A Mystery Case of Proptosis, Optic Neuropathy, and Peripheral Neuropathy

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History & Exam:
A 23-year-old female is referred for the evaluation of proptosis and ophthalmoplegia.

At 7, she had headaches and vision loss to count fingers in her left eye. She was diagnosed with left optic neuritis. Her vision gradually returned to 20/20 bilaterally, but she later developed bilateral optic nerve pallor.

At 13, she was diagnosed with multiple sclerosis based on MRI and repeated episodes of extremity numbness, foot drop, and intermittent diplopia. She continued to have flares while on disease-modifying therapy.

At 22, she developed diplopia thought to be bilateral INO.

Six months later, she noticed proptosis of the right eye and her diplopia persisted. Our examination showed acuity of 20/20 OU and a left relative afferent pupillary defect. She had 3 mm of right proptosis, -3 adduction deficit in her right eye and -2 abduction deficit in her left eye with -1 elevation deficit bilaterally. There was no nystagmus. Saccades were normal. She had one Lisch nodule and one café au lait spot less than 2 cm. The optic nerves appeared pale OS > OD. She had weakness of dorsiflexion, absent reflexes, absent vibration sense, and high arches.

On nerve conduction study her velocities were uniformly slow (15-25 m/s). Visual evoked potentials were normal. A lumbar puncture showed a solitary oligoclonal band, and a protein of 194 mg/dL.

Her identical twin had sequential bilateral optic neuritis at 8 years and a diagnosis of multiple sclerosis at age 12. She had repeated exacerbations of gait impairment while on disease modifying therapy.

MRI of the orbit showed tubular mass-like nerves in the orbits. These had enlarged considerably since imaging from four years before. The skullbase and orbital neural foramina were all enlarged. MRI of the lumbar spine showed fusiform enlargement of the cauda equina and lumbosacral plexus.

A procedure was performed.

Describe The Struggle/Dilemma Of The Clinical Presentation:
This case illustrates difficulty in diagnosing a rarely described clinical syndrome that mimics a common disease, MS. Initial presentations for both sisters were optic neuropathy presumed to be caused by a myelinopathy, but this was mistaken for optic neuritis. Additionally, the patient’s headaches were not from optic neuritis pain but rather from soft tissue involvement of enlarging cranial nerves. Prior to our examination, her ophthalmoplegia was misdiagnosed as INO.

Financial Disclosure: The authors had no disclosures.
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**Final Diagnosis:**
Combined central and peripheral myelinopathy

**Summary Of Case Including Pathology:**
A sural nerve biopsy showed nerve fascicles with loss of large and small myelinated nerve fibers. The large myelinated fibers exhibited thin myelin sheaths and frequent ‘onion-bulb’ formations with concentric layers of Schwann cell processes. There were no inflammatory cells. This was consistent with a chronic peripheral myelinopathy.

This finding lead us to review her sister’s MRI: MRI showed mildly thickened cranial nerves yet more prominent periventricular white matter abnormalities.

Thus, they were given a diagnosis of hereditary central and peripheral myelinopathy.

She returned for follow up ten months later. In the interim, she had gradual reduction in proptosis and the diplopia resolved. Her eye movements were improved and there was reduction of her right proptosis to 1mm.

We sent blood for commercial genetic testing. This evaluated for mutations of CX32, PMP22, and all known demyelinating Charcot Marie Tooths (CMTs). The results were negative.

CMTX involves mutations of CX32 and is known for both peripheral neuropathy and CNS lesions, but not known for hypertrophic nerves. The combination of hypertrophic nerves, biopsy with onion-bulbs, and uniformly decreased conduction velocity fits with CMT1. However, this diagnosis could not be confirmed by genetic testing. The presentation of ‘multiple sclerosis and hypertrophic demyelinating neuropathy’ has been described in fifteen cases brought to biopsy. Two of these cases involve a CIDP-like hypertrophic neuropathy coupled with a CNS demyelination that lacks CSF oligoclonal bands. The lack of oligoclonal bands, as in our case, may reflect a difference in the mechanism from that of MS. The CNS plus PNS demyelination syndrome has been considered an acquired autoimmune process. However, our patient had a twin with similar symptoms, which suggests on a hereditary pathogenesis. Therefore, there may exist an undiscovered mutation of CMT that embodies both hypertrophic nerves and CNS dysmyelination mimicking multiple sclerosis.

**Keywords:** Hypertrophic nerves, Charcot Marie Tooth, Chronic Inflammatory Demyelinating Disease, Myelinopathy, Multiple Sclerosis

**References:**