WHEN THE DIAGNOSIS DOESN'T COME EASY

Sometimes getting to the bottom of a patient's vision loss takes closer examination, additional testing, and a big dose of patience.

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A 30-year-old established Black male patient presented with a several-year history of slowly progressive vision loss in both eyes. He reported a significant decline in vision during the preceding 6 months that was similar in both eyes. He stated that he had experienced no trauma, pain, or other neurologic symptoms.

The patient's medical history was positive for type 2 diabetes mellitus, hypertension, and depression. His medical regimen included metformin, glimepiride, empagliflozin, dulaglutide, losartan, metoprolol, and trazodone. His family ocular history was unremarkable, but his family medical history was positive for breast cancer (grandmother). He had no known medical allergies. The patient stated that he used neither alcohol nor illicit drugs, but reported smoking approximately four cigarettes daily.

CLINICAL FINDINGS

The patient's UCVA was 20/200 OU, and there was no improvement with refraction or pinhole acuity testing. Approximately 4 years earlier, his BCVA had been 20/20 OU. An external ocular examination of each eye was within normal limits. Pupil and extraocular motility testing was normal OU. IOP measurements with Goldman applanation tonometry were 22 mm Hg OD and 20 mm Hg OS.

Confrontation visual fields were full to finger counting peripherally, but the patient described difficulty seeing fingers with his central vision OU. Amsler grid testing suggested central scotomas OU, and automated visual field testing using Humphrey visual field 30-2 and 10-2 protocols (Carl Zeiss Meditec) confirmed this (Figures 1 and 2). A red desaturation assessment showed a subjective reduction OU, and subsequent color vision testing showed a severe

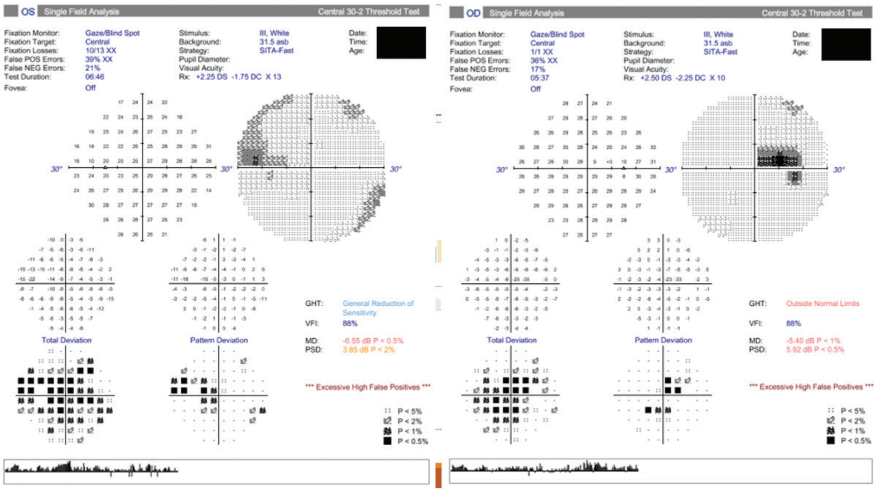


Figure 1. Humphrey visual field 30-2 testing. Note the central depressions OU.

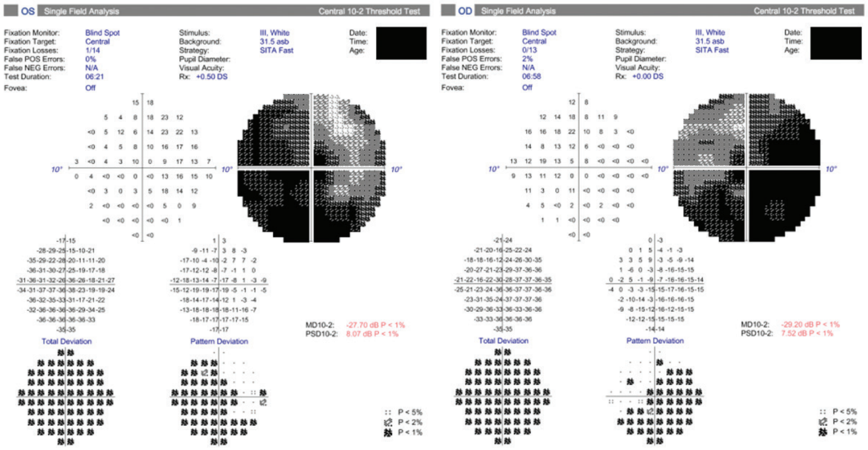


Figure 2. Humphrey visual field 10-2 testing. Note the dense central scotomas OU.

