Child Neurology: Genetically determined dystonias with childhood onset

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A previously healthy 10-year-old girl of Croatian descent presented to the pediatric neurology clinic with an abnormal gait. She first noted symptoms 1.5 years prior to presentation, which included flexion–inversion posturing of her left foot while playing soccer. She would drag her left foot, leading to excessive falling. Her family noted that she did not seem to have much difficulty ambulating at the beginning of the day and they did not notice any abnormal posturing of the foot when she woke up in the morning. However, by the evening, they noted her left foot, and occasionally her right foot, would develop a flexion–inversion posture. Her symptoms seemed to be worse when she was tired or after activity. She had previously been evaluated by 2 orthopedic surgeons and a pediatric neurologist and was most recently seen in an emergency department for this problem, with no diagnosis being provided. Workup included a normal lumbar spine MRI and X-rays of both legs.

Physical examination was notable for subtle equinovarus posturing of the patient's left foot only but was otherwise unremarkable. There was no family history of dystonia or parkinsonism. She was started on 100 mg/d of levodopa, with complete resolution of the dystonic posturing, and she was able to return to playing sports without difficulty. A dystonia gene panel was sent and revealed a heterozygous pathogenic variant in the GTP cyclohydrolase 1 gene (*GCH1*), diagnostic of DYT5a (Segawa disease), a form of autosomal dominant dopa-responsive dystonia (DRD).

Differential diagnosis

Dramatic and sustained response to low doses of levodopa distinguishes DRD from the other genetic dystonias (including *DYT1*) and other conditions such as cerebral palsy and hereditary spastic paraplegias. Other DRDs, including DYT-5b and DYT-SPR, tend to present earlier and have a more severe phenotype in comparison to DYT-5a. Early-onset Parkinson disease (PD) (*PINK1*, *PRKN*) can also initially present as gait disturbance due to foot dystonia. Development of motor fluctuations and dyskinesias from chronic levodopa therapy would be atypical in DRD, which can be helpful in distinguishing from PD. Improvement with sleep may be seen in early-onset PD, but typically not as dramatic or sustained as in DRD. Genetic testing is widely available to confirm the diagnosis of the most common forms of genetic dystonias.

Discussion

The term dystonia was first used in 1911 by Hermann Oppenheim in “About a peculiar cramping sickness in children and adolescents (dysbasia lordotica progressive, dystonia musculorum deformans).”¹ Even in this early description, there was speculation of a genetic etiology.¹ The first dystonia gene was discovered in 1994 (*GCH1*), and since then numerous dystonia genes have been identified.² There are 14 confirmed genetic forms that have typical childhood onset (table). Recently, classification of genetic dystonia by inheritance pattern or associated features (isolated dystonia [i.e., simple vs combined] with another movement

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Table Genetically determined dystonia (DYT) with typical childhood onset

Symbol	Gene	Gene locus	Inheritance	Phenotype	Comments
DYT1	<i>TOR1A</i>	9q32-q34	AD	Early-onset generalized dystonia	Most common Ashkenazi Jewish Good response to GPi DBS
DYT5a	<i>GCH1</i>	14q22.1-22.2	AD	Dopa-responsive dystonia	Clinical case
DYT5b	<i>TH</i>	11p15.5	AR	Dopa-responsive dystonia	More severe phenotype than DYT5a
—	<i>SPR</i>	2p14-p12	AR	Dopa-responsive dystonia	More severe phenotype than DYT5a
DYT6	<i>THAP1</i>	8p11.1	AD	Adolescent onset mixed phenotype	Later age at onset than DYT1 Prominent cranial involvement
DYT8	<i>MR1</i>	2q35	AD	Paroxysmal nonkinesigenic dyskinesia 1	
DYT10	<i>PRRT2</i>	16p11.2-q12.1	AD	Paroxysmal kinesigenic dyskinesia	
DYT11	<i>SGCE</i>	7q21.3	AD	Myoclonus-dystonia	Responsive to alcohol
DYT12	<i>ATP1A3</i>	19q13.2	AD	Rapid onset dystonia-parkinsonism	Poor response to levodopa and DBS
DYT18	<i>SLC2A1</i>	1p34.2	AD	Paroxysmal exertion-induced dyskinesia 2	
DYT26	<i>KCTD17</i>	22q12.3	AD	Myoclonus-dystonia	Dystonia more disabling than DYT11
DYT28	<i>KMT2B</i>	19q13.12	AD	Generalized dystonia	Prominent cranial, cervical, and laryngeal involvement
—	<i>ADCY5</i>	3q21.1	AD	Chorea, dystonia, and myoclonus	Diurnal paroxysms
—	<i>GNAO1</i>	16q13	AD	Hyperkinetic movement disorder	Good response to GPi DBS

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; DBS = deep brain stimulation; GPi = globus pallidus pars interna.

disorder [i.e., complex]) has been proposed.³ What follows is a concise review of known genetically determined dystonias with typical onset in childhood, organized by associated features.

