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

Bonnie M. Keung, MD, Lubdha M. Shah, MD, Danielle E. Eckart, MD, Kathleen B. Digre, MD, Steven S. Chin, MD, Judith E.A. Warner, MD

Dr Keung:

A 23-year-old woman with multiple sclerosis (MS) was referred to our institution for proptosis and ophthalmoplegia. At 7 years of age, she experienced pain and blurred vision in her left eye. Visual acuity in the left eye recovered from count fingers vision to 20/20. Her diagnosis, at that time, was optic neuritis. At age 13 years, she was diagnosed with MS based on episodes of lower extremity weakness, foot drop, and the results of magnetic resonance imaging (MRI). Between the ages of 14 and 22 years, she continued to have neurologic events including intermittent diplopia despite taking interferon beta-1a.

The patient presented to our neuro-ophthalmology clinic at the age of 23 with a 6-month history of diplopia and proptosis of the right eye. Examination revealed visual acuity of 20/20 bilaterally, a left relative afferent pupillary defect, and 3 mm of proptosis. Ocular motility showed deficits in adduction of the right eye, abduction of the left eye, and elevation bilaterally (Fig. 1). She had normal saccades and no nystagmus. Her optic nerves were pale bilaterally (Fig. 2).

On neurologic examination, she had weakness of the intrinsic hand muscles and ankle dorsiflexion bilaterally. She had absent reflexes and vibration sensation. The arches of her feet were high. MRI of the brain, orbits, and spine was performed for evaluation of these progressive neurologic symptoms.

Dr Shah:

The coronal short inversion time inversion recovery (STIR) images show bilateral T2 hyperintense, tubular, elongated masses in the superior aspects of the orbits, larger on the right than on the left (Fig. 3A). These lesions correspond to the expected location of the supraorbital nerves and show minimal enhancement after intravenous gadolinium (Figs. 3B, 3C). Other cranial nerves are also enlarged, including branches of the oculomotor nerves, maxillary and mandibular divisions of the trigeminal nerves, and the hypoglossal nerves (Supplemental Digital Content 1, Supplemental Digital Content 2). Previous MRI studies performed between 2006 and 2011 were reviewed and progressive enlargement of the cranial nerves, particularly the supraorbital nerves were revealed (Fig. 4). Computed tomography (CT) revealed smooth enlargement of the osseous margins of the neural foramina (Fig. 5). MRI of the lumbar spine demonstrates thickening and nodular enhancement of the cauda equina nerve roots (Fig. 6). Sagittal fluid attenuated inversion recovery (FLAIR) images show periventricular demyelinating lesions (Fig. 7).

Dr Keung:

A lumbar puncture was performed. Cerebrospinal fluid (CSF) was clear with normal cell count and normal glucose concentration; however, CSF protein was elevated at 194 mg/dL (normal <60 mg/dL) without oligoclonal bands. Nerve conduction studies and electromyography showed that the right peroneal motor amplitude was reduced with significantly slowed conduction velocity of 15.6 m/s (normal: >41 m/s) and prolongation of the distal latency. The right tibial motor amplitude showed...
a partial conduction block, reduced conduction velocity of 28 m/s (normal >41 m/s) and prolonged latency. The right ulnar motor amplitude showed a partial conduction block; the distal latency was prolonged with severe slowing of conduction velocity of 17.9 m/s (normal >49 m/s). F-wave latencies were markedly prolonged. These findings were consistent with a primary demyelinating polyneuropathy. Brain-stem auditory-evoked responses (BAERs) were normal bilaterally.

Genetic testing for demyelinating neuropathies showed no mutations of CX32, PMP22, and genetically known demyelinating Charcot–Marie–Tooth (CMT) types.

A sural nerve biopsy was performed.

**Dr Chin:**

Semithin plastic sections of the sural nerve biopsy were prepared and examined with toluidine blue O stain. All the
included nerve fascicles show significant loss of large- and
small-diameter myelinated nerve fibers. Some of the myelin
sheaths seem to be disproportionately thin. The most
prominent histopathologic feature is the presence of
frequent, well-formed so-called ‘onion-bulb’ formations
with concentric layers of Schwann cell processes (Fig. 8).
No significant inflammatory cell infiltrates or regenerative
type clusters of myelinated nerve fibers are identified. The
pathologic diagnosis is chronic, severe, peripheral neuropathy
consistent with a myelinopathy.

**Dr Keung:**

The patient received no treatment and returned for follow-
up 10 months later. During that time, she experienced
gradual reduction in proptosis, improvement in eye move-
ments, and resolution of diplopia. In the meantime, we
reviewed the medical history of the patient’s monozygotic

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**FIG. 3.** A. Coronal short inversion time inversion recovery magnetic resonance imaging demonstrates enlarged hyperintense
supraorbital nerves (arrows). The nerves appear dark on T1 image (B) and show minimal contrast enhancement (C).

