Clinical Reasoning: A 16-year-old boy with freezing of gait

Sheng-Han Kuo, MD
Paul Greene, MD

Address correspondence and reprint requests to Dr. Sheng-Han Kuo, Department of Neurology, The Neurological Institute of New York, 710 W. 168th Street, 3rd floor, New York, NY 10032
sk3295@columbia.edu

SECTION 1

A 16-year-old boy had a long history of clumsiness. He had an unremarkable birth history. He walked unassisted at the age of 16 months and ran at age 2. He started running with difficulty at age 10. He performed poorly in physical education classes and was never able to hop. He had normal cognition and good academic performance. His speech difficulty started at age 7. His speech was slurred and nasal and he had difficulty opening his mouth fully while talking or eating. He did not bite his tongue and had no trouble swallowing. His handwriting was tight and slow. He started to fall at age 13. When he was rushed or startled, his feet froze and he fell. He would fall in the middle of the street when the traffic light changed, when he got out of a chair quickly, or at the top of a flight of stairs. He did not have visual symptoms, weakness, sensory change, or bowel or bladder incontinence. He had no other past medical problems and took no medications. His brother had a similar neurologic problem. The pertinent neurologic examination is shown in video 1 on the *Neurology*® Web site at www.neurology.org.

Questions for consideration:

1. What is the phenomenology in this patient?
2. How do you describe the patient's speech?

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From the Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY.
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SECTION 2

In video 1, the boy had freezing of gait while getting up from a chair quickly. His speech was strained with voice breaks consistent with adductor spasmodic dystonia. His nasal speech could be attributed to soft palate dystonia whereas the dysarthria could be due to palate, tongue, and facial muscle dystonia with superimposed parkinsonism. His facial expression was hypomimic with a decreased blink rate. He could open his jaw fully to command but could not open it fully while speaking, consistent with task-specific jaw-closing dystonia. He had no tremor or bradykinesia. His gait was wide-based and his toes curled. He had no neck or truncal dystonia. When writing, he did not have dystonia in his hands. In addition to what is shown in video 1, his tone was normal and he was stable on the pull test. Funduscopic examination did not show any abnormalities and he had normal smooth pursuit and saccadic eye movements.

The core features in this boy were generalized dystonia involving vocal cord, tongue, face, jaw, and extremities, accompanied by parkinsonian signs such as hypomimia and freezing of gait without extremity bradykinesia or rest tremor. The clinical course was progressive, and he had a family history of similar neurologic symptoms. The differential diagnosis falls under the category of dystonia-parkinsonism. Lubag disease (DYT3), dopa-responsive dystonia (DYT5), and rapid-onset dystonia parkinsonism (DYT12) present with dystonia and parkinsonism at a young age. Juvenile PD with Parkin mutations (PARK2) can have prominent dystonia and dystonia-parkinsonism associated with PLA2G6 mutation (PARK14) should also be included in the differential diagnosis. Several forms of secondary dystonia due to heredodegenerative diseases (i.e., diseases with evidence of neuronal degeneration, usually of genetic etiology) should be considered such as Wilson disease, pantothenate kinase-associated neurodegeneration (PKAN), and mitochondrial diseases.[1] Non-hereditary causes should also be included such as secondary dystonia-parkinsonism from perinatal insults and tardive dystonia with drug-induced parkinsonism from dopamine receptor blocking drugs. The patient has tongue and jaw dystonia, which occur in tardive dystonia, Lesch-Nyhan syndrome, neuroacanthocytosis, and PKAN.[2]

Question for consideration:

1. What would you do next?

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SECTION 3

We next examined the patient's older brother, a 17-year-old boy with pervasive developmental disorder, impulsivity, and lack of executive planning. He developed twisting of his hand at age 8, and the abnormal postures spread to his left foot and his right side at age 10. He had difficulty eating and speaking because of abnormal movements of his tongue and jaw. The pertinent neurologic examination is shown in video 2.

Question for consideration:

1. What is the phenomenology in the brother?

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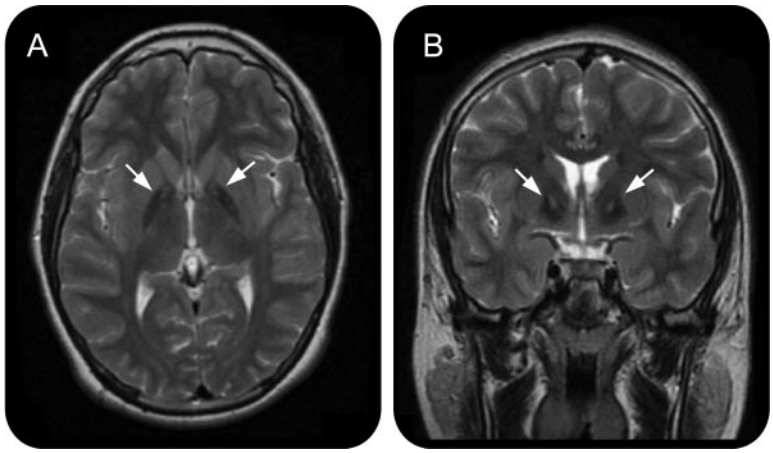
The neurologic examination (video 2) revealed both facial and tongue dystonia, which were exacerbated with speaking. He had generalized dystonia involving the trunk and all extremities. He walked with a broad and stiff-legged gait. In addition to what was shown on the video, his toes curled while walking. He had mild postural instability on the pull test.