Isolated dystonias

DYT1 is the most common hereditary dystonia. It is inherited in an autosomal dominant fashion, with reduced penetrance and variable expressivity. It is particularly common among patients of Ashkenazi Jewish descent. Symptoms typically start before 6 years of age as a focal dystonia in an extremity (more often lower extremity), with spread to other extremities and trunk muscles by the early teens.⁴ The face and neck are not typically involved.² Whereas pharmacologic therapies, including levodopa and anticholinergic drugs, may show variability in therapeutic benefit, deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) has more consistently produced favorable outcomes.⁵

DYT6 shares some similarities with DYT1, but tends to have a later age at onset (average age at onset 19 years), and has prominent cranial involvement.² Dysphonia is often a prominent feature. Treatment is similar to DYT1, with the caveat that GPi DBS has marginal effect on speech.⁶

Combined dystonias

Dystonia with parkinsonism

DYT5a is a result of a heterozygous mutation in the *GCH1* gene. Most individuals with DYT5a present in childhood with gait disturbance due to lower extremity dystonia, often a rigid pes equinovarus deformity of 1 foot, such as the patient in the case presentation. The dystonia spreads to involve other limbs and the trunk muscles by the teenage years and patients may develop parkinsonian features.⁴ In rare cases, parkinsonian features may be the only sign of the condition.² Early in the course, symptoms show a diurnal fluctuation, with symptoms becoming worse over the course of a day and improving with sleep.⁴ Symptoms become static by early adulthood. There is a female predominance, with possibly a higher prevalence in patients of Eastern European descent. DYT5a is exquisitely responsive to levodopa therapy, with a complete, or near complete, response of symptoms at relatively low doses. Despite being a highly treatable medical condition, there is often considerable diagnostic delay of about 13 years.²

DYT5b and DYT-SPR are both inherited in an autosomal recessive fashion (*SPR* gene mutations can be inherited in an autosomal dominant manner as well, although less commonly). As DRDs, they are exquisitely responsive to levodopa. These

disorders often have a much more severe phenotype resembling homozygous *GCH1* mutations, and may manifest as an infantile movement disorder with developmental delay.⁷

DYT12 is due to a mutation in the *ATP1A3* gene, and is inherited in an autosomal dominant pattern with reduced penetrance. It typically presents in teenagers or young adults with rapid-onset dystonia-parkinsonism (RDP). This is characterized by a sudden onset (hours to weeks) of dystonic spasms (usually the upper limbs), orofacial dystonia, and bulbar symptoms, and is sometimes accompanied by parkinsonian features.² It is often triggered by stressful events such as fever, prolonged exercise, or childbirth. Levodopa and DBS are not beneficial. In addition to RDP, mutations in *ATP1A3* are also known to cause alternating hemiplegia of childhood and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss).⁸

Dystonia with other dyskinetic movements

Paroxysmal nonkinesigenic dyskinesia (DYT8) is caused by 2 missense mutations in the myofibrillogenesis regulator 1 (*MR1*) gene. There is a 2:1 female predominance, and average age at onset is 4 years. Symptoms include attacks consisting of a combination of dystonia and chorea. Attacks last from minutes to hours, but may occur a few times daily in severe cases.² Attacks may be precipitated by alcohol, caffeine, stress, hunger, fatigue, and tobacco. The frequency of attacks tends to decrease with age. Management involves avoidance of precipitating factors; clonazepam may also be beneficial.

The inherited form of paroxysmal kinesigenic dyskinesia (PKD, DYT10) is caused by missense and truncating mutations in the *PRRT2* gene.² Age at onset is between 5 and 15 years, and boys are more commonly affected. Attacks consist of combinations of dystonia and chorea lasting a few seconds to minutes, during voluntary movements, several times daily. They are precipitated by startle or making a sudden voluntary movement after a period of rest. PKD responds well to carbamazepine, phenytoin, levetiracetam, and phenobarbital. Attacks diminish with age regardless of treatment.

Mutations in the *SLC2A1* gene can cause paroxysmal exertion-induced dyskinesias (DYT18). Attacks consisting of dystonia, chorea, and athetosis are triggered by sustained exercise. Attacks typically last 5–30 minutes. Management involves avoidance of prolonged exercise. Ketogenic diet may also be helpful.

KMT2B-related dystonia (DYT28) is characterized by a progressive disease course that evolves from a focal lower limb dystonia into a generalized dystonia with prominent cervical, cranial, and laryngeal involvement.⁹ Mean age at onset is 7 years. Additional features include developmental delay, choreoathetosis, myoclonus, seizures, eye movement abnormalities, psychiatric comorbidities, spasticity, and sensorineural hearing loss. GPi DBS may be beneficial, particularly in younger patients.⁹

ADCY5-related dyskinesia presents as a childhood-onset hyperkinetic movement disorder featuring a combination of chorea, myoclonus, and dystonia.¹⁰ Distinguishing features include diurnal paroxysms with nocturnal attacks of chorea and dystonia.¹⁰ Treatment with clonazepam or clobazam may be helpful.¹¹

In addition to an epileptic encephalopathy, mutations in the *GNAO1* gene can cause a childhood-onset progressive movement disorder. Described phenotypic features include chorea, athetosis, dystonia, myoclonus, and stereotypies.¹² GPi DBS appears to be the most effective treatment for *GNAO1*-related movement disorders.¹³

Dystonia with myoclonus

DYT11 involves a mutation in the *SGCE* gene causing myoclonus-dystonia syndrome (MDS). Inheritance may involve maternal imprinting as paternal inheritance results in almost 100% symptom expression and maternal inheritance only results in 10%.¹⁴ Symptoms typically begin in childhood or early adolescence and consist of myoclonus and dystonia that preferentially involves the upper body. Treatment is with valproate and benzodiazepines. DBS has been consistently reported to improve both myoclonus and dystonia in DYT11. There are reports that γ -hydroxybutyrate may be helpful.¹⁴ Symptoms are also very responsive to alcohol, which can lead to dependence in adults.

DYT26 is a more recently described cause of MDS that is a result of heterozygous mutations in the *KCTD17* gene. Range of onset is 3–10 years.¹⁵ Differentiating factors from DYT11 include that the myoclonus associated with DYT26 tends to be less pronounced in the neck and upper extremities, and the dystonia tends to be more disabling.¹⁵ There is no improvement with alcohol. GPi DBS may be beneficial.¹⁵

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Neil Friedman, MBChB	Cleveland Clinic, OH	Drafting and revision of manuscript
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