CASE REPORT

Dramatic levodopa responsiveness of dystonia in a sporadic case of spinocerebellar ataxia type 3

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A genetically confirmed case of spinocerebellar ataxia type 3 (SCA 3), presenting with disabling foot dystonia, peripheral neuropathy, and minimal cerebellar signs is reported. The dystonia improved dramatically with levodopa treatment in the absence of additional parkinsonian feature. A trial of levodopa for dystonia in SCA 3 may be of therapeutic benefit, at least in the initial stage of the disease.

Spinocerebellar ataxia type 3 (SCA 3), also known as Machado-Joseph disease, is characterised by puzzling clinical heterogeneity. Four subphenotypes have been described so far, based on the predominant clinical manifestations that include cerebellar, pyramidal, extrapyramidal, and peripheral neuropathic features, and age of onset.¹ Extrapyramidal features in SCA 3 include parkinsonism, dystonia, postural tremor, myoclonus, and chorea.² It has recently been reported that levodopa and other dopamine agonists have elicited a therapeutic response in a phenotype that resembles Parkinson's disease.^{3–5} Rarely dystonia can be the predominant feature in SCA 3.^{1 6–8} However, a meaningful response to levodopa in such phenotype has not been reported. Here, we report a sporadic case of SCA 3 presenting with dramatic levodopa responsive foot dystonia as the salient feature.

CASE REPORT

A 38 year old man from South India developed painful, involuntary curling of his toes and plantar flexion of the feet with asymmetric onset, resulting in gait impairment. The dystonia showed neither diurnal fluctuation nor sleep

benefit. Two years later, empirical treatment with levodopa/carbidopa 330 mg/day (110 mg three times a day) produced a dramatic improvement of the foot posture and facilitated easy ambulation. He had no appendicular ataxia, dysarthria, resting limb tremor, bradykinesia for activities of daily living, appendicular or axial rigidity, facial grimacing, nuchal or truncal dystonia, tics, self mutilation, or cognitive impairment. His family history disclosed no similar symptoms in his close relatives.

On examination at age 42, ocular saccades, pursuits, and optokinetic nystagmus were normal. Lingual fasciculation, chin quivering, and global hyporeflexia were noted in the absence of limb rigidity, wasting, weakness, or objective sensory impairment. When observed off the medication, he was incapacitated by the painful foot and toe dystonia noted earlier, especially on awakening in the morning. He could barely manage to walk one or two steps. One hour after taking 110 mg of levodopa/carbidopa, he had no foot dystonia either resting or when moving and could ambulate easily without any assistance. He could also walk on his toes and heels; the improvement lasted for 3–4 hours. There was minimal tandem gait ataxia noticed during this period, but no postural instability.

Diagnostic testing disclosed normal findings on haematology and serum chemistry. A peripheral smear for acanthocytes and slit lamp examination for Kayser-Fleischer ring were negative. Nerve conduction studies showed mild axonal motor sensory neuropathy in his lower limbs; the patient refused to undergo detailed electromyographic examination. Cranial magnetic resonance imaging demonstrated mild cerebellar atrophy and unremarkable basal ganglia structure (fig 1). Genetic study of CAG repeat of SCA 3 gene on chromosome 14q was carried out using polymerase chain

Figure 1 Cranial magnetic resonance image showing cerebellar atrophy and apparently normal basal ganglia. (A) Axial T1WI image at pontine level, (B) mid-sagittal T1WI image, and (C) axial T2WI image at level of basal ganglia.

Table 1 Extrapyrimal presentation of SCA 3

Confounding phenotypes	Authors and reference
Typical dopa responsive parkinsonism	Gwinn-Hardy <i>et al</i> ³ Schols <i>et al</i> ¹² Buhmann <i>et al</i> ⁴
Atypical levodopa responsive parkinsonism	Tuite <i>et al</i> ⁵ Subramony and Currier ¹³
Dystonia	Munchau <i>et al</i> ¹ Lange <i>et al</i> ⁷

reaction primer. On analysis, it was found that the CAG repeat units among alleles were 26 ± 3 and 67 ± 3 , indicating a mutated allele with expanded CAG repeat.

