Clinical Reasoning:
A case of treatable spastic paraparesis

SECTION 1
A 36-year-old man was referred for progressive lower extremity spasticity. He had a 4-year history of gradually progressive leg stiffness and ankle clonus and a 1-year history of gait disturbance and urinary urgency. There was no history of optic neuritis, diplopia, Lhermitte phenomenon, seizure, cognitive disturbance, paresthesias, or diarrhea. Family history showed no evidence of neurologic disorders in his parents, 4 siblings, and 3 children. Neurologic examination revealed normal mental status and cranial nerves. Cataracts were not seen by slit-lamp examination. There was lower extremity spasticity with sustained ankle clonus, diffuse hyperreflexia, bilateral Babinski and Hoffman signs, and a spastic gait (25-foot timed walking: 10 seconds). Vibratory sensation was impaired in the toes bilaterally. Cerebellar signs were not present. The Achilles tendons were enlarged (figure 1).

The clinical history and neurologic examination suggest upper motor neuron signs and involvement of large fiber sensory pathways, the combination of which suggests myelopathy or myeloneuropathy.

Questions for consideration:
1. What is the differential diagnosis of chronic progressive myelopathy?
2. What diagnostic tests would you order?
SECTION 2
Causes of myelopathy considered included mass lesions (e.g., spinal cord compression, intrinsic cord tumor, syrinx), autoimmune and inflammatory disorders (e.g., multiple sclerosis, neuromyelitis optica, transverse myelitis, sarcoidosis, paraneoplastic myelopathy, Sjögren disease), metabolic disorders (e.g., B12 deficiency, copper deficiency), toxins (e.g., chronic nitrous oxide exposure), infections (e.g., syphilis, HIV, human T-lymphotrophic virus, Lyme disease, Whipple disease, tuberculosis, and parasitic), vascular disorders (e.g., dural arteriovenous fistula), neurodegenerative disorders (e.g., primary lateral sclerosis), and hereditary disorders (e.g., hereditary spastic paraplegias, adrenomyeloneuropathy, proteolipid protein related disorders).

Brain, cervical, and thoracic spinal MRIs were normal. Chest x-ray was normal. Nerve conduction studies, needle EMG, visual evoked responses, and median somatosensory evoked responses were normal. Tibial somatosensory responses revealed a delayed P38 latency (56.8 msec) and a markedly prolonged N22-P38 interpeak interval 31 msec (normal 12.2–20 msec). Complete blood count, metabolic panel, vitamin B12, methylmalonic acid, copper, angiotensin converting enzyme, and very long chain fatty acids were normal. CSF examination was normal including cells, total protein, synthetic rate, and oligoclonal bands. Infectious, inflammatory, and common metabolic causes of myelopathy were excluded with appropriate laboratory testing. Autosomal recessive hereditary paraplegias were considered unlikely in view of the enlarged Achilles tendons.

Questions for consideration:
1. What is the significance of the enlarged Achilles tendons?
2. How would you further investigate this finding?
SECTION 3

The enlarged Achilles tendons without prior trauma or surgery raised the suspicion of tendon xanthomas which are associated with a rare autosomal recessive metabolic disorder. Ankle MRI confirmed the clinical suspicion of xanthomatous enlargement of the Achilles tendons (figure 2). The Achilles tendon xanthomas led to biochemical screening for cerebrotendinous xanthomatosis despite the absence of cataracts, mental retardation, and cerebellar signs. Serum cholestanol level was subsequently found to be elevated at 10.6 μg/mL (normal 3.0–5.4 μg/mL), confirming the diagnosis of cerebrotendinous xanthomatosis (CTX). CYP27A1 gene sequencing was not performed. Serum cholestanol levels were normal in his asymptomatic siblings.