**FIG. 4.** Sagittal fluid attenuated inversion recovery images reveal that supraorbital nerve in 2011 (A) is larger compared with
2006 (B).

**FIG. 5.** Coronal computed tomography reformatted images depict smooth osseous enlargement of the foramen ro-
tundum bilaterally (arrows).
twin sister. She had sequential attacks of optic neuritis at age 8 and episodes of vertical diplopia. She reported multiple episodes of lower extremity weakness, leading to severe gait impairment and progression of disease despite treatment with interferon beta-1a and glatiramer acetate. Brain MRI of the twin sibling was reviewed.

**Dr Shah:**

The twin sibling’s MRI, at age 23, demonstrates periventricular white matter lesions in a “Dawson’s fingers” pattern (Fig. 9). There is cranial nerve hypertrophy as well, but to a lesser degree than that of her sister (Fig. 10).

**FIG. 6.** Lumbar spine. (A) Contrast-enhanced T1 sagittal magnetic resonance imaging with fat saturation demonstrates thickening of the cauda equina with small foci of nodular enhancement (arrows). (B) Contrast T1 coronal scan with fat saturation reveals thickened cauda equina nerve roots with nodular enhancement (arrows).

**FIG. 7.** Sagittal fluid attenuated inversion recovery scans show multiple hyperintensities within the periventricular and subcortical white matter of both cerebral hemispheres.

**FIG. 8.** A. Sural nerve biopsy transverse section includes seven nerve fascicles with loss of large myelinated nerve fibers (toluidine blue 0, ×40). B. At higher magnification, there are multiple, prominent onion-bulb formations with concentric layers of Schwann cell processes. There is loss of large and small myelinated nerve fibers (toluidine blue 0, ×400).
Final Diagnosis
Familial central and peripheral myelinopathy.

Dr Keung:
The differential diagnosis of nerve hypertrophy includes neurofibromatosis type 1, neurosarcoidosis, chronic inflammatory demyelinating polyneuropathy (CIDP), leprosy, Refsum disease, and the inherited peripheral neuropathies.

The patient and her twin sister were diagnosed with MS at a young age. The poor response to immunomodulating therapy, the absence of oligoclonal bands in the CSF, and normal BAERs in these individuals are all unusual in MS patients. It is uncertain if the siblings had optic neuropathy from optic neuritis, from compression by hypertrophied cranial nerves, or from both mechanisms. The return of good acuity argues more for the first mechanism.

Central demyelination occurs in CIDP and in some types of CMT. Peripheral neuropathy in patients with MS is not common (1). Conversely, patients with CIDP frequently have supratentorial demyelinating lesions on MRI (2). This may be because of the presence of shared autoantigens in the structures of peripheral and central myelin (3). In cases of combined central and peripheral demyelination, central nervous system (CNS) symptoms have been observed to precede the onset of peripheral nervous system (PNS) symptoms. In addition, there is high CSF protein, no oligoclonal bands, and the absence of nerve conduction block (4). There are 3 cases in the literature of CIDP with central demyelination and hypertrophied nerves (5, 6). Similar to our case, these patients had elevated CSF protein without oligoclonal bands. Our patient is unique because she had severely and uniformly slowed nerve conduction velocities; these velocities are more suggestive of CMT1a than CIDP. Her twin sister had a similar disease process, suggesting an inherited rather than an acquired disease process. Two families have been reported with hereditary combined central and peripheral demyelination (7, 8).

Of the inherited peripheral neuropathies, X-linked CMT is known to cause white matter lesions and a mixed axonal and demyelinating neuropathy (9,10). It is caused by a mutation in a gene (GJB1) that encodes the gap junction protein, connexin-32. This protein is found in both the CNS and PNS leading to central and peripheral neuropathies. However, there are no reported cases of X-linked CMT associated with hypertrophic nerves and our patient tested negative for this disease mutation.

We found 3 documented cases of genetically confirmed CMT1a and CNS white matter disease (11,12). Most patients had a relapsing and remitting course. The unanswered question is whether CMT and MS occur coincidentally or if there is a unifying genetic defect. One theory is that the inherited peripheral neuropathy exposes the immune system to antigens that trigger an autoimmune disorder of CNS myelin (12).

Although our patient did not have known CMT X mutations, her sister’s similar clinical course suggests that they share an inherited disorder. The association of inherited neuropathy with hypertrophic cranial nerves and CNS demyelination has previously not been reported. The recognition and evaluation of future cases will determine if this is yet another type of hereditary neuropathy.
REFERENCES


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