

# Leber Hereditary Optic Neuropathy Mimicking Neuromyelitis Optica

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**Abstract:** Leber hereditary optic neuropathy (LHON) is rarely associated with multiple sclerosis–like features. We present a case of a 65-year-old African American woman with LHON masquerading as neuromyelitis optica (NMO). We highlight the features of the clinical examination and MRI that were suggestive of an alternative diagnosis and review the literature regarding LHON and multiple sclerosis. The diagnosis of LHON should be considered in all cases of acute or subacute bilateral optic neuropathy, including presumed seronegative NMO.

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Neuromyelitis optica (NMO), also known as Devic disease or the optic-spinal variant of multiple sclerosis (MS), is an inflammatory condition of the central nervous system marked by simultaneous or sequential acute or subacute bilateral optic neuritis and transverse myelitis. Initially felt to be a variant of MS, evidence now supports NMO as a unique disease entity demonstrating an aggressive clinical course with poor response to standard MS immunomodulatory therapies; characteristic features include 1) T2-hyperintense spinal cord lesions extending for greater than 3 vertebral segments, 2) the presence of NMO-IgG serum antibodies, and 3) a brain MRI not meeting the diagnostic criteria for MS (1). The presence of 2 of the 3 latter characteristics in the setting of optic neuritis and acute myelitis is diagnostic of NMO (Table 1) with an estimated 99% sensitivity and 90% specificity (2). Limited reports have suggested a possible link between NMO and autoimmune disorders, such as systemic lupus erythematosus,

Hashimoto thyroiditis, and Sjogren syndrome, although the strength of this association remains unclear (3,4).

Leber hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease marked by acute or subacute onset optic neuropathy in 1 eye with frequent simultaneous or sequential involvement of the contralateral eye (5). More than 90% of European families demonstrate 1 of 3 mitochondrial DNA (mtDNA) point mutations named for the position of the nucleotide mutation (11778, 14484, and 3460) (6). While LHON is classically isolated to pathology of the optic nerves, rarely patients with LHON have an associated MS-like disease (7–10). We present a case of LHON masquerading as NMO.

## CASE REPORT

A 65-year-old African American woman was referred to our clinic after sequential subacute onset of simultaneous painless vision loss 3 months prior. One year before the onset of visual symptoms, the patient first noted bilateral lower extremity pain, weakness, and gait imbalance. The diagnosis of idiopathic cervical myelopathy was established following an extensive workup by several neurologists. The evaluation included the following unremarkable studies: complete blood count, comprehensive metabolic profile, B-12/folate, vasculitis panel, syphilis serology, infectious hepatitis panel, thyroid function tests, serum angiotensin-converting enzyme, and paraneoplastic panel (including CRMP-5 antibody). A lumbar puncture revealed normal cerebrospinal fluid (CSF) composition, normal CSF IgG index/synthesis, and a negative CSF-VDRL. NMO IgG antibody was sent and was negative. Electromyography (EMG) and nerve conduction studies demonstrated mild axonal sensory polyneuropathy. A subsequent sural nerve biopsy showed axonal degeneration without inflammation, vasculitis, or amyloid. CT of the chest was unremarkable. A spinal MRI study revealed a longitudinal nonenhancing T2 hyperintensity of the posterior columns throughout the entire cervical spine (Fig. 1).

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**TABLE 1.** Diagnostic criteria for NMO

Optic neuritis
Acute myelitis
Two of 3 supporting criteria
Contiguous spinal cord MRI lesion extending $\geq 3$ vertebral segments
Brain MRI not meeting diagnostic criteria for MS
NMO-IgG seropositive status

Adapted from reference 2.

The patient's myelopathy-related deficits remained stable for more than 1 year. She then developed subacute onset of simultaneous painless vision loss in both eyes, and the visual acuity was 20/300, right eye, and 20/200, left eye. The optic discs were noted to be "hyperemic" with no comment regarding telangiectasias. Two months later, vision was 6/200 in both eyes. Visual fields showed cecentral scotomas in each eye. Pupils were minimally reactive to light without an afferent pupillary defect. The patient was unable to recognize any color plates. Tonometry, external and anterior segment examinations, and cranial nerve testing were all unremarkable. The optic discs were pale temporally (Fig. 2). Contrast-enhanced MRI of the brain and orbits was normal (Fig. 3).

Review of the patient's medical history revealed well-controlled hypertension and mild chronic obstructive pulmonary disease presumably due to a history of smoking. She quit smoking 1 year ago and denied current or past alcohol



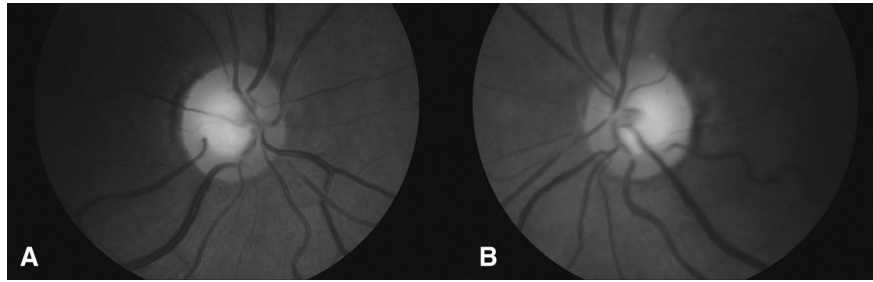
**FIG. 1.** T2 sagittal MRI through the cervical spine revealing a longitudinal hyperintensity along the posterior columns (arrows).

abuse. Her family history was negative for autoimmune disease, neurologic degeneration, and serious vision problems. Genetic testing for LHON revealed the pathologic mtDNA 14484 point mutation.

