LETTER TO THE EDITOR

Diagnosing Unusual Presentations of Dopa-Responsive Conditions: Thinking on your Feet

Keywords: Dopa-responsive, Foot dystonia, Tremor

The classical description of dopa-responsive dystonia (DRD) was first given by Segawa et al in 1972. They described two important features of this disorder, namely marked diurnal fluctuations and remarkable response to levodopa. Since then, several disorders have been grouped under this broad term of “DRD” with phenotypic and genotypic heterogeneity but with the unifying feature of levodopa responsivity. We hereby highlight two cases whose phenotypic presentations raised the possibility of a dopa-responsive condition.

A 57-year-old female presented with asymmetrical tremor in both upper limbs for 30 years. The tremor was predominantly on the first dose of levodopa, she had a remarkable and sustained improvement in her tremor as well as her gait. We did not subject the patient to molecular diagnostic testing. Unusual phenotypes described with DRD-plus and a third group called DRD-look-alike. The DRD and DRD-plus group involve nigrostriatal dopaminergic pathways with the difference being in their clinical presentation. The “DRD-look-alike” group encompasses disorders with involvement of non-nigrostriatal dopaminergic system and disorders with nigrostriatal dopaminergic cell loss. The common denominator amongst these “dopa-responsive” conditions is the exceptional response to levodopa irrespective of the genotype or clinical phenotype.

Dopa-responsive dystonias have varied genetic aetiologies involving both nigrostriatal dopaminergic and non-dopaminergic pathways. The most common genetic mutation affecting the nigrostriatal dopaminergic pathway is GCH1 (GTP cyclohydrolase 1) gene, but testing for mutations in this gene to supplement the clinical diagnosis is not easily available. The difficulty in demonstrating pathogenic mutations in GCH1 gene in typical cases has been reported by several authors. On the other hand, presence of a GCH1 mutation does not necessarily support a diagnosis of DRD as the penetrance of the mutation is only 30%. Mutations in PARK2 can also have a similar presentation as DRD, further emphasizing that a clinical phenotype of “DRD” may have a varied genetic background (Table 1). As already noted, gene mutations in non-dopaminergic pathways can also potentially present with dopa-responsive symptoms. These cases have been summarized in Table 1.

To further add to this complexity, GCH1-deficient DRD can have varied phenotypic presentations which may or may not be responsive to levodopa treatment. Unusual phenotypes described with GCH1 gene mutations are frequent falls and asymmetrical leg atrophy. Also, presence of GCH1 mutations increases the risk for not only DRD but also Parkinson’s disease (PD). To differentiate between individuals presenting with a phenotype of PD or DRD in the presence of GCH1 mutations, dopamine transporter (DAT) imaging becomes indispensable. Subjects with DRD-Parkinsonism presentation have an abnormal DAT imaging but those with classic DRD presentation have a normal scan. Thus, functional brain imaging can help differentiate DRD from early-onset PD.

Under the broad rubric of “dopa-responsive symptoms” are also included those conditions without identifiable gene mutations in the dopaminergic system but clinical phenotype is such that they respond to levodopa. Such clinical presentations include

asymmetrical action tremor was observed in both upper limbs. Rapid alternating movements revealed mild bradykinesia. At rest, he had dystonic posturing of the toes with flexion of the toes which worsened during walking. He was started on levodopa/carbidopa 100/25 mg three times a day and reported that there was remarkable improvement in his tremor and gait. He also did not undergo any genetic testing or dopamine transporter scan and his treatment was solely based on clinical phenotype.

Dopa-responsive dystonia is characterized by selective nigrostriatal dopaminergic deficiency that classically presents in childhood with lower limb dystonia and diurnal fluctuations and responds exquisitely to dopamine replacement therapy. To add to this repertoire, several phenotypes have been described in the literature as being “dopa-responsive” which may or may not be associated with selective nigrostriatal dopamine deficiency but respond remarkably well to dopaminergic drugs. In a recent review, Lee et al have tried to segregate these disorders into DRD, DRD-plus and a third group called DRD-look-alike. The DRD and DRD-plus group involve nigrostriatal dopaminergic pathways with the difference being in their clinical presentation. The “DRD-look-alike” group encompasses disorders with involvement of non-nigrostriatal dopaminergic system and disorders with nigrostriatal dopaminergic cell loss. The common denominator amongst these “dopa-responsive” conditions is the exceptional response to levodopa irrespective of the genotype or clinical phenotype.

