

Painful vision loss in Leber hereditary optic neuropathy with novel ND1 variant mimicking optic neuritis

More than 90% of Leber hereditary optic neuropathy (LHON) cases are caused by 1 of 3 primary mitochondrial DNA mutations.¹ They are *MT-ND4* (m.11778G>A, p.Arg340His), which accounts for ~70% of all cases; *MT-ND6* (m.14484T>C, p.Met64Val); and *MT-ND1* (m.3460G>A, p.Ala52Thr) found in genes coding protein subunits of NADH dehydrogenase (complex I) of the electron transport chain, resulting in defective energy production.² Most patients with LHON presents with sudden unilateral painless vision loss followed by fellow-eye involvement within weeks to months.^{1,2} Peak age of onset is during the second and third decades of life.² Penetrance is sex biased, with the LHON phenotype affecting more males (up to ~50%) than females (~5%–10%) carrying the same primary mutation.² Secondary unidentified genetic and environmental factors (e.g., smoking, alcohol, toxic drug exposure, and vitamin B₁₂ and folate deficiency) also may drive variability in penetrance and clinical presentation.² We report an atypical case of painful sequential vision loss in a female with a novel G>T mutation at locus 3460 superficially masquerading as optic neuritis due to the presence of ipsilateral pain and central scotoma.

A 27-year-old female presented with right eye vision loss, ocular pain aggravated by eye movements, and dyschromatopsia that progressed over the course of a day. Pupillary light reflex was intact without relative afferent pupillary defect despite diminished visual acuity (right eye 20/200, left eye 20/50-2). Contrast-enhanced magnetic resonance imaging of brain and orbits was unremarkable (Fig. 1A, B). Fundus photographs showed slight peripapillary atrophy bilaterally and mildly hyperemic neuroretinal tissue without optic disc swelling, pallor, or telangiectasis (Fig. 1C). Automated perimetry visual field testing showed moderate to severe generalized depression in the right eye (mean deviation, -24.44 dB; false-negative error rate, 16%) and moderate generalized depression in the left eye (mean deviation, -7.49 dB; false-negative error rate, 8%) consistent with subclinical second-eye involvement (Fig. 1D). Symptoms worsened over 5 days despite empirical prednisone 1250 mg orally for 5 days for presumed optic neuritis. Vitamin B₁₂ was low (243 mg/dL), with normal thyroid-stimulating hormone (5.17 mIU/L). Investigations were negative for *Bartonella henselae*, *Borrelia burgdorferi*, HIV, antinuclear antibody, rheumatoid factor, aquaporin-4, and myelin oligodendrocyte glycoprotein autoantibodies. Serum lactate was elevated (4.8 mmol/L). Lumbar puncture revealed normal opening pressure with normal cell counts, glucose, and protein and no oligoclonal bands. Optical coherence

tomography (OCT) demonstrated normal peripapillary retinal nerve fibre layer (ppRNFL) thicknesses of the right eye (92 μ m) and left eye (93 μ m; Fig. 1F), though early ganglion cell layer change was evident on macular OCT bilaterally (right more than left eye; Fig. 1E).

Left (contralateral) eye vision loss began and progressed precipitously 20 days later (right eye, counting fingers at 2 ft; left eye, 20/400). Repeat OCT showed stable ppRNFL at 1 month (right eye, 92 μ m; left eye, 94 μ m) and normal values at 3 months (right eye, 102 μ m; left eye, 105 μ m; Fig. 1F). Mitochondrial genome analysis revealed a novel homoplasmic missense variant m.3460G>T, p.(Ala52Ser) in the *ND1* gene, predicted to be pathogenic, at a locus well known to cause LHON. The patient started idebenone 300 mg orally 3 times daily and vitamin C 500 IU daily without improvement in vision. Unfortunately, the patient was lost to follow-up and declined further visual testing. However, a telephone correspondence 7 months after the onset disclosed that her vision had not improved subjectively.

This report highlights a case of painful LHON caused by a novel G>T point mutation at mitochondrial DNA locus 3460 in the *ND1* gene not previously published in the MITOMAP database or the literature that superficially mimicked optic neuritis early on. Despite pain and central scotoma mimicking optic neuritis, corticosteroid unresponsiveness, pupil visual dissociation, absent relative afferent pupillary defect, discordant retinal nerve fibre layer and ganglion cell layer changes on OCT, and normal neuroimaging were important early clues to LHON.

The primary 3460 mutation that typically causes LHON results from a missense substitution of nonpolar hydrophobic alanine with polar hydrophilic threonine at position 52 of the *ND1* protein. In contrast, the missense variant in our patient resulted in substitution with serine. Although the precise impact of these amino acid substitutions on pathogenic mechanisms and clinical phenotype is unknown, threonine and serine are both polar hydrophilic amino acids that ostensibly drive LHON pathogenesis in a similar manner.³

Despite ocular pain in about half (47.6%) of patients with coexisting multiple sclerosis-like illness (e.g., true optic neuritis) and LHON (sometimes called *Harding's disease*), vision loss in LHON is characteristically painless.⁴ However, poor visual recovery, preserved pupillary light reflex, absent relative afferent pupillary defect, normal magnetic resonance imaging, and relative RNFL preservation such as those in our patient help to distinguish LHON from optic neuritis.