DISCUSSION

This sporadic case, with SCA 3 gene mutation, presented with the combined syndrome of painful, disabling foot dystonia, peripheral neuropathy, and minimal cerebellar dysfunction. Interestingly, there was a dramatic improvement of the dystonia with levodopa treatment in the absence of florid symptoms or signs of parkinsonian phenotype. To the best of our knowledge, a meaningful response of dystonia in SCA 3 to levodopa has not previously been reported. In a family of African origin presenting with a parkinsonian phenotype of SCA 3, one of the subjects, a 51 year old woman (No 3018), was noted to have left foot dystonia, especially in the morning.³ However, her response to levodopa treatment was not known. In a Ghanaian patient with Machado-Joseph disease, the manifestation of dopamine agonist responsive parkinsonian phenotype was associated with levodopa induced motor fluctuation (in the form of freezing and wearing off phenomenon), while dystonia was not the predominant feature.⁴ Severe generalised dystonia was the presenting feature in a German patient reported by Munchau *et al*.¹ Like the case reported here, he was heterozygous for SCA 3 gene mutation, but showed only a mild improvement of his dystonia after starting levodopa. The response lasted for two weeks only, unlike the significant benefit seen for two years in our patient. In a study by Jardim and colleagues, dystonia in SCA 3 was correlated with a higher mean CAG repeat length, varying from 69 to 85.⁹ Shinotoh *et al* observed dysfunction of the nigrostriatal dopaminergic system in a

Box 1: Syndromes characterised by levodopa responsive dystonia

- Dopa responsive dystonia:
  - Autosomal dominant: guanosine triphosphate cyclohydrolase 1 deficiency.
  - Autosomal recessive: tyrosine hydroxylase deficiency.
- Familial Parkinson's disease:
  - PARK gene mutation.
- Advanced idiopathic Parkinson's disease:
  - "Off" dystonia (on levodopa).
- Spinocerebellar ataxia type 3:
  - (Present case)

Learning points

- SCA 3 is characterised by wide range of clinical manifestations, including four subphenotypes.
- SCA 3 can present as levodopa responsive dystonia phenotype.
- Awareness of the atypical presentations of SCA3 has diagnostic and therapeutic relevance.

patient with Machado-Joseph disease with moderate dystonia, using 6 fluoro-L-dopa positron emission tomography.¹⁰

There are a few clinical syndromes characterised by dystonia that are responsive to levodopa (box 1).

The onset of dystonia in the fourth decade, the absence of diurnal fluctuation and sleep benefit distinguish the present case from dopa responsive dystonia. In some patients "off" dystonia is actually the presenting sign of Parkinson's disease, with foot posturing on awakening being the most common symptom.¹¹ This dystonia can create significant distress for patients and respond to dopaminergic agents. The dystonia in our patient, though lacking the parkinsonian phenotype, mimicked the features encountered in "off" dystonia of advanced Parkinson's disease. Before the availability of genetic tests for autosomal dominant cerebellar ataxia, the phenotypic classification required the presence of ataxia as an initial or predominant clinical feature. However recent reports indicate the occurrence of movement disorders as the predominant or presenting feature, overshadowing ataxia in SCA 3 (table 1). In such a scenario, ordering the appropriate genetic test remains a diagnostic challenge. When encountered in standard neurological practice, these patients would receive a diagnosis of Parkinson's disease, multisystem atrophy, and primary dystonia respectively. Awareness of these atypical clinical presentations and observation of intrafamilial phenotypic variability among members of the same family may help diagnose the appropriate genetic disorder. This also has significant relevance during genetic counselling.

In the light of SCA 3/Machado-Joseph disease presenting as levodopa responsive parkinsonian and dystonic phenotypes (as evident in our case), a therapeutic trial of levodopa may be considered for dystonia (even in the absence of parkinsonian feature), at least in the initial stage of the disease. In the near future, further genetic and functional neuroimaging studies may throw more light on the diverse clinical manifestations of this degenerative disorder and provide the scientific basis for anticipating levodopa responsiveness of the extrapyramidal features.

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