bilateral loss of color discrimination (Figure 3). A dilated fundus examination was normal, except for temporal optic nerve pallor OU (Figure 4). OCT imaging demonstrated temporal thinning of the retinal nerve fiber layer (RNFL) and extensive loss of the ganglion cell layer OU (Figures 5 and 6).

Given the bilateral optic nerve pallor/atrophy, an MRI of the brain was obtained, and it was entirely normal. Additional lab work was ordered, including a CBC with differential; antinuclear antibody, angiotensin-converting enzyme, and fluorescent treponemal antibody test absorption tests; erythrocyte sedimentation rate; rapid plasma reagin; tests for vitamins B1 and B12 and folate; and genetic testing (ID Your IRD, Spark Therapeutics).

DIFFERENTIAL DIAGNOSES

Because the patient stated that he had no history of trauma,[1] traumatic optic nerve atrophy was ruled out. The patient had a normal brain MRI, and the vision loss in both eyes was slowly progressive,[1] therefore, optic neuritis was deemed unlikely. The normal MRI also ruled out compressive optic neuropathy, which is slowly progressive, can be bilateral or unilateral, and can compress the visual pathway, but is typically evident on neuroimaging.

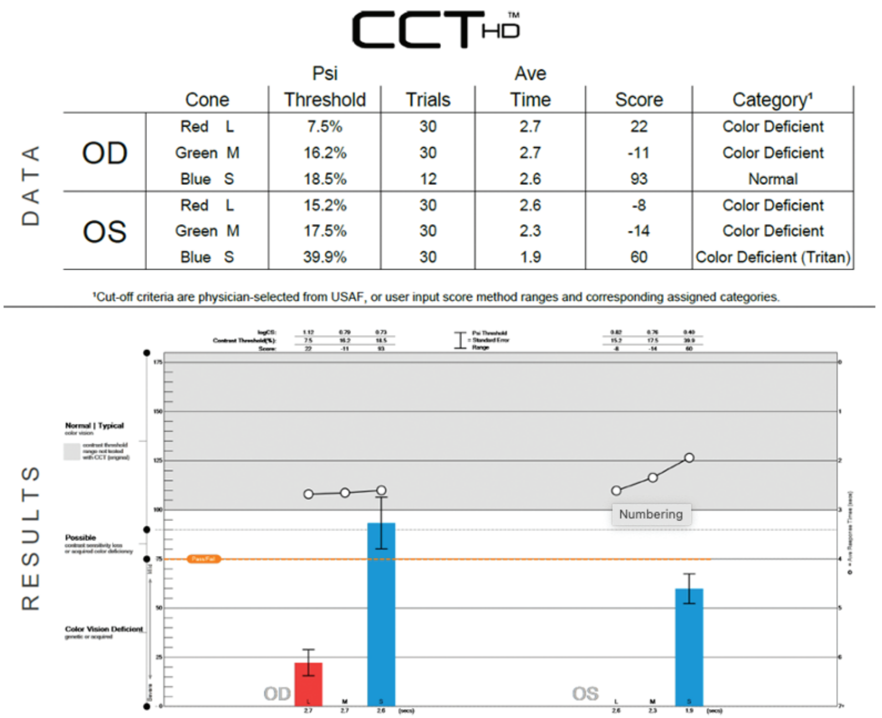
In consideration of nonarteritic ischemic optic neuropathy, the patient had many of the associated risk factors; however, he also had symmetrical temporal optic nerve pallor/atrophy and central scotomas in each eye, making this diagnosis unlikely as well. The patient's CBC with differential, vitamins B1 and B12 tests, folate and antinuclear antibody tests, and ESR were normal, ruling out yet another potential diagnosis: nutritional optic neuropathy, which causes bilateral, progressive, painless loss of vision.[1]

Another potential cause of optic atrophy is an underlying chronic or acute syphilis infection, but the patient's negative/normal rapid plasma reagin and fluorescent treponemal antibody test absorption test ruled out syphilitic optic neuropathy.

