Clinical Reasoning:

A demure teenager and her dystonic foot

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SECTION 1

A 13-year-old girl presented with a 4-year history of abnormal gait. At age 9, her parents noticed that she would run awkwardly “on the balls of her feet” and subsequently, that the rhythm of her running would break down with sustained exercise. There was no diurnal variation in her symptoms. There was no history of perinatal insults and early development was normal. There was no significant medical or

psychiatric comorbidity and her family history was unremarkable. Examination of the patient’s gait is demonstrated in video 1 at Neurology.org.

Questions for consideration:

1. What is the clinical phenomenology?
2. What diagnoses would you consider at this point?
3. What investigations would you request in the first instance?

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Supplemental data
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SECTION 2

The phenomenology here is exercise-induced right foot plantar flexion giving the appearance of foot drop on that side. However, resting motor and sensory examination was normal, leading to a phenomenologic classification of dystonia. The age and anatomic distribution of dystonia at onset, as well as any precipitating circumstances, are important factors in considering the potential etiology.¹ In this setting, there are a number of potentially treatable diagnoses to consider, including inherited dystonias, paroxysmal dyskinesias, dystonia due to acquired structural disease, and functional dystonia.

Isolated dystonia refers to pure dystonic syndromes with or without the accompaniment of tremor. The age at onset tends to dictate the anatomic pattern of symptoms, with young-onset isolated dystonia tending to first affect a limb before generalizing.² A single GAG deletion in the *TOR1A* (DYT1) gene is most commonly implicated and inherited in an autosomal dominant manner.²

Dopa-responsive dystonia (DRD) is another condition that may present with childhood-onset limb dystonia. Most commonly, DRD is an autosomal dominant condition due to a heterozygous mutation in the guanosine triphosphate cyclohydrolase 1 (*GCH-1*) gene resulting in reduced enzymatic production of tetrahydrobiopterin, required for the conversion of tyrosine to dopamine.³ Less commonly, autosomal recessive mediated deficiency of other enzymes involved in dopamine biosynthesis may produce a similar clinical phenotype, including tyrosine hydroxylase, sepiapterin reductase, and 6-pyruvoyl tetrahydrobiopterin synthase (guanosine triphosphate cyclohydrolase 1 deficiency may also be autosomal recessive).^{e1} Single case reports have also described DRD phenotypes caused by hereditary spastic paraplegia type 11, spinocerebellar ataxia type 3, and ataxia telangiectasia.^{e1} Diurnal variation is typical in the early stages, with symptoms worsening toward the end of the day and marked benefit from sleep. In addition to dystonia, DRD may also present with pyramidal, parkinsonian, and cerebellar signs.^{e2}

Paroxysmal dyskinesias are a rare group of disorders characterized by recurrent episodes of

involuntary movements, which may be dystonic, choreiform, ballistic, or a combination of these.⁴ They are classified clinically into 3 groups based on the precipitating factor, specifically, paroxysmal kinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia (PED), and paroxysmal nonkinesigenic dyskinesia.⁴ These conditions may be secondary to another identifiable disorder^{e3} or inherited, with an algorithm having been developed for delineating the latter by Erro et al.⁴ A diagnostic algorithm has also been formulated specifically for PED, which suggests that a fasting CSF sample be taken in cases of childhood or early adult onset PED with structurally normal MRI brain looking for low CSF/serum glucose ratio or low CSF glucose value with normal lactate (suggestive of a mutation in the glucose transporter type 1 gene), or low levels of tetrahydrobiopterin, homovanillic acid, and 5-hydroxyindolacetic acid (suggestive of DRD).⁵

An important and potentially treatable consideration in young-onset movement disorders is neurologic Wilson disease. The age at onset is typically the second or third decade of life with the presentation comprising dystonia in approximately one-third of cases (may be generalized, segmental, multifocal, or focal).⁶

When the symptoms and signs of a gait disorder are incongruent with known patterns of disease, the possibility of a functional disorder arises. Positive signs of functional gait disorders should be sought, including “huffing and puffing” (excessive displays of effort during ambulation characterized by grunting, grimacing, and breath holding), astasia abasia (inability to stand upright without assistance and exaggerated truncal sway without falling), and subjective complaints of poor balance accompanied by objective evidence of preserved balance control.⁷ The clinical spectrum of functional gait disorder is vast but classification into 1 of 4 categories has been suggested to aid diagnosis, as follows: movement disorder mimics, neurologic (non-movement disorder) mimics, musculoskeletal or biomechanical mimics, and isolated disequilibrium or balance disorders.⁷

Question for consideration:

1. What initial treatment would you offer?

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SECTION 3

The patient's dystonia responded minimally to a trial of levodopa (levodopa/carbidopa 50/12.5 mg 3 times daily) and exhibited no diurnal variation, making a diagnosis of DRD less likely. Basic biochemical tests were unrevealing and there were no extra neurologic stigmata or neuroimaging features of Wilson disease. Mutational analysis was negative for the c.907_909del mutation in the *TOR1A* gene. The patient's normal developmental history and normal MRI brain rendered an acquired,

structural cause of dystonia unlikely in this case. The abnormal movements were stereotyped, always present during walking or running, and there were no positive signs of a functional gait disorder. The rest of the clinical examination recorded 1 year from initial presentation is shown in video 2.

