Broadening the Phenotype of Childhood-Onset Dopa-Responsive Dystonia

Elijah C. Chaila, MRCPI; Dominick J. H. McCabe, PhD, MRCPI; Norman Delanty, FRCPI; Danny J. Costello, MRCPI; Raymond P. Murphy, FRCPI

Background: Dopa-responsive dystonia (DRD) may cause early-onset dystonia, with extrapyramidal or pyramidal tract dysfunction.

Objective: To broaden the phenotype of DRD.

Setting: Tertiary referral university hospital.

Patients: We describe 4 female siblings with genetically confirmed DRD, 3 of whom presented with "unsteadiness" and 1 with scoliosis. All had dystonia and pyramidal tract signs, 3 had additional extrapyramidal features (resting tremor, bradykinesia, or rigidity), and at least 2 had definite signs of cerebellar dysfunction.

Main Outcome Measures: The subjective response to treatment with 62.5 mg of a combination product of levodopa and carbidopa 3 times daily was assessed at both 6- and 12-month follow-up visits with the 7-item Patient's Global Impression of Change scale as very much improved, much improved, a little improved, no different, a little worse, much worse, or very much worse.

Results: All patients showed a good response to levodopa therapy 41 to 49 years after symptom onset.

Conclusion: Cerebellar signs may be observed in patients with DRD and may improve in response to levodopa.

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One important subgroup of patients with dystonia responds to levodopa therapy.1 We describe 4 family members who were initially assessed as part of a research study on patients with a prior clinical diagnosis of Friedreich ataxia or an unclassified progressive ataxic syndrome.2 Although each family member had at least mild cerebellar signs, none fulfilled the Harding clinical diagnostic criteria for Friedreich ataxia, and the results of polymerase chain reaction analysis for a GAA trinucleotide repeat expansion were negative.2 Further assessment established a diagnosis of dopa-responsive dystonia (DRD) in the fifth and sixth decades.

PATIENT 1

Patient 1 (sibling II-2 in the Figure) was a 55-year-old right-handed woman who was the eldest of the 4 affected siblings. She initially presented with unsteadiness at the age of 6 years, with in-turning of the left foot, which led to occasional falls while walking. She also experienced intermittent involuntary flexor posturing of the left wrist. Her symptoms were maximal in the evening, exacerbated by fatigue or stress, and more pronounced during her men-""
cigarettes per day and consumed moderate amounts of alcohol.

Neurologic examination revealed mild horizontal gaze–evoked nystagmus, mild dysarthria, right leg dystonia, an asymmetric spastic quadriparesis with bilateral extensor plantar responses, mild upper and lower limb incoordination, and moderate gait ataxia (Table).

### Table. Clinical Characteristics of 4 Affected Siblings

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoliosis</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pes cavus (right and left)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Horizontal gaze–evoked nystagmus</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Smooth pursuit eye movements</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Brisk jaw jerk</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Mild conductive</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Torticollis</td>
<td>No</td>
<td>No</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Mild</td>
<td>No</td>
<td>Mild</td>
<td>No</td>
</tr>
<tr>
<td>Limb rigidity</td>
<td>No</td>
<td>Mild in left arm and leg</td>
<td>Mild right &gt; left upper and lower limbs</td>
<td>Milder rigidity in lower limbs</td>
</tr>
<tr>
<td>Limb spasticity</td>
<td>Mild in upper limbs, moderate in lower limbs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pyramidal weakness</td>
<td>Mild in lower limbs</td>
<td>Mild in lower limbs</td>
<td>Moderate in lower limbs</td>
<td>Moderate in lower limbs</td>
</tr>
<tr>
<td>Upper limb incoordination</td>
<td>Mild</td>
<td>No</td>
<td>Mild and upper limb postural tremor</td>
<td>No</td>
</tr>
<tr>
<td>Lower limb incoordination</td>
<td>Mild</td>
<td>No</td>
<td>No, dystonic right foot</td>
<td>No</td>
</tr>
<tr>
<td>Ataxia of gait</td>
<td>Moderate</td>
<td>No</td>
<td>Moderate</td>
<td>No, bradykinetic and dystonic legs</td>
</tr>
<tr>
<td>Upper limb reflexes</td>
<td>Normal</td>
<td>Normal</td>
<td>Brisk</td>
<td>Normal</td>
</tr>
<tr>
<td>Lower limb reflexes</td>
<td>Brisk</td>
<td>Brisk knee jerks</td>
<td>Brisk</td>
<td>Normal</td>
</tr>
<tr>
<td>Right and left plantar responses</td>
<td>Extensor</td>
<td>Extensor</td>
<td>Extensor</td>
<td>Flexor</td>
</tr>
<tr>
<td>Sensory testing</td>
<td>Impaired distal vibration sensation in legs</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Dystonic posturing</td>
<td>Right foot and toes, worse with exercise</td>
<td>Right foot only on walking</td>
<td>Right foot, worse with foot tapping</td>
<td>Arms and legs, leg dystonia worse with walking</td>
</tr>
<tr>
<td>Additional extrapyramidal signs</td>
<td>No</td>
<td>Bradykinesia and decrement of fine finger movements</td>
<td>Bradykinesia and decrement of fine finger movements</td>
<td>Moderate upper limb and mild lower limb resting tremor</td>
</tr>
</tbody>
</table>

