LETTER TO THE EDITOR

To the Editor

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

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The classical description of dopa-responsive dystonia (DRD) was first given by Segawa et al in 1972.[1] 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.[2] 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 action initially, which later progressed to rest tremor. There was a diurnal variation in the tremor severity. She also gave a history of progressive difficulty in walking with abnormal posturing of her feet for the past 5 years. Her feet would progressively turn inwards and stiffen forcing her to rest even after ambulating short distances. When probed further, she revealed that she had a "reducible foot deformity" noticed since her early 20s and it was only in the past 5 years that she had a worsening of her gait. She has been on propranolol for her limb tremor for nearly 30 years without much efficacy. Family history was notable for her son presenting with writing tremor since his teenage years.

On examination, she had hypomimia and a mild voice tremor. There was asymmetrical rigidity in all four limbs and brisk deep tendon reflexes. She had a prominent asymmetrical kinetic tremor in her upper limbs which was more pronounced than postural and rest components. Dystonic posturing of upper limbs was noted when held outstretched in addition to tremor. There was marked bradykinesia on rapid alternating movements in all four limbs. Feet examination revealed dystonic posturing with clawing of toes, inversion and plantar flexion of her feet which progressively worsened as she walked. On the basis of clinical presentation, she was started on levodopa/carbidopa 100/25 mg 1 tablet once a day and gradually increased to 1 tablet three times a day. Following 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.

The second case was a 79-year-old male who presented with asymmetrical onset of upper limb action tremor for 5 years. He also complained of gradual worsening of his gait for the past 1.5 years. Patient described his gait as being clumsy and his toes "would get caught on the rug present on his living room floor". He, however, denied any history of weakness in his feet. On further questioning, he mentioned that he has had "curled up toes" since his childhood which his mother would describe as "hammer toes". Patient's maternal grandfather had history of "action tremor".

On examination, he had mild hypomimia. There was activated rigidity in right upper and lower limb. Bilateral deep tendon reflexes were brisk except bilateral ankle jerks, which were barely elicitable. There was no tremor at rest, but a prominent 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.[1,2] 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.[2] 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.[2] The DRD and DRD-plus group involve nigrostriatal dopaminergic pathways with the difference being in their clinical presentation.[2] The "DRD-look-alike" group encompasses disorders with involvement of non-nigrostriatal dopaminergic system and disorders with nigrostriatal dopaminergic cell loss.[2] 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.[3] 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.[4–8] 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%.[7] 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).[9] 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.[10–12]

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.[13,14] Also, presence of *GCH1* mutations increases the risk for not only DRD but also Parkinson's disease (PD).[15] 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.[15–17] 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

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

Author and year	Number of cases	Clinical presentation	Mutations in *GCH1*, TH, SR genes	Final molecular diagnosis	Response to levodopa
Potulska-Chromik et al, 2017	8 patients from 4 families	Progressive gait difficulties	–	*GCH1* gene mutations recorded in 3 families and PARK2 mutations in 1 family	Marked improvement with levodopa in majority of patients
Charlesworth et al, 2013	3	Cervical dystonia	Negative	Pathogenic compound heterozygous variants in ATM gene causing ataxia telangiectasia	Good and persistent
Baschieri et al, 2014	1	Paroxysmal exercise-induced dystonia	Not done	GLUT1 (glucose transporter 1) mutation	Marked improvement
Wilder-smith et al, 2003	1	Progressive lower limb dystonia with diurnal fluctuations	Not done	Mutation at the SCA 3 (spinocerebellar ataxia) locus	Good response
Oravivattanakul et al, 2014	1	Progressive camptocormia	Negative for GCH1 and TH gene mutations	–	Beneficial response
Van Gerpen, 2006	1	Progressive camptocormia	Not done	–	Good and sustained response
Schneider et al, 2006	4	Young-onset cervical dystonia	Negative for GCH 1 and TH gene mutations	–	Excellent sustained response
Harper et al, 2008	1	Dystonic posturing of right leg and action tremor of hands at age 79. History of "jumpy legs" for 30 years	Not done	Not done	Excellent response
Harwood et al, 1993	3	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	Not done	Not done	Excellent response

progressive camptocormia and cervical dystonia (Table 1).[18–20] 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[21,22] (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.[3] 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

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