Figure Brain MRI



(A, B) MRI of the brain revealed central hyperintensity in the bilateral globus pallidus surrounded by hypointense signal on T2 sequence, consistent with the eye-of-the-tiger sign.

The patient also had a younger sister, who was healthy. No other family members had dystonia. Therefore, the hereditary pattern is likely to be autosomal recessive or X-linked. Among the hereditary dystonias, dopa-responsive dystonia can be autosomal recessive and DYT3 is X-linked. Wilson disease, Lesch-Nyhan syndrome, neuroacanthocytosis, and PKAN are all inherited in an autosomal recessive manner.[1]

MRI of the brain in the patient and his brother revealed hyperintensity in the bilateral putamen surrounded by hypointensity on the T2 sequence, consistent with the eye-of-the-tiger sign (figure, A and B). Genetic analysis of the patient's brother showed pathogenic homozygous Y117C mutations in the *PANK2* gene. They were diagnosed with PKAN.

Question for consideration:

1. How do you treat freezing of gait?

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SECTION 5

Freezing of gait is an uncommon presentation in the setting of generalized dystonia. It occurs more frequently in parkinsonian syndromes such as PD and Parkinson plus syndromes, such as progressive supranuclear palsy and corticobasal degeneration. It can also happen in normal pressure hydrocephalus or vascular parkinsonism.[3] Freezing of gait sometimes can respond to levodopa. However, levodopa-unresponsive freezing of gait is very difficult to treat. Motor tricks sometimes can help with freezing of gait, such as walking sideways, redistribution of body weight, marching, and taking long steps. Sensory cueing can also help; for example, walking to music, clapping hands, and stepping over a line.[4] To our knowledge, freezing of gait has been reported in 5 cases of PKAN and may not be levodopa-responsive.[5-8] In one case, the freezing of the gait was responsive to anticholinergics.[8] Therefore, we treated this patient with trihexyphenidyl 5 mg, 3 times a day, and the patient had less freezing and falls.

DISCUSSION **Pantothenate kinase–associated neurodegeneration.** PKAN, once called Hallervorden-Spatz syndrome, is caused by a mutation in the *PANK2* gene. PKAN belongs to a group of diseases known as neurodegeneration with brain iron accumulation. The clinical presentation of PKAN can be divided into a classic form and atypical presentations.[6] Classic PKAN has age at onset before 6 years and usually presents with postural difficulties. The predominant features are dystonia involving trunk, face, and voice. Patients usually become wheelchair-bound by 15 years after the disease onset. Pigmentary retinal degeneration is associated with classic PKAN. In atypical PKAN, the age at onset is in the second or third decade and the progression is slower. Dystonia and rigidity are less severe than in the classic form. Patients usually have the ability to ambulate in adulthood. Psychiatric symptoms are prominent in atypical cases such as hyperactivity, obsessive-compulsive disorders, and behavioral problems. Extrapyramidal signs such as spasticity and hyperreflexia are common in PKAN. Genotype and phenotype correlation of PKAN is limited but generally, null mutation results in early onset of the disease and missense mutation leads to late-onset presentation.[9]

MRI of the brain in PKAN often shows the eye-of-the-tiger sign; i.e., central hyperintensity surrounded by hypointensity in the bilateral globus pallidus on a T2 sequence (figure, A and B). Occasionally, the hypointensity in T2 sequence can also be observed in the red nucleus, dentate nucleus, putamen, or caudate. This sign is relatively specific for PANK2 mutations.[10] The postmortem examination of patients with PKAN shows iron deposition in the globus pallidus and substantia nigra. Axonal spheroids in the CNS can be observed microscopically.[9]

Dystonia usually requires treatment in PKAN. Benzodiazepines, baclofen, and anticholinergics have been used as therapy for generalized dystonia. Botulinum toxin injections can alleviate focal dystonias such as blepharospasm, cervical dystonia, limb dystonia, or spasmodic dysphonia. Deep brain stimulation targeting the bilateral internal globus pallidus has produced benefit in several patients.[9] Although PKAN is associated with excessive iron accumulation and defective pantothenate metabolism, chelating agents or supplemental pantothenate have not been proven to modify disease progression. Both the patient and his brother received trihexyphenidyl and baclofen and had significant improvement of limb and trunk dystonia. The patient's older brother also received botulinum toxin injections for blepharospasm with a good response.

DISCLOSURE

Dr. Kuo serves on the Resident & Fellow Section editorial team for *Neurology*®. Dr. Greene serves on a scientific advisory board for GE Healthcare and receives research support from the Parkinson's Disease Foundation.

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