Slowly progressive retinal photoreceptor degeneration can cause painless, bilateral vision loss. The patient underwent hereditary retinal genetic testing, which revealed a possible genetic variant for autosomal recessive cone-rod

AT A GLANCE

- ▶ Leber hereditary optic neuropathy (LHON) can result in significant vision loss in the form of visual acuity and/or central scotomas.
- ▶ The diagnosis of LHON should be based on careful history, evaluation of structural and functional vision testing, and on genetic confirmation of pathogenic mtDNA mutations.
- ▶ Because LHON is an incompletely penetrant disease, not all individuals with the genotype experience vision loss.



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DATA

	Cone	Psi Threshold	Trials	Ave Time	Score	Category¹
OD	Red L	7.5%	30	2.7	22	Color Deficient
	Green M	16.2%	30	2.7	-11	Color Deficient
	Blue S	18.5%	12	2.6	93	Normal
OS	Red L	15.2%	30	2.6	-8	Color Deficient
	Green M	17.5%	30	2.3	-14	Color Deficient
	Blue S	39.9%	30	1.9	60	Color Deficient (Tritan)

¹Cut-off criteria are physician-selected from USAF, or user input score method ranges and corresponding assigned categories.

Figure 3. Color vision test (ColorDx, Konan Medical) of patient. Notice severe red and green color deficiencies with relative sparing of blue color discrimination.

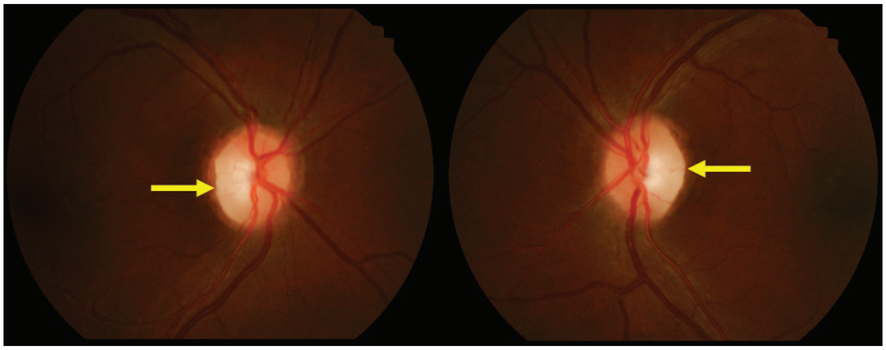


Figure 4. Standard color photography of patient's optic nerves. Note the temporal optic nerve pallor OU (yellow arrows).

dystrophy, however, full-field ERG testing was normal, which ruled out outer and inner retinal dysfunction. Moreover, visual evoked potential was abnormal, which suggested optic nerve dysfunction, rather than retinal dysfunction (Figure 7). Cone-rod retinal dystrophy was therefore unlikely.

The patient had many clinical characteristics associated with dominant optic atrophy,[1,2] but the *OPA1* abnormality appropriate to the diagnosis was absent on genetic testing, making this diagnosis unlikely. This left us with Leber hereditary optic neuropathy (LHON), which produces central or cecocentral scotomas, symmetrical vision loss, and dyschromatopsia, and can cause sectoral or diffuse optic atrophy/pallor. This form of hereditary optic nerve/retinal ganglion cell degeneration is associated with specific mitochondrial genetic defects (m.11778G>A, m.3460G>A, m.1448T>C).[1,2] The patient's clinical profile fit a diagnosis of LHON. Genetic testing was positive for the m.1448T>C genetic defect, which confirmed a diagnosis of LHON.

