Child Neurology: Spastic paraparesis and dystonia with a novel *ADCY5* mutation

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We describe a 21-year-old woman with lower extremity spasticity, dystonia, and weakness. She was born full term without complications. At 5 years of age, she began dragging her right foot, which slowly progressed to bilateral toe walking and a wide-based stance. By 14 years of age, she walked with her legs in a fixed posture with knees extended, and by 21 years of age, she was unable to stand unassisted. Family reported an intermittent hand action tremor and large "jerks" of her legs in the evening. They also noticed intermittent slurred speech that was difficult to understand. She reported occasional tingling in her fingers and toes. She completed the 5th grade, but schooling was eventually stopped because of learning difficulties. There is no family history of similar problems or consanguinity. Neurologic examination showed scanning and slurred speech, decreased strength and spasticity in the lower extremities, and a mild, low-amplitude, high-frequency terminal action tremor of both hands. Reflexes were increased at the knees (grade 3) with upgoing plantar responses, and there was decreased vibration and proprioception sensation at the toes. Upon standing, she had dystonic posturing of bilateral lower extremities.

MRI of the brain showed diffuse T2 and T2 fluid-attenuated inversion recovery hyperintensities in the white matter that were most prominent in the left frontal lobe (figure, A), right cerebellum, left caudate, and left lateral putamen (figure, B). There was also mild cerebellar vermis atrophy (figure, C), and magnetic resonance spectroscopy showed a low *N*-acetylaspartate peak (figure, D). An extensive workup, including metabolic and heavy metal screening, CSF analysis, EMG, nerve conduction studies, and muscle biopsy, was unremarkable. A hereditary spastic paraplegia (HSP) panel with next-generation sequencing was unrevealing. A 6-week trial of high-dose carbidopa/levodopa did not improve symptoms, and baclofen caused significant sedation.

Whole genome sequencing (WGS) revealed a likely pathogenic heterozygous missense mutation in exon 1 (M1 domain) of the *ADCY5* gene (c.697T>C; p.Tyr233His). Previously reported pathogenic *ADCY5* mutations have been associated with dyskinesias, including dystonia, chorea, and diurnal exacerbations of movement disorders.[1–5] More recently, a phenotype resembling spastic paraparesis was reported in association with an *ADCY5* mutation.[6] In this article, we discuss the approach to patients with multiple abnormal movements, along with a brief overview of the *ADCY5* mutation phenotype.

Initial evaluation and diagnostic approach for multiple abnormal movements

When a patient presents with multiple abnormal movements, the most important first step is to correctly define the phenomenology. This includes recognition of hyperkinetic movements such as chorea, dystonia, and tremor, as well as hypokinetic movements such as bradykinesia and akinesia. Once the movements are defined, the clinician should identify the most prominent abnormal movement, as this will guide the differential diagnosis and workup. The age at onset, progression of symptoms, and accompanying clinical features may add additional clues to the diagnosis. A detailed family history, including presence of consanguinity, should be

