Clinical Reasoning: Childhood-onset atrophy and spasticity

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, prosis, 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 proximal 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?
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.

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?
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. 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). Senataxin mutations are associated with a rare form of juvenile ALS characterized by slow disease progression, distal-predominant weakness, and a normal lifespan. 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/trunkal ataxia, oculomotor apraxia, and sensorimotor axonal peripheral neuropathy.

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. 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 (BSCL2) gene, which causes Silver syndrome (SPG17).

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. 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. Pathophysiology is thought to be axonal degeneration of the distal corticospinal tract and dorsal columns, sometimes with loss of anterior horn cells. 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. 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.

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**REFERENCES**
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