Treatment with chenodeoxycholic acid (750 mg/day) and simvastatin was initiated. The level of cholestanol decreased to 2.5 μg/mL on follow-up 8 months later and remained normal on subsequent tests. His spastic gait had improved at a 12-month follow-up visit (25-foot timed walking: 4.9 seconds), and remained unchanged at a 6-year follow-up visit (4.8 seconds). Tibial somatosensory evoked responses also improved on repeat testing at 36 months, with improvement in the N22-P38 interpeak interval (26.4 msec), but remained abnormal at the 6-year follow-up visit. Six years after the initial presentation, a repeat spinal MRI revealed abnormal increased signal in the posterior columns on T2-weighted images of the thoracic cord. The patient developed no additional neurologic signs or cataracts during follow-up of 6 years. His Achilles tendon xanthomas persisted unchanged.

DISCUSSION CTX is a rare, autosomal recessive lipid storage disorder caused by a deficiency of the mitochondrial enzyme sterol 27-hydroxylase (CYP27) with resulting cholestanol and cholesterol accumulations in various tissues including the CNS and peripheral nerves. Diagnosis is confirmed by high plasma cholestanol levels and elevated bile alcohols in urine. Molecular genetic testing of the CYP27A1 gene located on chromosome 2q23 has shown sequence variants and deletions. Classic clinical manifestations of CTX are childhood-onset diarrhea, premature cataracts, and tendon xanthomas developing in adolescence. Neurologic symptoms and signs begin in adolescence or adulthood, and include bilateral premature cataracts (90%), pyramidal signs (67%), cerebellar dysfunction (60%), intellectual decline (57%), tendon xanthomas (45%), intractable diarrhea (33%), peripheral neuropathy (24%), and seizures (24%). MRI abnormalities are found in two-thirds of cases, with typical findings consisting of cerebral and cerebellar atrophy, and hyperintense lesions of dentate nucleus and globus pallidus with extension into adjacent white matter on T2-weighted images. Our case presented with progressive spasticity and Achilles tendon xanthomas, which is atypical for classic CTX.

A rare spinal phenotype presenting with progressive spasticity and posterior column signs has been described in the medical literature in fewer than 10 patients. Although genetically indistinguishable from classic CTX, this restricted form of xanthomatosis, so-called “spinal xanthomatosis,” does not present with cerebellar signs, cognitive decline, or peripheral neuropathy, and results in a more benign phenotype. Most but not all patients had juvenile cataracts and few had tendon xanthomas. Spinal MRI studies revealed posterior and lateral column white matter abnormalities on T2-weighted images. Consequently, spinal xanthomatosis should be considered in the differential diagnosis of chronic myelopathies in patients who also have juvenile onset cataracts, chronic unexplained diarrhea, and tendon xanthomas. Biochemical testing for serum cholestanol levels should be obtained in such patients. Early diagnosis is crucial because further neurologic deterioration can be prevented by appropriate treatment.

AUTHOR CONTRIBUTIONS

J. McKinnon was responsible for preparation of the manuscript, including figures and references. He takes full responsibility for the data, the analyses and interpretation, and the conduct of the case report. He has had full access to all of the data and has the right to publish any and all data separate and apart from any sponsor. E.P. Bosch was responsible for identification of an appropriate case for submission, mentorship, and revising the manuscript. He serves as the senior author in this submission.
DISCLOSURE

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

REFERENCES

Clinical Reasoning: A case of treatable spastic paraparesis
Jonathan H. McKinnon and E. Peter Bosch
Neurology 2012;79:e50-e53
DOI 10.1212/WNL.0b013e3182635673

This information is current as of August 6, 2012

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/79/6/e50.full

References
This article cites 6 articles, 0 of which you can access for free at:
http://n.neurology.org/content/79/6/e50.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Evoked Potentials/Somatosensory
http://n.neurology.org/cgi/collection/evoked_potentials-somatosensory
Gait disorders/ataxia
http://n.neurology.org/cgi/collection/gait_disorders-ataxia

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 © 2012 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.