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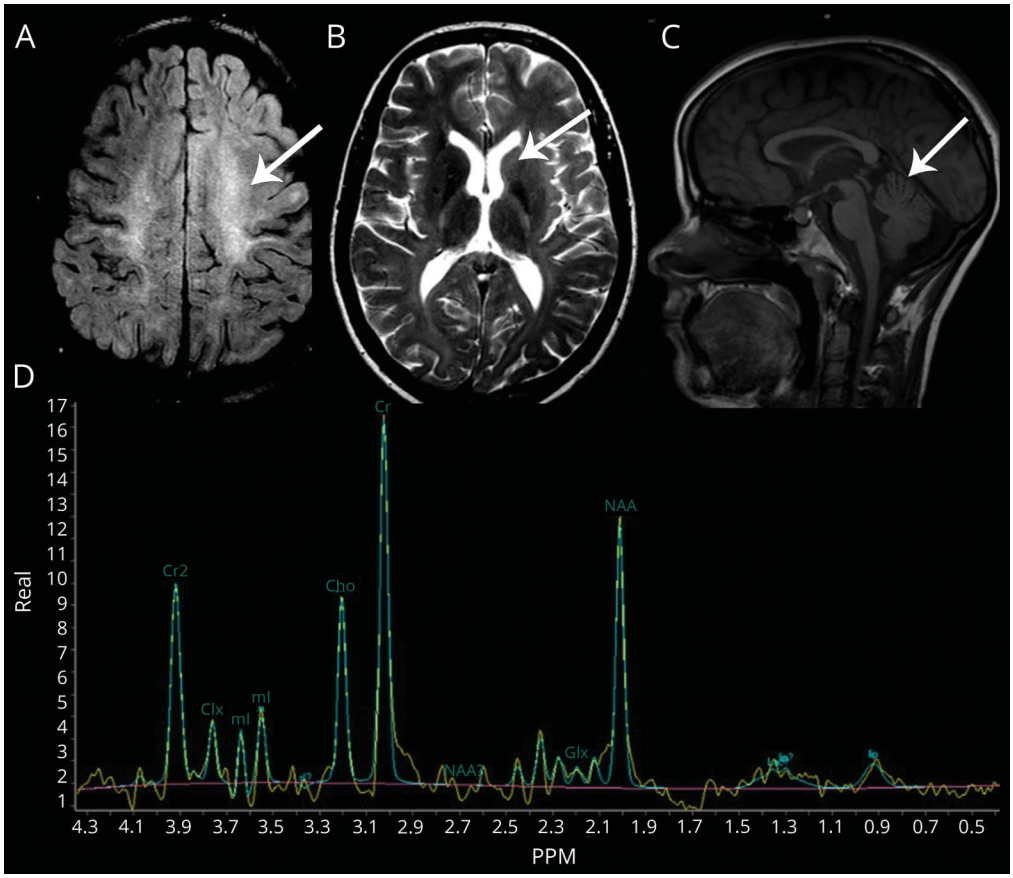
Figure MRI and magnetic resonance spectroscopy of the brain



(A) Axial T2-weighted fluid-attenuated inversion recovery image shows diffuse hyperintensities within the white matter, more pronounced on the left (arrow). (B) Axial T2-weighted image shows hyperintensities within the left caudate (arrow) and left putamen. (C) Midline sagittal axial T1-weighted image demonstrates mild cerebellar vermis atrophy (arrow). (D) Magnetic resonance spectroscopy obtained from voxels positioned in the cerebellar vermis reveals a low *N*-acetylaspartate peak.

obtained to aid in identifying a mode of inheritance: autosomal dominant, autosomal recessive, X-linked recessive, or sporadic. Based on the phenomenology, most prominent abnormal movement, clinical and family histories, and accompanying examination features, a proper differential diagnosis can be created and a workup initiated.[7] It is, however, important to realize that these steps are merely a guide. If an initial workup is unrevealing for the dominant abnormal movement, one should consider a workup based on the accompanying abnormal movements.

In our case, both spastic paraparesis and dystonia were prominent abnormal neurologic findings. Spastic paraparesis is formally defined as lower limb spasticity and weakness. While spastic paraparesis is not usually considered a movement disorder, it can lead to abnormal gait patterns and abnormal movements. Dystonia refers to "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both."[8,9] When dystonia and spastic paraparesis coexist, identifying the dominant clinical symptom, along with the age at onset, can help guide the workup.[8] For example, if childhood-onset spastic paraparesis is the most prominent symptom, an initial workup should include MRI of the brain and spinal cord in order to identify structural lesions or white matter abnormalities. In contrast, if childhood-onset dystonia is the most prominent symptom, the initial workup should include MRI of the brain as well as CT imaging of the head to evaluate for basal ganglia calcifications. In addition, screening for potentially treatable diseases (table) is highly advisable for patients with spastic paraparesis or dystonia.

