Hereditary spastic paraplegia presenting as limb dystonia with a rare *SPG7* mutation

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Neurology: Clinical Practice December 2018 vol. 8 no. 6 e49-e50 doi:10.1212/CPJ.0000000000000552

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Hereditary spastic paraplegias (HSPs) are rare neurologic disorders that are genetically and clinically heterogeneous. They may be categorized as pure (pyramidal) or complex (including other neurologic signs and symptoms). Spastic paraplegia type 7 (SPG7) is an autosomal recessive type of HSP that clinically encompasses pure and complex forms.¹

SPG7 encodes for the mitochondrial protein paraplegin. Many patients present with ataxia, spasticity, and hyperreflexia. Impaired distal vibratory sensation is common.¹ Other rarer findings include progressive external ophthalmoplegia and ptosis,^{1,2} dysphagia,² myopathy and amyotrophy,^{2,3} optic neuropathy or atrophy,^{1,4} sensory changes,³ vestibular dysfunction,⁵ and intellectual disability.¹ Two patients with cervical dystonia (CD) have been described: one homozygous for c.2115_2131del, p.(Leu706Glnfs*30) mutation and one compound heterozygous for c.2228T>C (p.Ile743Thr) and c.861dupT, p.Asn288* mutations.¹

Herein, we present a case of a patient who presented with limb dystonia and was found to have HSP associated with a rare compound heterozygous *SPG7* mutation.

PRACTICAL IMPLICATIONS

Evaluate carefully for any spasticity or ataxia in a patient who presents with focal dystonia to determine appropriateness of genetic testing for *SPG7*.

MORE ONLINE

▶ Video

Case report

A 40-year-old right-handed man of British descent with a history of type 1 diabetes mellitus presented to our center with difficulty writing. For 3 months, when writing, his thumb and index finger would extend. He had difficulty using utensils to eat or stir. He endorsed mild imbalance, but no falls. His medications included insulin, atorvastatin, and vitamin D supplements. The remainder of the medical and family histories were noncontributory.

On examination, the patient was noted to have right thumb abduction and index finger extension while writing with either hand (video 1). He had right hand ulnar deviation with writing, dystonic posturing of the fingers more prominently on the left, and incoordination bilaterally, particularly with heel tapping and heel-to-shin testing. Reflexes were brisk throughout with bilateral ankle clonus and positive left Babinski sign. Lower extremity tone was mildly spastic. The remainder of the neurologic examination was unremarkable.

MRI of the brain and cervical and thoracic spine was unremarkable. On nerve conduction studies, the right median nerve motor study had a distal latency of 4.76 ms and the orthodromic sensory study had a peak latency of 2.69 ms, indicating a moderate right median neuropathy at the wrist. Thyroid studies, serum levels of vitamins B₁, B₁₂, and E, ceruloplasmin, copper, erythrocyte sedimentation rate, C-reactive protein, anti-glutamic acid decarboxylase antibodies, and human T-cell lymphotropic virus serology were all unremarkable.

The patient underwent onabotulinum toxin A injection of 20 units each to the right extensor indicis proprius and the abductor pollicis longus under EMG guidance. The injections caused

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

weakness and did not improve his function. Carbidopa/levodopa 25/100 mg twice daily was started due to concern for dopamine-responsive dystonia, but was ineffective. Baclofen up to 10 mg 3 times daily was not effective.

Genetic studies revealed compound heterozygous *SPG7* mutations—c.2096dupT, p.(Met699Ilefs*4) and c.1529C>T (p.Ala510Val). In addition, the patient had a heterozygous *AP4S1* mutation (c.289C>T, p.Arg97*) (appendix e-1, links. lww.com/CPJ/A55).

Discussion

SPG7 mutations are a potentially underrecognized cause of spasticity, ataxia, and other neurologic syndromes. The p.Ala510Val mutation, found in our patient, is the most common mutation in *SPG7* patients of British ancestry.⁵ Although most cases of neurologic dysfunction with this mutation have been associated with homozygous or compound heterozygous mutations, there have been reports of isolated heterozygous p.Ala510Val mutations associated with clinical changes.^{2,6} The patient's second *SPG7* mutation, c.2096dupT p.(Met699Ilefs*4), is rare.

Dystonia is an uncommon presenting feature of HSP. CD, which our patient did not have, has been described in only 2 patients with *SPG7*.¹ The homozygous mutation c.2115_2131del, p.(Leu706Glnfs*30) found in one CD case is predicted to cause premature protein truncation. The heterozygous mutation c.861dup, p.Asn288* found in the other CD case leads to a premature termination codon and the mRNA is predicted to undergo nonsense-mediated decay. Our patient's novel mutation, c.2096dupT, p.(Met699Ilefs*4), leads to frameshift and is predicted to cause either protein truncation or nonsense-mediated mRNA decay. At this point it is unclear whether these mutations are causally linked to the dystonia phenotype.

This patient also had a heterozygous *AP4S1* mutation. Homozygous *AP4S1* mutations have been associated with early-onset spastic paraparesis, intellectual disability, and seizures, now classified as *SPG52*.⁷ Our patient demonstrated spasticity without intellectual disability or seizures. It is possible that our patient's presentation is entirely explained by compound heterozygous *SPG7* mutations. However, it is also possible that the heterozygous *AP4S1* mutation acts as a genetic modifier and contributes to the given HSP phenotype.

We have presented a case of HSP stemming from a rare compound heterozygous *SPG7* mutation, with the initial presenting symptom of limb dystonia. One of our patient's *SPG7* mutations, c.1529C>T, p.Ala510Val, is widely reported in the literature, while the other, c.2096dupT, p.(Met699Ilefs*4), appears to be exceedingly rare.

Author contributions

S.M. Schaefer: drafting and revising the manuscript for intellectual content. A.M. Szekely: revising the manuscript with expertise in genetics. J.J. Moeller: revising the manuscript for intellectual content. S. Tinaz: revising the manuscript for intellectual content.

Acknowledgment

The authors thank Taylor Zuck at GeneDx for providing details of the genomic information.

Study funding

No targeted funding reported.

Disclosure

S.M. Schaefer reports no disclosures. A.M. Szekely receives research support from Collaborative Center for X-linked Dystonia and Parkinsonism, MGH/Harvard Medical School. J.J. Moeller receives publishing royalties from UpToDate, Inc., Compendium of Therapeutic Choices (Canada). S. Tinaz receives research support from NIH/NCATS and Connecticut Advocates for Parkinson's. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Received March 15, 2018. Accepted in final form July 14, 2018.

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