Questions for consideration:

1. What is the phenomenology illustrated in video 2?
2. What further genetic studies would you consider?

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SECTION 4

There is intermittent bilateral upper limb postural tremor, symmetrically reduced amplitude of finger taps, impassivity of facial expression, and a slightly stooped posture. Although not visible in video 2, mild upper limb rigidity was appreciable clinically. Further mutational studies were performed, revealing compound heterozygosity for the c.823C > T pathogenic mutation in exon 7 and the c.1289 G > A pathogenic mutation in exon 12 of the *parkin* gene, thus confirming a clinical diagnosis of autosomal recessive juvenile parkinsonism. Treatment was commenced with procyclidine 5 mg TDS. Videos 3 and 4 show excerpts from the clinical examination approximately 18 months after diagnosis with current treatment consisting of procyclidine 20 mg TDS.

Questions for consideration:

1. How would you counsel the patient and her parents?
2. What are the treatment considerations?
3. How has the clinical phenomenology evolved?

DISCUSSION Akinesia is not frequently associated with juvenile patients, particularly in the adult clinic. A much more frequent encounter is the demure teenager reluctant to engage in the clinical process. Here, one could be forgiven for accepting the latter scenario were it not for the grossly abnormal finger tapping on formal testing. This finding (which, in retrospect, unmasks a more generalized hypokinesia) could easily be overlooked.

Juvenile parkinsonism (JP) is a rare entity, defined by convention as parkinsonism presenting before age 21 years.^{e4} The most frequent cause of JP is mutation of the *parkin* gene; however, there are several other considerations in addition to those described above.^{e4} Rarely, JP may be part of the clinical syndrome caused by other heritable diseases, including Westphal variant Huntington disease, spinocerebellar ataxia types 2 and 3, neuroacanthocytosis, and rapid-onset dystonia-parkinsonism.^{e5} Infectious (Epstein-Barr virus encephalitis, Japanese encephalitis, subacute sclerosing panencephalitis, *Mycoplasma pneumoniae* infection), toxic (organo-phosphate, carbon monoxide, cyanide poisoning), and drug-induced (chloroquine, sodium valproate) causes of JP have also been described.^{e5} Recessive Parkinson disease (PD) refers to a typical parkinsonian syndrome resulting from a single gene mutation. *Parkin* (*PARK2*) gene mutations are most frequently responsible (responsible for an estimated 8.6% of young-onset, <45 years, PD⁸), followed by mutations in *PINK1* and *DJ1*. Clinical features that may differentiate *parkin*-related disease from PD without mutations include slower disease progression and dystonia, which is often the initial feature.⁹

Other causes of dystonia-parkinsonism syndromes include Wilson disease, X-linked dystonia-parkinsonism/Lubag (DYT3), rapid-onset dystonia-parkinsonism (DYT12), and neurodegeneration with brain iron accumulation.¹

Patients and their families should be counseled with regard to the heritability of this recessive condition. Importantly, rates of cognitive decline are not increased with *parkin* mutations, progression tends to be slower, and response to levodopa is typically very good.⁹ However, given the lengthy anticipated duration of treatment in recessive PD, patients are at high risk of developing dyskinesias and as such, it would seem prudent to prolong the time to commencement of levodopa with alternatives such as an anticholinergic agent. Deep brain stimulation has also been shown to be effective in recessive PD.¹⁰

Eighteen months after diagnosis and with treatment consisting of procyclidine 20 mg TDS, the clinical signs of bradykinesia and hypomimia are less apparent. However, the patient's gait has become broad-based and there is persistent, exercise-induced, dystonic posturing of both legs, most evident during tandem gait. There have been several clinical reports of cerebellar signs, including broad-based gait ataxia, in patients with *parkin*-related disease,^{e6–e8} supported by pathologic findings of *parkin* mRNA expression in the cerebellum^{e7} and neuronal loss in the Purkinje cell layer and dentate nucleus.^{e8}

AUTHOR CONTRIBUTIONS

Patrick W. Cullinane: conceptualization, design, and drafting of the manuscript. Patrick Browne: critical revision of the manuscript. Michael J. Hennessy: conceptualization and critical revision of the manuscript. Timothy J. Counihan: conceptualization, design, and critical revision of the manuscript.

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REFERENCES

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013;28:863–873.
2. Albanese A, Asmus F, Bhatia KP, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol* 2011;18:5–18.
3. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). *Ann Neurol* 2003;54(suppl 6):S32–S45.
4. Erro R, Sheerin U, Bhatia KP. Paroxysmal dyskinesias revisited: a review of 500 genetically proven cases and a new classification. *Mov Disord Clin Pract* 2014;29:1108–1116.

5. Erro R, Stamelou M, Ganos C, Skorvanek M, Han V. The clinical syndrome of paroxysmal exercise-induced dystonia: diagnostic outcomes and an algorithm. *Mov Disord Clin Pract* 2014;1:57–61.
6. Svetel M, Kozić D, Stefanova E, Semnic R, Dragasevic N, Kostic VS. Dystonia in Wilson's disease. *Mov Disord* 2001;16:719–723.
7. Fung VSC. Functional gait disorder. In: Hallett M, Stone J, Carson A, eds. *Functional Neurologic Disorders*. 1st ed. Amsterdam: Elsevier; 2016:263–270.
8. Kilarski LL, Pearson JP, Newsway V, et al. Systematic review and UK-based study of PARK2 (parkin), PINK1, PARK7 (DJ-1) and LRRK2 in early-onset Parkinson's disease. *Mov Disord* 2012;27:1522–1529.
9. Grünwald A, Kasten M, Ziegler A, Klein C. Next-generation phenotyping using the parkin example: time to catch up with genetics. *JAMA Neurol* 2013;70:1186–1191.
10. Moro E, Volkmann J, König IR, et al. Bilateral subthalamic stimulation in Parkin and PINK1 parkinsonism. *Neurology* 2008;70:1186–1191.

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