DISCUSSION

Three point mutations account for 90% to 95% of LHON cases (m.11778G>A in 60–90% of cases, m.3460G>A in 4–19% of cases, and m.14484T>C in 7–30% of cases). The most common mutation, 11778G>A, is associated with the worst visual prognosis (< 20% recover 15 letters of vision).[1-9] Visual recovery typically includes the recovery of color vision and an improvement in visual fields and visual acuity.[1] The best chance of recovery (up to 60% recover 15 letters of vision) is associated with m.14484T>C.[1,5]

Pathophysiology

Because LHON is an incompletely penetrant disease, not all individuals with the genotype experience vision loss.[1,4,5,10] The risk of developing LHON is 50% and 10% risk for men and women, respectively.[1,3-5,8] Current evidence suggests that LHON is a complex disease with multifactorial genetic and environmental triggers that interact with the LHON mitochondrial DNA mutation.[5]

Most mitochondrial disorders produce multiple areas of systemic dysfunction throughout the body so that multiple organ systems are involved. LHON, however, involves the eyes almost exclusively.[4] It is unknown why LHON mutations typically do not cause other systemic dysfunction/findings.[4] When extraocular manifestations (ie, cardiologic and/or neurologic) occur, it is referred to as *LHON plus syndrome*.[1,4]

Epidemiology

Because LHON is a mitochondrial DNA mutation, and mitochondria are passed from the mother to the offspring, LHON only follows a maternal inheritance pattern.[2,4,6] The prevalence of LHON genotype is approximately one in 8,500 people, but the prevalence of the disease has been reported in several studies to be approximately one in 27,000 to 50,000.[2,4-7,11] Males are affected in approximately 80% to 90% cases.[4,6,11,12] Age at symptom onset has a large range, reportedly from 2 to 87 years of age; however, symptoms typically start in second to third decades of life (ie, 15 to 35 years of age).[2,4,5,7,11] Less than 10% of patients are 12 years of age or younger when symptoms first start.[5] However, approximately 95% of LHON carriers will have their onset of visual symptoms before 50 years of age.[1] Approximately 40% of patients deny a family history of LHON, although 60% do report a family history.[1,11]

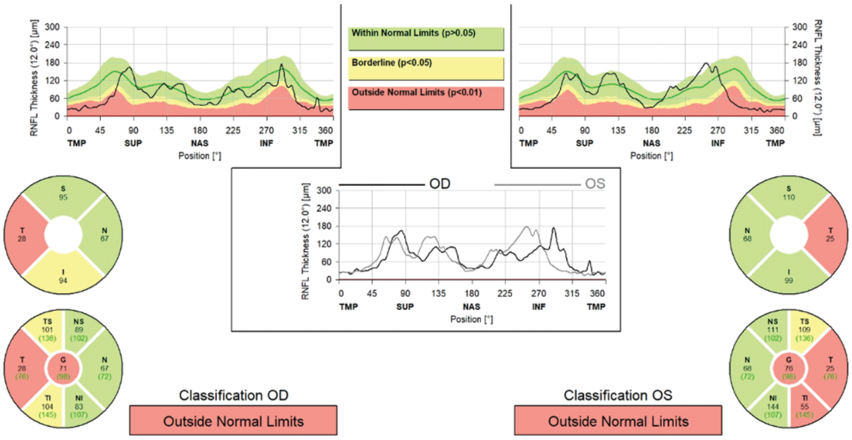


Figure 5. Retinal nerve fiber layer (RNFL) OCT of patient's optic nerves (Spectralis, Heidelberg Engineering). Notice the abnormal RNFL thinning present OU in the temporal sector, consistent with the pallor/atrophy seen on clinical examination.

