Clinical Reasoning: Childhood-onset atrophy and spasticity

Magdala Poon, MD
Thy P. Nguyen, MD

Correspondence to
Dr. Nguyen:
thy.p.nguyen@uth.tmc.edu
or Dr. Poon:
magdala.poon@gmail.com

SECTION 1

A 46-year-old woman who had been adopted presented with progressive weakness. Motor development had been normal until age 10 years. At that time, she had noted difficulty walking, imbalance, falls, and urinary frequency. By middle school, she had developed weakness and atrophy in her hands. In her mid-30s, she noted progressive bilateral foot drop. She had begun to use a walker 10 years ago. She recently had more trouble going upstairs, with frequent falls. After a fall 1 year ago, she began having sharp pain radiating into both thighs, with numbness and tingling.

She denied dysphagia, diplopia, ptosis, dyspnea, or facial weakness. She has a double master's degree. She denied migraines, seizures, hearing loss, or myoglobinuria. She reported mild elevations of creatine kinase in the past.

The patient's mental status, language, and cranial nerves were normal. Tongue fasciculations were absent. Motor examination revealed spastic paraparesis with distal atrophy. Strength was normal in the prox-

imal arms but decreased in the distal arms (wrist flexion/extension Medical Research Council [MRC] grade 4, finger flexion/extension MRC grade 2). Strength in the legs was mildly decreased proximally (hip flexion, adduction, knee extension, hip abduction, knee flexion MRC grade 4) and decreased distally (dorsiflexion and toe extension MRC grade 2). Pes planus was noted. Sensation was decreased to temperature in the distal legs, but intact to vibration and proprioception.

Reflexes were 3+ in bilateral arms and patella, but absent in the ankles. Plantar responses were extensor bilaterally. Hoffman, jaw jerk, snout, and glabella reflexes were absent. The cerebellar examination was normal. Gait was scissoring, with bilateral steppage.

Questions for consideration:

1. Where is the localization of the patient's weakness based on the symptoms and examination?
2. What differential diagnosis should be considered?
3. What further testing would help narrow the differential diagnosis at this point?

[GO TO SECTION 2](#)

SECTION 2

The patient's hypertonia, spasticity, hyperreflexia, and Babinski sign suggest an upper motor neuron lesion, localizing to the corticospinal tract. The distribution of weakness and atrophy is distal more than proximal and generalized, suggesting a superimposed diffuse lower motor neuron lesion. Sensory involvement appears limited to small fiber modalities. With selective motor involvement, distal pattern, absent ankle jerks, and significant atrophy, lower motor neuron involvement may be due to anterior horn cell or motor nerve. Her examination is consistent with a combined corticospinal tract and anterior horn cell or motor nerve process.

Given the presence of both upper and lower motor neuron signs, complicated hereditary spastic paraplegia (HSP), motor neuron disease (such as sporadic or hereditary amyotrophic lateral sclerosis [ALS]), mitochondrial disorders, rare Charcot-Marie-Tooth (CMT) variants, leukodystrophy, and myelopolyradiculopathy are in the differential diagnosis. Further testing should include MRI of the neuraxis and EMG and nerve conduction studies (NCS). MRI of the neuraxis should be performed to evaluate for structural lesions/inflammation suggestive of myelopolyradiculopathy, corticospinal tract degeneration, or characteristic findings in hereditary leukodystrophies (Krabbe disease). Electrodiagnostic studies can evaluate for characteristic findings in CMT or leukodystrophy (demyelinating neuropathy in Krabbe disease).

The patient had already undergone urologic studies, muscle biopsy, MRI, and genetic testing prior to our evaluation. Urologic studies showed findings of a neurogenic bladder. A muscle biopsy was nondiagnostic (showing nonspecific mitochondrial changes). MRI brain was unremarkable. MRI thoracic spine showed a small caliber cord, suggestive of spinal cord atrophy (figure). Lumbar MRI showed multilevel degenerative changes with moderate to severe central canal stenosis and mild to moderate bilateral foraminal stenosis at L3–L4 and L4–L5. Bilateral nerve root sheath cysts were seen from L1 to L5. The lumbosacral MRI findings were deemed unrelated to her progressive condition.