Differential diagnosis for childhood-onset spastic paraparesis and dystonia

The differential diagnosis for childhood-onset spastic paraparesis and dystonia includes several conditions (table). If present, additional clinical features may assist in narrowing the differential diagnosis further. In our patient, we considered metabolic disorders such as Krabbe disease, metachromatic leukodystrophy, cerebral folate deficiency, cerebrotendinous xanthomatosis (CTX), biotinidase deficiency, and primary

Table Differential diagnosis for childhood-onset spastic paraparesis and dystonia

Diagnosis	Additional clinical features	Diagnostic test
Wilson disease[a]	Kayser-Fleischer rings, behavioral changes	Serum ceruloplasmin, 24-hour urinary copper excretion
Glucose transporter 1 deficiency[a]	Seizures, developmental delay	CSF glucose, SLC2A1 gene testing
Primary monoamine neurotransmitter disorders[a]	Diurnal variation of symptoms	Levodopa trial
GTP-CH1 deficiency		
AADC deficiency	Developmental delay, hypotonia, oculogyric crises	CSF neurotransmitters
Demyelinating disease (such as multiple sclerosis)	Fluctuating neurologic, ocular, or psychiatric symptoms	MRI of the brain and spine
Fahr disease	Developmental delay, microcephaly, ataxia	CT head
Mitochondrial disease	Other organ system involvement	EMG, nerve conduction studies, or muscle biopsy
CTX[a]	Cataracts, early atherosclerosis	Serum cholestanol, *CYP27A1* gene testing
Vitamin E deficiency[a]	Ataxia, neuropathy	Serum vitamin E level
Vitamin B_{12} deficiency[a]	Neuropathy, myelopathy	MRI of the spine, serum vitamin B_{12} and methylmalonic acid levels
Biotinidase deficiency[a]	Hearing loss, cutaneous signs	Urine organic acids, plasma acylcarnitine, serum biotinidase level
Hereditary spastic paraparesis	Urinary or GI symptoms, other neurologic symptoms (cognitive problems, epilepsy) in complex HSPs	HSP gene panel, WGS
Leukodystrophies	Epilepsy, neuropsychiatric symptoms, developmental delay	Enzymatic testing
Krabbe disease (galactocerebroside β-galactosidase deficiency)		Galactocerebroside β-galactosidase
Tay-Sachs disease (hexosaminidase A deficiency)		Hexosaminidase A
Metachromatic leukodystrophy (arylsulfatase A deficiency)		Arylsulfatase A
Torsion dystonias	Tremor	Dystonia gene panel, WGS
***ADCY5*-related dyskinesias**	Axial hypotonia, developmental delay, other hyperkinetic movements	WGS

Abbreviations: AADC = aromatic L-amino acid decarboxylase; CTX = cerebrotendinous xanthomatosis; GI = gastrointestinal; GTP-CHI = guanosine triphosphate cyclohydrolase I; HSP = hereditary spastic paraplegia; WGS = whole genome sequencing.
[a] Potentially treatable disorders.

monoamine neurotransmitter disorders.[10] It is important to recognize that primary monoamine neurotransmitter disorders (commonly referred to as dopa-responsive dystonias) improve with treatment of levodopa, and that these disorders may also present with a phenotype that resembles spastic paraparesis. Finally, Wilson disease should be considered as many phenotypes, including those with multiple abnormal movements, have been described in association with this treatable disease.

Genetic testing for spastic paraparesis and dystonia

There are many options available for genetic testing, including testing for single genes, gene panels, whole exome sequencing, and WGS. If spastic paraparesis is a prominent finding on examination, then genetic testing with an HSP panel is an appropriate first step. Likewise, if dystonia is believed to be a more prominent finding, then a dystonia panel may be considered first for genetic testing. If no pathogenic variants are identified through panel testing, then we recommend considering WGS since it is now readily available for clinical use.

In our patient, the first genetic test that was ordered was an HSP panel, which did not reveal any pathogenic variants. We then proceeded to WGS, which revealed a novel variant in the *ADCY5* gene. This variant was determined to be likely pathogenic based on several criteria. The variant had not been reported in large population databases (1000 Genomes or the ExAC databases), thus indicating it is not a common variant.