Environmental Risk Factors

Given the known incomplete penetrance, other environmental risk factors (ie, smoking/tobacco and alcohol) have been suspected and sought after in hopes of at least partially explaining this incomplete penetrance.[1,4,5] Specifically, environmental risk factors (ie, smoking and alcohol use) that can increase reactive oxygen species appear to have the ability to overtax or overburden the mitochondria, leading to LHON symptom onset.[1,5]

For example, smoking resulted in clinical penetrance in 93% of men with the LHON mutation in one study.[4]

INTERNATIONAL CONSENSUS GUIDELINES

Below are some important points from the international consensus statement.[6]

- Clinical stages of LHON can be defined according to time from onset and clinical investigations:
    - Asymptomatic mutation carriers
    - Subacute (< 6 months onset)
    - Dynamic (6 to 12 months onset)
    - Chronic (> 12 months onset)
- Diagnosis can be made by patient/family history, baseline examination/testing, and mitochondrial DNA testing.
- It can take months to reach a confirmed diagnosis.
- Other optic neuropathies (eg, demyelination, compression, nutritional, toxic, maculopathies, nonorganic vision loss) should be ruled out.
- Idebenone should be started as soon as possible with 900 mg/day in patients with disease less than 1 year.
- In subacute/dynamic patients, treatment at 900 mg/day should be continued for at least 1 year to assess response.
- There is not enough evidence to recommend treatment in patients with chronic disease between 1 and 5 years (after disease onset in the second eye).
- Treatment is not recommended for relatives of patients with LHON, but lifestyle counseling is recommended.

Heavy alcohol consumption has also been shown to be a risk factor for LHON symptoms.[1,4,5] Other substances (ie, medications, toxins) have been suspected of being harmful in LHON, but have not been strongly connected with symptom onset at this time.[1,4] Therefore, carriers of the LHON mutation should be strongly advised not to smoke and to avoid excessive alcohol intake, as these are the most modifiable risk factors for these patients.[5]

Clinical Presentation

Acute or subacute, unilateral, painless progressive central visual acuity loss (typically ≤ 20/200) with dyschromatopsia, and central or cecocentral scotomas in male patients is the usual way LHON patients present.[1-7] Involvement of the second eye can occur 1 to 4 months later, but 95% to 97% of second eye involvement occurs within 1 year.[1-4,6,7] Interestingly, the longest span documented between fellow eye involvement in LHON is 41 years.[13] Approximately 25% of cases report simultaneous bilateral vision loss at onset.[7] However, visual acuity has been reported to range significantly from mildly subnormal to light perception.[1,4] Although many patients with LHON end up being classified as legally blind, complete blindness in LHON is considered rare and unusual.[2,8]

Posterior pole findings can include RNFL swelling around the optic nerve with optic nerve hyperemia,