Figure MRI thoracic spinal cord in sagittal T2 plane

MRI of the thoracic spinal cord in T2 sagittal plane demonstrates small caliber thoracic spinal cord, suggestive of spinal cord atrophy.

Sensory nerve conduction studies were normal for age. Motor nerve conduction studies showed low amplitude or no responses on median, ulnar, peroneal, and tibial nerves with normal conduction velocities (when elicited). Needle EMG showed distal more than proximal chronic neurogenic changes (large-amplitude, long-duration motor units with reduced recruitment) in the right arm and leg without active denervation. Thoracic myotomes and lumbar paraspinals were normal. Needle EMG of the tongue was declined.

Question for consideration:

1. At this point, what genetic testing would you consider?

GO TO SECTION 3

SECTION 3

Genetic testing, performed prior to our evaluation, for Charcot-Marie-Tooth disease (CMT1A), peripheral myelin protein 22 (*PMP22*) gene, had discordant results. Fluorescence in situ hybridization DNA analysis showed duplication of *PMP22* gene based on analysis of 50 nuclei examined, but 10 metaphases examined did not show duplication. The discordant results were of uncertain significance. Genetic ataxia panel showed variants of unknown clinical significance in polymerase gamma (*POLG*) and *Senataxin* genes. The *POLG* gene encodes a mitochondrial DNA polymerase, which proofreads during mitochondrial DNA replication.¹ *POLG* mutations result in a variety of phenotypes ranging from Alpers-Huttenlocher syndrome (progressive encephalopathy, intractable epilepsy, hepatic failure) to ataxia neuropathy spectrum (sensory ataxia, neuropathy, dysarthria, ophthalmoplegia) and autosomal dominant progressive external ophthalmoplegia (ptosis, ophthalmoplegia, myopathy, sensorineural hearing loss, axonal neuropathy, ataxia, parkinsonism).¹ *Senataxin* mutations are associated with a rare form of juvenile ALS characterized by slow disease progression, distal-predominant weakness, and a normal lifespan.² It is inherited in an autosomal dominant manner. *Senataxin* mutations are also the second most frequent cause of autosomal recessive cerebellar ataxia, which causes severe gait imbalance, mild limb/trunk ataxia, oculomotor apraxia, and sensorimotor axonal peripheral neuropathy.³

Question for consideration:

1. Consider the posttesting analysis of this patient's known genetic test results. How should clinicians approach pretesting and posttesting analysis in patients with genetic tests?

DISCUSSION As a clinician, the first step prior to ordering genetic testing is establishing a specific phenotype. Specific neurologic syndromes show increased yield in whole exome sequencing.⁴ We considered phenotype-genotype correlation in this patient's posttesting analysis.

Our patient had childhood-onset gait impairment, urinary frequency, and distal atrophy. Examination showed spastic scissoring gait and atrophy and weakness of the distal muscles without large fiber sensory symptoms. Electrodiagnostic findings confirmed lower motor neuron involvement with normal sensory NCS. CMT1A was ruled out due to spasticity, lack of large fiber sensory involvement, and normal sensory nerve conduction velocities, despite the inconclusive *PMP22* genetic results. Juvenile ALS due to *Senataxin* mutation was considered. However, urinary involvement is unusual due to the sparing of

the Onuf nucleus in ALS. Clinically, the patient had no fasciculations. Additionally, scissoring gait and small caliber spinal cord were atypical. Muscle biopsy findings, history, and examination were not consistent with mitochondrial disorders or clinical ataxia and did not correlate with previously described *POLG* phenotypes.