**PATIENT 2**

Patient 2 (sibling II-4 in the Figure) was a 53-year-old right-handed woman who initially presented with scoliosis at the age of 7 years. She also noted gait difficulties secondary to in-turning of the right foot after prolonged exercise and toward the end of the day, and she experienced cramping of her right hand with prolonged writing. At the age of 10 years, she developed discomfort and involuntary right lateral neck flexion, occasionally relieved by touching the right lower part of the face. Her symptoms were minimal in the morning and exacerbated by stress and tiredness. Her right foot symptoms increased during the early teenage years and stabilized after leaving school at the age of 13 years, but her neck discomfort and deviation gradually increased over time. She was a former smoker who rarely consumed alcohol. She was undergoing treatment with 5 mg/d of diazepam, 500 mg of naproxen sodium twice daily, and loperamide hydrochloride as needed for irritable bowel syndrome.

Neurologic examination revealed mild horizontal gaze–evoked nystagmus, right foot dystonia, and left upper and lower limb rigidity. She also had mild bilateral lower limb pyramidal signs with bilateral extensor plantar responses, but limb coordination was normal (Table).

**PATIENT 3**

Patient 3 (sibling II-5 in the Figure) was a 51-year-old right-handed woman who also presented at the age of 7 years with unsteadiness. She was symptom free in the morning but had weakness and spasmodic in-turning of...
the right foot that occurred after exercise and increased as the day progressed. More recently, she had noted involuntary neck deviation to the right. She was independently mobile, although she had fallen intermittently because of her right foot symptoms. She was taking 2 mg of diazepam twice daily.

Neurologic examination revealed mild horizontal gaze-evoked nystagmus with interrupted pursuit eye movements, an absent gag reflex, and mild dysarthria. She had right foot dystonia with asymmetric rigidity and pyramidal weakness of the upper and lower limbs, bilateral brisk reflexes, and extensor plantar responses. The patient also had a mild postural tremor of both hands with mild incoordination of all 4 limbs and moderate gait ataxia (Table).

PATIENT 4

Patient 4 (sibling II-7 in the Figure) was a 48-year-old right-handed woman who developed unsteadiness while walking at 7 years of age when her left foot began to turn inward and downward and both legs felt slightly weak. She noted clumsiness of both upper limbs at the age of 9 years. Between the ages of 10 and 11 years, she developed an asymmetric upper and lower limb resting tremor, with intermittent spasms of the left arm and leg, and her left hand and foot tired easily. Her mobility gradually deteriorated so that she needed assistance to walk at the age of 14 years, and by the age of 40 years, she could only walk short distances and required a wheelchair for longer distances. She was undergoing treatment with cimetidine, 400 mg 2 times daily, spironolactone, 25 mg daily, and clobazam, 10 mg 3 times daily.

Neurologic examination revealed mild horizontal gaze-evoked nystagmus, upper and lower limb dystonia, mild upper limb cogwheel rigidity, and bilateral lower limb rigidity, with moderate lower limb pyramidal signs. Limb coordination was normal, but heel-to-toe walking was impossible because of bilateral lower limb dystonia (Table).

RESULTS

The results of genetic analysis for DYT1, spinocerebellar ataxia (SCA) 1, SCA2, SCA3, and SCA6 mutations were negative in all patients. Anti-glutamic acid decarboxylase antibodies were weakly positive in patient 3 but not detected in the other siblings.

On the basis of the history and clinical findings, a diagnosis of DRD was made, and all patients were initially prescribed 62.5 mg of a combination product of levodopa and carbidopa 3 times daily while awaiting the results of further genetic screening. This subsequently revealed a mutation in the coding region of the guanosine triphosphate cyclohydrolase 1 (GTPCH1) gene on chromosome 14q11-14q24.3,4 Levodopa-carbidopa maintenance doses between 375 and 675 mg/d were required to achieve adequate symptomatic relief.