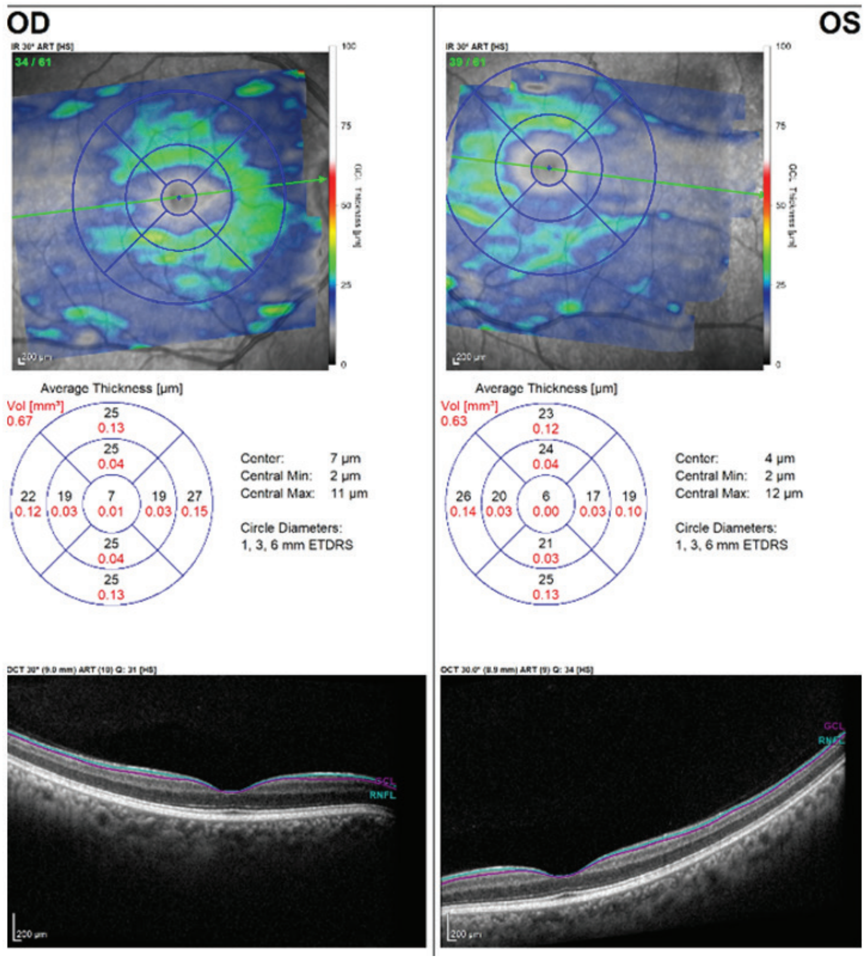


Figure 6. Ganglion cell layer thickness OCT of patient. Notice the bilateral extensive loss of GCL OU, consistent with optic nerve pallor and RNFL thinning in clinical examination.

circumpapillary telangiectasia, lack of disc leakage on intravenous fluorescein angiography, and tortuous and engorged retinal vessels.[1,2,4,5] Rarely, hemorrhages and exudates have been attributed to LHON, also.[4] Additionally, some patients with acute LHON develop optic nerve cupping following visual loss without any of the typically expected fundoscopic findings.[2,4] Approximately 20% of patients with LHON will have normal appearing optic nerves during the early/acute phases.[1,7]

Chronic findings of LHON will include resolution of the circumpapillary telangiectasias and retinal vessel tortuosity, RNFL thinning (usually within 4–6 months after onset, but can occur up to 12 months later), and optic nerve pallor as the retinal ganglion cells atrophy.[1,2,4-6,10] Vision loss is usually considered permanent, but more than 50% of patients with LHON with the 14484 mutation can have some spontaneous visual improvement.[3,4] In fact, chance of vision recovery is tied to the specific mutation that LHON patients carry.[4] Patients with the m.14484T>C mutation have shown visual improvement in up to 65% cases, compared to only 4% of patients with the m.11778G>A mutation.[4]

Clinical Workup

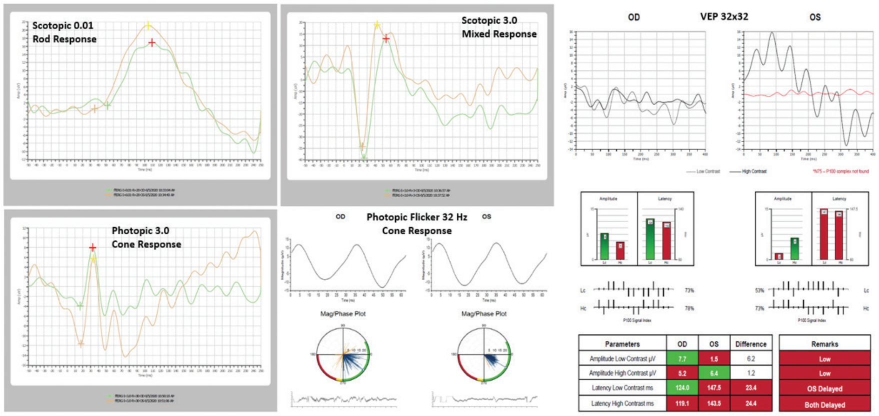
Consensus agreement on appropriate clinical workup should include an extensive case history, visual acuity, color vision, fundus examination, automated visual field perimetry (ie, 30-2, 24-2, 10-2), and OCT imaging (ie, RNFL and ganglion cell layer).[1,6,10] Additionally, strong consideration should be given to neuroimaging (ie, MRI) to help rule out compression, demyelination, etc. that can mimic some of the findings associated with LHON.[6] Other suggested ancillary testing include Amsler grid, fundus photography, OCT angiography, and electrophysiology (ie, visual evoked potentials and pattern ERG).[1,5,10]