We proceeded with genetic testing for HSP and the patient was found to have a pathogenic mutation in Berardinelli-Seip congenital lipodystrophy 2 (*BSC2*) gene, which causes Silver syndrome (SPG17).⁵

HSP is clinically and genetically heterogeneous and should be on the differential for patients with combined upper motor neuron and lower motor neuron localization, particularly with urinary involvement and childhood onset. HSP is divided into 2 groups: uncomplicated and complicated.⁶ Uncomplicated HSP is characterized by progressive lower extremity spasticity, hypertonic bladder, and mildly decreased vibration sense in the legs. Onset may occur in childhood (phenotypically similar to static diplegic cerebral palsy) or in adulthood with slow progression. Urinary symptoms and leg paresthesias are common, but the arms remain unaffected. Complicated HSP is characterized by additional findings such as amyotrophy, ataxia, peripheral neuropathy, thin corpus callosum, or cognitive impairment. Inheritance is autosomal dominant, autosomal recessive, or X-linked. There are currently more than 56 genetic loci for HSP, named spastic paraplegia *SPG1*–*SPG56*, in order of their discovery.⁶ Pathophysiology is thought to be axonal degeneration of the distal corticospinal tract and dorsal columns, sometimes with loss of anterior horn cells.^{5–7} Diagnosis can be confirmed by molecular genetic testing.

Silver syndrome is clinically characterized by spastic paraparesis, urinary incontinence, distal amyotrophy/weakness, and often with decreased vibration sense and pes cavus/planus. Onset of symptoms ranges from the first to the seventh decade. Disease severity is variable between families and between affected members of the same family. Our patient did not have known affected family members. Disease progression is slow, with normal lifespan. Management is supportive and targeted at symptoms: physical therapy, orthopedic shoes, and adaptive equipment for gait.

Due to significant advances in genetic testing, we are able to diagnose many patients by molecular genetics. However, genetic testing also has drawbacks. Up to 89% of patients who undergo whole exome sequencing have diagnoses of variants of uncertain significance.^{4,8} Our patient carried several diagnoses with variants of uncertain significance in *PMP22*, *POLG*, and *Senataxin*. Once a clinical phenotype

was defined, diagnosis of HSP-Silver syndrome was verified through molecular genetic testing, ending the patient's diagnostic odyssey.^{4–6}

AUTHOR CONTRIBUTIONS

M.P.: acquisition and analysis of data, study concept and design, drafting and revision of manuscript. T.P.N.: analysis of data, study concept and design, supervision of study, revision of manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Cohen BH, Naviaux RK. The clinical diagnosis of POLG disease and other mitochondrial DNA depletion disorders. *Methods* 2010;51:364–373.
2. Chen YZ, Bennett CL, Huynh HM, et al. DNA/RNA helicase gene mutations in a form of juvenile amyotrophic

lateral sclerosis (ALS4). *Am J Hum Genet* 2004;74:1128–1135.

3. Nanetti L, Cavalieri S, Pensato V, et al. SETX mutations are a frequent genetic cause of juvenile and adult onset cerebellar ataxia with neuropathy and elevated serum alpha-fetoprotein. *Orphanet J Rare Dis* 2013;8:123.
4. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA* 2014;312:1870–1879.
5. Ito D. BSCL2-related neurologic disorders/seipinopathy. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. *GeneReviews*. Seattle, WA; 1993. Available at: www.genereviews.org. Accessed on October 1, 2015.
6. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. *Acta Neuropathol* 2013;126:307–328.
7. Windpassinger C, Auer-Grumbach M, Irobi J, et al. Heterozygous missense mutations in BSCL2 are associated with distal hereditary motor neuropathy and Silver syndrome. *Nat Genet* 2004;36:271–276.
8. Shashi V, McConkie-Rosell A, Schoch K, et al. Practical considerations in the clinical application of whole-exome sequencing. *Clin Genet* 2016;89:173–181.

Neurology®

Clinical Reasoning: Childhood-onset atrophy and spasticity

Magdala Poon and Thy P. Nguyen

Neurology 2016;86:e140-e143

DOI 10.1212/WNL.0000000000002519

This information is current as of March 28, 2016

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/86/13/e140.full
References	This article cites 7 articles, 0 of which you can access for free at: http://n.neurology.org/content/86/13/e140.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Genetics http://n.neurology.org/cgi/collection/all_genetics Amyotrophic lateral sclerosis http://n.neurology.org/cgi/collection/amyotrophic_lateral_sclerosis_ Anterior nerve cell disease http://n.neurology.org/cgi/collection/anterior_nerve_cell_disease EMG http://n.neurology.org/cgi/collection/emg Spastic paraplegia http://n.neurology.org/cgi/collection/spastic_paraplegia
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2016 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.