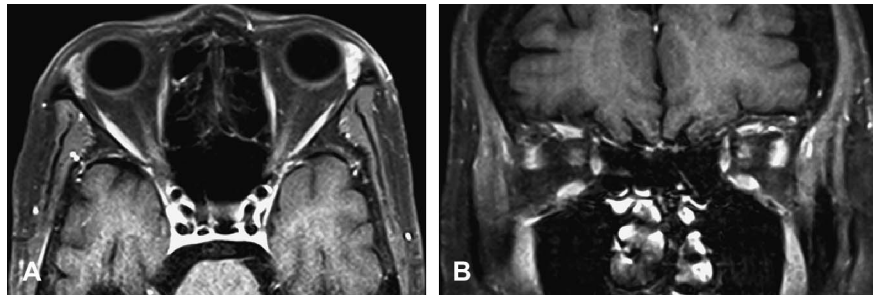
## DISCUSSION

In 1970, Wallace (7) published a report highlighting an association between LHON and other neurologic signs, including encephalopathy, spasticity, and increased deep tendon reflexes. In 1992, Harding further described a rare subset of LHON patients with MS-like features (LHON-MSL), which has led some to refer to LHON-MSL as "Harding syndrome" (8,9). Since that time, there have been less than 30 reported cases of LHON-MSL. All 3 of the most common causative LHON mtDNA point mutations have been reported in LHON-MSL, with the 11778 mutation being the most frequent (10). Perez compiled 17 cases of LHON-MSL from the literature and found a surprising 1.8:1 female to male ratio (F:M) in contrast to the previously published F:M of 1:3—1:8 in LHON without MSL (ratios depending on specific mutation) (10,11). The neurologic manifestations of LHON-MSL are highly variable and often result in severe disability, with 75% (8 of 12) of patients demonstrating difficulty walking due to nonvisual neurologic disease over a mean 13-year follow-up period (10). Visual decline consistent with LHON precedes other neurologic sequelae in 70% of cases by an average of 4.3 years. Central nervous system white matter changes on MRI often have an appearance similar to inflammatory demyelinating plaques of MS, and 87% of LHON-MSL patients demonstrate CSF oligoclonal bands during the disease course. Histologic examination of CNS tissue in LHON-MSL has demonstrated findings consistent with inflammatory demyelinating MS-like plaques (12). The postmortem histology of an LHON-MSL patient with T2 hyperintensity of the dorsal spinal tracts reported by Jaros et al (13) demonstrated changes consistent with a primary spinal cord neurodegeneration plausibly from mitochondrial dysfunction rather than inflammatory demyelination. In our case, the spinal cord changes detected on MRI involved predominately the posterior columns, in contrast to typical NMO lesions, which involve the entire spinal cord with expansion. While the underlying pathophysiology for LHON-MSL remains elusive, the volume of case reports in the literature seems to support an association between LHON and white matter CNS disease, not explainable by chance alone.

An NMO-like presentation of LHON has only rarely been described (13). Key features distinguishing NMO from LHON-MSL include the location and characteristics of spinal cord lesions, the presence of a known pathogenic LHON mtDNA mutation, the absence of NMO-IgG serum antibodies, and the clinical differences between NMO associated optic neuritis and LHON-MSL associated optic neuropathy.



**FIG. 2.** Right (A) and left (B) optic discs showing temporal pallor.



**FIG. 3.** No abnormalities of the optic nerves or brain are detected on contrast-enhanced T1 axial (A) and coronal (B) MRI.

Demyelinating optic neuritis was also a diagnostic consideration in our patient. This optic neuropathy is characterized by an acute onset of eye pain (92.2%) with vision loss, good visual recovery with 92% of affected eyes demonstrating better than or equal to 20/40 vision at 15 years of follow-up, and enhancement of the affected optic nerve on MRI (14,15). In contrast, LHON typically is associated with painless vision loss, tends to be familial (50%) and only rarely demonstrates enhancement on MRI (5). Spontaneous recovery of vision is unusual in LHON and primarily associated with the 14484 mtDNA mutation (16). Optic neuritis associated with NMO produces more severe long-term visual impairment than demyelinating optic neuritis. Papais-Alvarenga et al (17) reported that 63% of affected eyes with NMO optic neuritis were left with severe visual loss (<20/200) over a median follow-up period of 8 years.

We acknowledge the possibility that our patient might have co-occurrence of seronegative NMO and LHON. However, we consider this highly unlikely for the following reasons: 1) the lack of pain at the onset of visual loss, 2) slow progression of visual loss over months rather than weeks, and 3) lack of enhancement or high T2 signal within either optic nerve on MRI.

In conclusion, LHON is occasionally associated with MS-like features, which can confound the diagnosis. We present a case of LHON-MSL masquerading as NMO. Establishing the correct diagnosis is critical, since the prognosis and

management options for the 2 conditions are very different. While NMO may respond to potent immunosuppressive agents, no treatment to date has been shown to be effective for LHON. The diagnosis of LHON should be considered in all cases of acute or subacute bilateral optic neuropathy, including presumed seronegative NMO.

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