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progressive camptocormia and cervical dystonia (Table 1). Also, several cases of “overlooked and subtle gait abnormality since childhood” presenting in adulthood with a different symptom complex responding very well to levodopa have also been described in the literature (Table 1). The unifying feature of these cases is the good response of the symptoms to levodopa. Therefore, it has been recommended that the first step in diagnosing these conditions is to give a trial of levodopa. Thus, to recognize a “dopa-responsive” phenotype, one needs to be vigilant and look for “subtle clinical clues” as these conditions are remarkably responsive to levodopa.

Therefore, DRD can have a wide array of clinical presentations as well as have wide-ranging genetic mutations. The fact that both our patients had onset of dystonic posturing of feet during childhood which remained stationary and asymptomatic until much later in life when they presented with rapid worsening of gait in conjunction with other symptoms and responded excellently to levodopa are important points. Our cases were initially diagnosed as essential tremor and PD, respectively, and the diagnosis was questioned only because of the long-standing foot dystonia, which was also dopa-responsive. The genetic heterogeneity of a DRD-like presentation makes molecular testing expensive and impractical in the presence of an excellent levodopa response. Dopamine transporter imaging was unavailable at our centre. These cases highlight the fact that levodopa trial should be given in patients with prominent postural limb tremor in the presence of a background of subtle limb dystonia (“reducible foot deformity”) even in the absence of a molecular diagnosis.

DISCLOSURES

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SS and AM have nothing to disclose.

STATEMENT OF AUTHORSHIP

SS and AM: Writing of the first draft, manuscript preparation, review and critique
MJ: Conception, execution, review and critique

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Table 1: Levodopa responsiveness in cases with varied phenotypic and genotypic presentations

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of cases</th>
<th>Clinical presentation</th>
<th>Mutations in GCH1, TH, SR genes</th>
<th>Final molecular diagnosis</th>
<th>Response to levodopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potolska-Chromik et al, 2017</td>
<td>8 patients from 4 families</td>
<td>Progressive gait difficulties</td>
<td>–</td>
<td>GCH1 gene mutations recorded in 3 families and PARK2 mutations in 1 family</td>
<td>Marked improvement with levodopa in majority of patients</td>
</tr>
<tr>
<td>Charlesworth et al, 2013</td>
<td>5</td>
<td>Cervical dystonia</td>
<td>Negative</td>
<td>Pathogenic compound heterozygous variants in ATM gene causing ataxia telangiectasia</td>
<td>Good and persistent</td>
</tr>
<tr>
<td>Baschieri et al, 2014</td>
<td>1</td>
<td>Paroxysmal exercise-induced dystonia</td>
<td>Not done</td>
<td>GLUT1 (glucose transporter 1) mutation</td>
<td>Marked improvement</td>
</tr>
<tr>
<td>Wilder-smith et al, 2003</td>
<td>1</td>
<td>Progressive lower limb dystonia with diurnal fluctuations</td>
<td>Not done</td>
<td>Mutation at the SCA 3 (spinocerebellar ataxia) locus</td>
<td>Good response</td>
</tr>
<tr>
<td>Oravivattanakul et al, 2014</td>
<td>1</td>
<td>Progressive camptocormia</td>
<td>Negative for GCH1 and TH gene mutations</td>
<td>–</td>
<td>Beneficial response</td>
</tr>
<tr>
<td>Van Gepen, 2006</td>
<td>1</td>
<td>Progressive camptocormia</td>
<td>Not done</td>
<td>–</td>
<td>Good and sustained response</td>
</tr>
<tr>
<td>Schneider et al, 2006</td>
<td>4</td>
<td>Young-onset cervical dystonia</td>
<td>Negative for GCH1 and TH gene mutations</td>
<td>–</td>
<td>Excellent sustained response</td>
</tr>
<tr>
<td>Harper et al, 2008</td>
<td>1</td>
<td>Dystonic posturing of right leg and action tremor of hands at age 79. History of “jumpy legs” for 30 years</td>
<td>Not done</td>
<td>Not done</td>
<td>Excellent response</td>
</tr>
<tr>
<td>Harwood et al, 1993</td>
<td>3</td>
<td>Upper limb tremor in one subject; upper limb tremor with torticollis in one subject; kyphoscoliosis and limb rigidity in one subject. All had history of gait abnormality since childhood</td>
<td>Not done</td>
<td>Not done</td>
<td>Excellent response</td>
</tr>
</tbody>
</table>
REFERENCES