The subjective response to treatment was assessed at both 6- and 12-month follow-up visits with the 7-Item Patient’s Global Impression of Change Scale as very much improved, much improved, a little improved, no different, a little worse, much worse, or very much worse.4 At both time points, patient 2 felt that she had much improved, and her 3 siblings rated themselves as very much improved. None experienced treatment-related adverse effects. Patient 1 was able to see her toenails as her toes straightened. The neck discomfort resolved, and the lateral flexor was no longer required a wheelchair. Clinical examination revealed a marked improvement in dystonic and parkinsonian features, mobility, and gait ataxia. The nystagmus completely resolved in patients 1 and 3 and improved in patients 2 and 4. The hyperreflexia decreased, and the plantar responses became flexor within 6 to 12 months of treatment in the patients in whom these signs were initially present.

Dopa-responsive dystonia is most commonly inherited in an autosomal dominant manner and caused by a mutation in the gene encoding for the enzyme GTPCH1, which catalyzes the rate-limiting step in the synthesis of tetrahydrobiopterin.5 Dopa-responsive dystonia is characterized by childhood-onset dystonia, which may be worse in the evening and after exercise and which responds well to levodopa.6 Patients may have additional pyramidal and extrapyramidal signs.

In addition to the classic signs of dystonia and pyramidal tract dysfunction, with or without additional extrapyramidal signs, all 4 affected siblings had gaze-evoked nystagmus, and 2 had definite upper and lower limb incoordination consistent with cerebellar dysfunction. These data broaden the phenotype of DRD to include clinical features of cerebellar dysfunction or at least dysfunction of cerebellar connection circuits. We suggest that a diagnosis of DRD should be considered in patients with a presumed early-onset ataxic syndrome, especially in the presence of additional clinical features of DRD, when initial screening test results for other more common hereditary ataxic syndromes are negative.

Intrafamilial phenotypic variability has been described in DRD, even between monozygotic twins,7 and our data confirm that some siblings within affected families may have an ataxic phenotype, whereas others may not. Therefore, the presence of an ataxic phenotype in some affected family members with an apparent autosomal dominant inherited dystonic syndrome should not detract from genetic testing for DRD. The cause of intrafamilial phenotypic variability in DRD is undetermined, but other authors have speculated on potential responsible mechanisms.7

One affected sibling (patient 3) had a low serum anti-glutamic acid decarboxylase antibody titer, which may be associated with a cerebellar syndrome. However, the response to levodopa in this case led to the firm conclusion that these antibodies were not pathogenic.9

Some patients with autosomal dominant inherited spinocerebellar ataxic syndromes, especially those with
SCA3, may have other dystonic and extrapyramidal features in addition to pyramidal and cerebellar signs. Wilder-Smith et al recently described 2 Chinese first-degree relatives with SCA3, at least 1 of whom experienced a marked reduction in lower limb dystonia with levodopa. However, the CAG repeat number in these patients was low (59 repeats; reference range, 13-41), and they underwent screening for DRD with only a phenylalanine loading test, which may miss a significant proportion of patients with DRD. Jr Dysotnia has also been reported in patients with Friedreich ataxia, but it appears to affect the upper limbs more commonly than the lower limbs. Jr The diurnal fluctuation of dystonic symptoms that predominantly affect the lower limbs should raise the suspicion of DRD in patients who have been labeled as having atypical Friedreich ataxia. This is particularly important in presumed compound heterozygous patients in whom a GAA trinucleotide repeat expansion has been identified on only 1 arm of chromosome 9q and in whom there was believed to be an undetected mutation on the other allele. It may be worth screening some of these patients for DRD and considering a levodopa trial.

In keeping with previous reports, all affected siblings exhibited a subjective and objective improvement in their clinical features of extrapyramidal and pyramidal tract dysfunction in response to levodopa therapy, despite a delay in accurate diagnosis of between 41 and 49 years. This article illustrates that cerebellar dysfunction in DRD may improve in response to delayed levodopa therapy.

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Correspondence: Raymond P. Murphy, FRCPI, Department of Neurology, The Adelaide and Meath Hospital, incorporating the National Children's Hospital, Tallaght, Dublin 24, Ireland (Raymond.Murphy@amnch.ie).

Author Contributions: Study concept and design: Chaila, McCabe, Delanty, and Murphy. Acquisition of data: Chaila, McCabe, Delanty, Costello, and Murphy. Analysis and interpretation of data: Chaila, McCabe, Delanty, Costello, and Murphy. Drafting of the manuscript: Chaila. Critical revision of the manuscript for important intellectual content: Chaila, McCabe, Delanty, Costello, and Murphy. Administrative, technical, and material support: Chaila, McCabe, Delanty, and Costello. Study supervision: McCabe, Delanty, and Murphy.

REFERENCES