Maintenance of the pupillary light reflex (i.e., pupil-vision dissociation) is an important clue for LHON, thought to result from relative preservation of melanopsin retinal ganglion cells in mitochondrial optic neuropathies.⁵

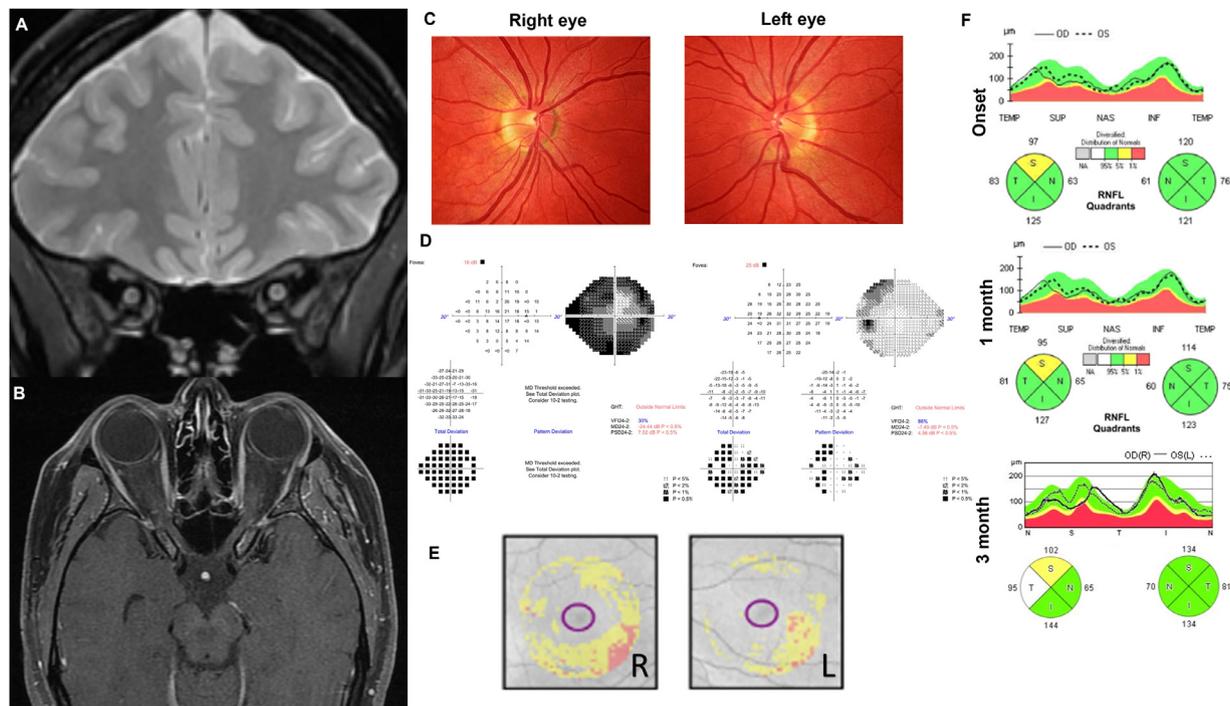


Fig. 1—Magnetic resonance imaging, fundus, perimetry, and optical coherence tomography findings. T₂-weighted coronal sequence of brain (A) and T₁-weighted axial scan of orbits with fat suppression after gadolinium administration (B) were unremarkable. Fundus photographs showed slight peripapillary atrophy bilaterally and mildly hyperemic neuroretinal tissue without optic disc swelling, pallor, or telangiectasis (C). Automated perimetry showed moderate to severe generalized depression in the right eye at onset and moderate nonspecific generalized depression in the left eye (D) with accompanying asymmetric ganglion cell complex thinning on macular optical coherence tomography (E) consistent with subclinical second-eye involvement. Optical coherence tomography measurements in the right eye (left) and left eye (right) showed stable peripapillary retinal nerve fibre layer at 1 month and normal values at 3 months following severe sequential right then left eye vision loss (F).

Early ganglion cell complex (GCC) layer thinning with preserved RNFL (i.e., GCC-RNFL discordance) on OCT is another important clue for LHON in the early acute phase. However, early subclinical second-eye involvement as detected in our patient on automated perimetry and GCC macular OCT is not rare. Furthermore, the preserved ppRNFL at 1 month and unexpected slight increase (pseudodema) at 3 months in our patient may result from a compensatory aggregation of mitochondria in nerve fibres in response to dysfunction but are often followed by postevent optic atrophy detected on both ppRNFL and GCC scans at later time points.²

Although the elevated lactate seen in our patient is atypical for LHON, mutations in the *ND1* gene have been associated with overlap syndromes between LHON and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).¹ Whether ocular pain and elevated lactate in LHON predict higher respective risk for concomitant multiple sclerosis-like or MELAS overlap phenotypes is unknown but warrants prospective evaluation. It is also possible low vitamin B₁₂ may have been an aggravating factor in our patient.²

Early genetic testing when LHON is suspected may identify patients who could be enrolled in a treatment trial for LHON before more irreversible vision loss or fellow-eye involvement occurs.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this correspondence. Informed

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