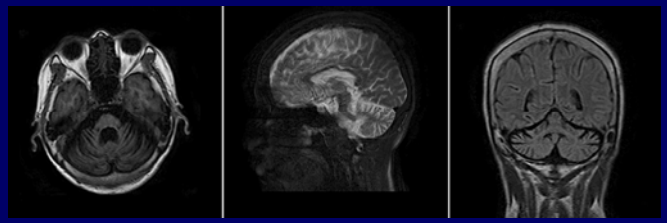
This 56-year-old Chinese woman presented to our clinic at age 46 with a 2-year history of progressive instability and impaired manual dexterity. Her initial physical examination revealed broad-based gait, mild dysmetria and facial fasciculations, later complicated by parkinsonian rigidity and bradykinesia.

Her family history was notable for similar symptoms—predominantly ataxia—in 3 of her 5 siblings. MRI showed brainstem and cerebellar atrophy (Figure 1), and genetic testing confirmed spinocerebellar ataxia type 2 (SCA2) with 39 CAG repeats.

The patient was initiated on carbidopa-levodopa, which meaningfully lessened her parkinsonism; however, within three years she began to demonstrate wearing-off phenomena. After 6-7 years of treatment, she developed severe motor and nonmotor fluctuations, manifesting as peak-dose levodopa-induced dyskinesias (LID) with hypomania in the "on" state (Figure 2), alternating with off-state depression.

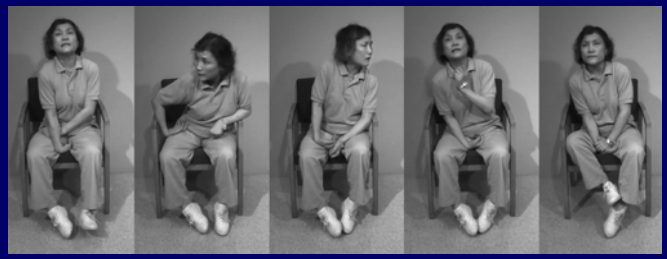
Lower doses of levodopa provided in closer intervals produced some improvement in her LID but resulted in intolerable "off" symptoms. Accordingly, the patient elected to return to higher doses despite the LID. Deep brain stimulation has not been feasible because of cognitive deficits.

Figure 1



Axial T1, sagittal T2 and coronal FLAIR MRI of the brain (left to right) demonstrating brainstem and cerebellar atrophy

Figure 2



Sequential still images extracted from video showing the spectrum of dyskinetic movements over a 15 second period

References

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Discussion

Over the past decade, increasing evidence suggests that some patients with SCA2 present with levodopa-responsive parkinsonism, particularly when CAA trinucleotides interrupt CAG tracts,[2] and a minority of patients develop mild LID.[1]

In contrast to idiopathic Parkinson's disease (PD), LID are unusual in atypical parkinsonian syndromes, with the exception of multiple system atrophy (MSA). MSA is typically associated with a characteristic pattern of levodopa-induced facial dystonia, which may occur in the absence of a therapeutic effect, rather than the choreatic and stereotypic trunk and limb dyskinesias usually seen in PD. Thus, in patients who demonstrate a robust and sustained (>5-year) response to levodopa, the development of levodopa-induced limb chorea generally solidifies the clinical diagnosis of PD.[3,4] Levodopa-responsive parkinsonism has been noted in other spinocerebellar ataxias, notably SCA3 and -6, yet LID have not been reported in those disorders.[5-7]

The pathophysiology of LID is incompletely understood. Degeneration of the substantia nigra appears to be an important precondition, since patients without nigrostriatal dopaminergic depletion are less vulnerable to LID, even when treated with large doses of levodopa.[8] SCA2 affects multiple brain regions, including the cerebellar cortex and various brainstem nuclei; however, like PD, SCA2 is associated with both nigral degeneration on neuropathology and dopaminergic nerve terminal loss on functional neuroimaging.[2]

The development of LID in patients with SCA2 raises both diagnostic and treatment implications. Our patient has findings that are inconsistent with the diagnosis of idiopathic PD (ataxia, fasciculations and familial occurrence of disease); however, some patients with SCA2-related parkinsonism are clinically indistinguishable from those with PD,[2] highlighting the etiopathogenic heterogeneity of the PD phenotype and complexities in our current diagnostic criteria for PD. LID were mild in previously reported patients with SCA2-related parkinsonism, but have been disabling in our patient. Since early use of a dopamine agonist rather than levodopa forestalls the development of LID in PD patients,[8,9] a similar strategy may be warranted in patients with SCA2.