Treatment and Management

An international consensus statement for the treatment and management of LHON has been published with helpful management recommendations (see *International Consensus Guidelines*).[6] There is no cure for LHON, and prognosis is quite poor in most cases, leading to legal blindness.[2,4-6,8] More than 70% cases are ≤ 20/200 within 3 months of symptom onset.[12] However, LHON is an active area of research in the scientific community.[3-5,7] Various treatments have been attempted to improve adenosine triphosphate production through mitochondrial oxidative phosphorylation and electron transport chain function in some manner.[3-5] These treatments have included: idebenone, coenzyme Q10, creatine, alpha lipoic acid, L-carnitine, L-arginine, dimethylglycine, cysteine, dichloroacetate, corticosteroids, cyclosporine, brimonidine, minocycline, succinate, and vitamins B1, B2, C, K1, K2, and E,[1-7] but many of these have resulted in insufficient evidence to support mainstream use.[14]

The most popular treatment continues to be idebenone,[3,5,6,12] which is a cousin molecule of coenzyme Q10 that helps to prevent reactive oxygen species from forming by bypassing complex I to complex III in the electron transport chain, and ultimately limiting oxidative damage to mitochondria and other cell membranes, causing the optic nerve and retinal ganglion cell degeneration.[3-5,12]

Other treatments under investigation include EPI-743 (a para-benzoquinone with higher antioxidant activity than idebenone), triphenylphosphonium,



Parameters	OD	OS	Difference
Amplitude Low Contrast µV	7.7	1.5	6.2
Amplitude High Contrast µV	5.2	6.4	1.2
Latency Low Contrast ms	124.0	147.5	23.4
Latency High Contrast ms	119.1	143.5	24.4

Remarks
Low
Low
OS Delayed
Both Delayed

Figure 7. Electrophysiology testing (Diopsys NOVA) of patient. Scotopic rod response (top left) was normal, scotopic mixed response (top center) was normal, photopic cone response (bottom left) was normal, photopic flicker cone response (bottom center) was normal, visual evoked potential (VEP; far right) showed reduced amplitude and increased latencies OS>OD. Normal ERG findings rule out possible cone-rod dystrophy, and abnormal VEP is suggestive of optic nerve dysfunction OU.

mitoquinone mesylate, Decyl(triphenyl)phosphonium, MTP-131, vitamin-E-derived molecule KH176, cysteamine bitartrate, elamipretide, estrogen, methylene blue, near-infrared therapy, mitophagy modulation, stem cell therapy, mitochondrial replacement therapy, and gene therapy.[1-5,7,8,15-17] However, many of these potential therapies have several hurdles that need to be overcome at this stage prior to mainstream implementation.[4,15]

Genetic counseling remains an important part of the LHON management protocol, as it helps identify offspring and/or other relatives at risk.[1,3,4] Discussion of open clinical trials with patients may be encouraged.[1] Because LHON is mitochondrially inherited, men cannot pass the gene on to their offspring, but all children of women with LHON will carry the mutation.[2] Additionally, low vision consultation is a necessary and sometimes underutilized referral, as significant quality-of-life issues can be present, given the amount of vision loss related to LHON cases.[1,3,4] Finally, substances and habits that could increase risk or promote mitochondrial dysfunction (ie, tobacco use and heavy alcohol consumption) should be avoided by patients with LHON and their relatives who are at risk for vision loss from LHON.[1,3-5]

LHON LESSONS

Our patient has been formally diagnosed with LHON and was counseled on smoking cessation with avoidance of alcohol. We discussed genetic testing for his relatives and we are following him every 6 to 12 months, although we elected not to start idebenone treatment based on cost and the patient being outside the timeline (< 1 year from symptom onset) per the international idebenone treatment consensus guidelines.[6] He has visited our low vision department multiple times and has obtained low vision devices that have enabled him to continue his employment in the food service industry.