In addition, this variant was predicted to cause dysfunction to the *ADCY5* gene through in silico analysis (damaging by SIFT, probably damaging by PolyPhen, and a CADD score of 22.2). Parental studies, including maternal and paternal identity testing, indicated the variant arose de novo, meaning the variant was not present in either parent. Previously reported pathologic variants within the *ADCY5* gene produced dyskinesias, chorea, or dystonia in affected patients.[1–5] For these combined reasons, the variant was predicted to be likely pathogenic by the American College of Medical Genetics and Genomics guidelines (PS2, PM2, PP3, PP4).[11]

ADCY5 gene mutations and clinical phenotypes

The *ADCY5* gene encodes adenylyl cyclase 5, which converts adenosine triphosphate into cyclic adenosine monophosphate.[12] Pathogenic *ADCY5* variants are usually expressed in an autosomal dominant pattern, although an autosomal recessive inheritance pattern has recently been described.[1,2] It is important to recognize that when there is no family history of a similar phenotype, it is possible that a pathogenic mutation may arise de novo as well.

Neurologic symptoms associated with an *ADCY5* gene mutation were first described in a German family, which was originally classified as autosomal dominant familial dyskinesia with facial myokymia.[2] Subsequently, additional individuals with *ADCY5* genetic variants have been described. These individuals most frequently exhibit hyperkinetic movements, especially chorea.[3,4] Other common clinical features include axial hypotonia, facial chorea/dystonia, diurnal exacerbations of movement disorders, minimal to no cognitive impairment, and little to no progression of symptoms.[4] Of these common features, our patient only exhibited diurnal exacerbations of movement disorders that were described as large jerks of her legs at night. She had less common features of developmental delay/cognitive impairment and progression of her symptoms. For a review of *ADCY5* phenotypes, see "Phenotypic insights into *ADCY5*-associaed disease."[5] Interestingly, a recent case report describes a woman with a phenotype more closely resembling our patient: spastic paraparesis, dystonia, hyperreflexia, and progression of symptoms.[6] This patient had a missense mutation within the M2 domain of the *ADCY5* gene, while our patient's mutation lies within the M1 domain. Sensory symptoms have not been well-described in *ADCY5* gene mutation patients. However, since no other cause was identified in our patient, we postulate that her sensory symptoms may be related to her gene mutation.

Brain MRI abnormalities were not reported in the initial cases of *ADCY5* gene mutations and are not typically associated with the disorder. However, one patient with an *ADCY5* pathogenic variant exhibited hypointensities within the globus pallidus interna bilaterally, but this pattern was different from that seen in our patient.[4] In addition, the recently reported case with a spastic paraparesis phenotype did not have abnormalities on brain MRI.[6] Because the finding in our patient of white matter involvement on brain MRI is not a common feature of *ADCY5* mutations, we evaluated for other causes of leukoencephalopathy. However, none was found, and thus we suspect this finding may be attributable to the *ADCY5* variant.

Treatment options for *ADCY5*-related dyskinesias

There is currently no specific treatment for *ADCY5*-related dyskinesias. Medications are selected based on the specific abnormal movement but have resulted in limited success in *ADCY5*-associated dyskinesias.[13] Preventative treatment should be utilized through a multidisciplinary approach with physical therapy and occupational therapy to prevent future complications from immobility and spasticity.

When evaluating a child with multiple abnormal movements, accurate identification of the phenomenology guides further workup and management. For a patient presenting with childhood-onset spastic paraparesis and dystonia, MRI should be included in the initial workup. In addition, treatable conditions need to be considered for these patients, which includes dopa-responsive dystonia, CTX, vitamin E deficiency, Wilson disease, and biotin deficiency, among others (table). When an etiology is not revealed, WGS may be a helpful tool to identify rare disorders. With this additional case of a spastic paraparesis and dystonia phenotype associated with an *ADCY5* gene mutation, we propose the addition of *ADCY5* to spastic paraparesis gene panels.

Author contributions

M. Dean: drafting and revising the manuscript, study concept and design. L. Messiaen: revising the manuscript, analysis and interpretation of data. G.M. Cooper: revising the manuscript, analysis and interpretation of data. M.D. Amaral: revising the manuscript, analysis and interpretation of data. S. Rashid: revising the manuscript and study concept. B.R. Korf: revising the manuscript, analysis and interpretation of data. D.G. Standaert: revising the manuscript, analysis and interpretation of data.

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