The diagnosis of LHON should be based on careful history, evaluation of structural and functional vision testing, and on genetic confirmation of pathogenic mtDNA mutations.[5,6] LHON can result in significant vision loss in the form of visual acuity and/or central scotomas.[6] Thus, LHON can be a frustrating disease for patients and their physicians.[8] Due to symptom onset at a relatively young age in the majority of cases, quality of life and the ability to maintain employment and/or continue with education is a challenge many patients with LHON face. Thus, low vision specialists can be a valuable resource for patients with LHON, and we feel that low vision consultation should be encouraged in all cases. Treatment options are limited, but idebenone can be considered for any patients diagnosed early in the course of the disease.[3,6] Hopefully, future research will provide better treatment options with improved patient outcomes. ■

1. Pilz YL, Bass SJ, Sherman J. A review of mitochondrial optic neuropathies: from inherited to acquired forms. *J Optom*. 2017;10:205-214.
2. Chun BY, Rizzo JF. Dominant optic atrophy and Leber's hereditary optic neuropathy: update on clinical features and current therapeutic approaches. *Semin Pediatr Neurol*. 2017;24:129-134.
3. Peragallo JH, Newman NJ. Is there treatment for Leber hereditary optic neuropathy? *Curr Opin Ophthalmol*. 2015;26:450-457.
4. Rasool N, Lessell S, Cestari DM. Leber hereditary optic neuropathy: bringing the lab to the clinic. *Surv Ophthalmol*. 2016;31:107-116.
5. Jurkute N, Yu-Wai-Man P. Leber hereditary optic neuropathy: bridging the translational gap. *Curr Opin Ophthalmol*. 2017;28:403-409.
6. Carelli V, Carbonelli M, de Coo IF, et al. International consensus statement on the clinical and therapeutic management of Leber hereditary optic neuropathy. *J Neuroophthalmol*. 2017;37:371-381.
7. Jurkute N, Harvey J, Yu-Wai-Man P. Treatment strategies for Leber hereditary optic neuropathy. *Curr Opin Neurol*. 2019;32:99-104.
8. Kim US, Jurkute N, Yu-Wai-Man P. Leber hereditary optic neuropathy-light at the end of the tunnel? *Asia-Pac J Ophthalmol*. 2018;7:242-245.
9. Stenton SL, Sheremet NL, Catarino CB, et al. Impaired complex I repair causes recessive Leber's hereditary optic neuropathy. *J Clin Invest*. 2021;13:e138267.
10. Parisi V, Ziccardi L, Sadun F, et al. Functional changes of retinal ganglion cells and visual pathways in patients with chronic leber's hereditary optic neuropathy during one year of followup. *Ophthalmology*. 2019;126:1033-1044.
11. Meyerson C, Van Stavern G, McClelland C. Leber hereditary optic neuropathy: current perspectives. *Clin Ophthalmol*. 2015;9:1165-1176.
12. Catarino CB, bon Livonius B, Priglinger C, et al. Real-world clinical experience with idebenone in the treatment of Leber hereditary optic neuropathy. *J Neuroophthalmol*. 2020;40(4):558-565.
13. Winters J, Kini A, Al Othman B, Lee AG. Leber hereditary optic neuropathy: 41-year interval between fellow eye involvement. *Can J Ophthalmol*. 2020;55(1):e44-e46.
14. Pfeffer G, Majaama K, Turnbull DM, et al. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev*. 2012:CD004426.
15. DeBusk A, Moster ML. Gene therapy in optic nerve disease. *Curr Opin Ophthalmol*. 2018;29:234-238.
16. Hage R, Vignal-Clermont C. Leber hereditary optic neuropathy: review of treatment and management. *Front Neurol*. 2021;12:651639.
17. Zuccarelli M, Vella-Szijj J, Serracino-Inglott A, Borg JJ. Treatment of Leber's hereditary optic neuropathy: an overview of recent developments. *Eur J Ophthalmol*. 2020;30(6):1220-1227.

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