The Case of the Blind Bibliophile

Lee Berry* was a distraught 64-year-old bibliophile who could no longer read. Six months prior to seeing us, she had experienced a rapid decline in vision, lasting one month, in both eyes. Over the next five months, a continuing, more gradual deterioration made her daily activities, such as reading and grocery shopping, increasingly difficult and, ultimately, impossible.

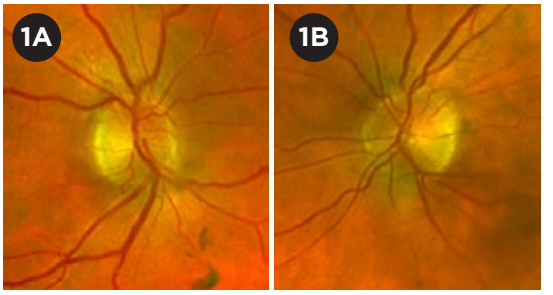
Initial testing. Perplexed by Ms. Berry's normal eye exam, several eye care providers coordinated a thorough diagnostic workup. Her medical record indicated normal or unremarkable results for the following imaging studies: magnetic resonance imaging (MRI) of the brain and orbits with and without contrast, optical coherence tomography (OCT) of the macula and peripapillary retinal nerve fiber layer (RNFL), and fluorescein angiography.

Concern for possible occult cancer and cancer-associated retinopathy (CAR) prompted computed tomography (CT) scans of the chest, abdomen, and pelvis. The latter showed only a few borderline enlarged mediastinal lymph nodes.

During the search for an answer, Ms. Berry underwent bilateral blepharoplasty for potentially vision-obstructing dermatochalasis and cataract surgery in the right eye. Neither procedure improved her vision. She was referred to us for a neuro-ophthalmologist's opinion.

We Get a Look

Ms. Berry told us that her central vision seemed worse than her peripheral vision, and she reported no associated pain or photopsias. Her medical history was notable for hypertension, coronary artery disease, dyslipidemia, depression, and anxiety. Surgical history included a cholecystectomy and a remote hysterectomy for benign fibroids. Her medications included buproprion, fluoxetine, clopidogrel, spironolactone, atorvastatin, and metoprolol. She admitted to drinking two vodka cocktails and smoking half of a pack of cigarettes daily for the past 40 years. She also reported an affinity for junk food but denied any restrictive dietary practices or eating disorders. Her family history was significant for a deceased maternal uncle who had ill-defined vision problems.



FUNDUS. *Color fundus photos demonstrating mild temporal optic nerve pallor bilaterally in the right eye (1A) and left eye (1B).*

Testing. On examination, her best-corrected visual acuity was counting fingers at 3 feet in both eyes. Her pupils were isocoric, with sluggish reactivity to light and no afferent pupillary defect. The remainder of the cranial nerve exam was unremarkable. She failed to recognize any of the Ishihara color plates in either eye, including the control plate. Her ocular motility, peripheral visual fields to confrontation (finger counting in each quadrant), and intraocular pressures were normal bilaterally.

Her slit-lamp exam was notable for a posterior chamber IOL in good location in the right eye, and a 1 to 2+ nuclear sclerotic cataract in the left eye.

The funduscopic exam was normal in both eyes, apart from mild bilateral temporal optic nerve pallor (Fig. 1).

Automated static perimetry (size V, 30-2) demonstrated similar findings in both eyes: global depression on the total deviation plot and cecocentral scotomas on the pattern deviation plots (Fig. 2).

Spectral-domain OCT (SD-OCT) of the peripapillary RNFL revealed normal thickness in both eyes (Fig. 3). Macular sections were grossly normal in the right eye, and a subtle epiretinal membrane was seen in the left eye. Fundus autofluorescence was unremarkable.

A full-field electroretinogram was essentially normal in both eyes. There was a normal cone response in both eyes, which was not consistent with CAR.

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Differential Diagnosis

In the context of Ms. Berry's bilateral cecocentral visual field defects and normal macular exam, our differential diagnosis included both optic neuropathies and occult retinopathies.

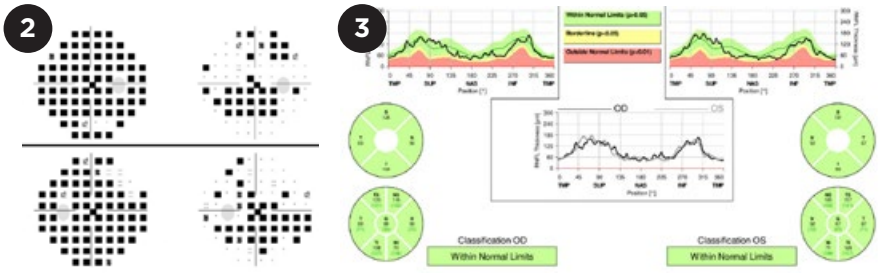
Retinal etiologies to consider included CAR, autoimmune retinopathy, or one of the enlarged blind spot syndromes (e.g., acute zonal occult outer retinopathy, multiple evanescent white dot syndrome, idiopathic big blind spot syndrome, etc.).

Narrowing the possibilities. While Ms. Berry had risk factors for occult malignancy such as her age, smoking, and drinking, she denied photopsias typical of CAR and had a negative body CT. Autoimmune retinopathy and occult CAR were essentially excluded with a normal ERG. She lacked typical clinical features of the big blind spot syndromes, including outer retinal disruption on SD-OCT, extensive enlarged blind spots on automated perimetry, photopsias, and acute-onset nonprogressive vision loss.

Organic vision loss. The presence of mild temporal optic nerve pallor, cecocentral scotomas, and sluggish pupils made it clear that there was organic vision loss and indicated the possibility of bilateral optic neuropathies. Bilateral optic neuropathy from chiasmal compression (e.g., meningiomas, pituitary adenomas, craniopharyngiomas) is relatively common but typically demonstrates a bitemporal pattern of visual field loss and is visible on a good quality MRI. Similarly, optic neuritis can be bilateral and cause any pattern of visual field loss, but it is usually painful, occurs in patients younger than 50, is rarely progressive for six months, and should be visible on MRI with dedicated orbital sequences.

Further options. Nonarteritic anterior ischemic optic neuropathy (NAION) is characterized by acute painless vision loss with associated optic disc edema at the time of vision loss, nerve fiber layer type visual field defects, and marked atrophy within several months of vision loss. Vision loss progression beyond the first month is highly atypical in NAION.

Mitochondrial optic neuropathies are marked by bilateral, often symmetric, cecocentral visual field loss, dyschromatopsia, and acuity loss. Depending on the cause of mitochondrial failure, the rate of vision loss varies from rapid (Leber hereditary optic neuropathy [LHON]) to subacute (ethambutol toxicity, thiamine deficiency) to chronic (most nutritional optic neuropathies).



TESTS. *(2) Low vision protocol 30-2 automated static perimetry demonstrating global depression in the right eye (top left) and left eye (bottom left) on total deviation plot and a cecocentral scotoma in the right eye (top right) and left eye (bottom right) on pattern deviation plot. (3) SD-OCT of the optic nerve showing normal RNFL bilaterally as compared to age-matched controls.*

Diagnosis

Although the SD-OCT showed normal peripapillary RNFL, which could point away from a diagnosis of optic neuropathy, we looked at the segmentation of retinal layers, which allowed quantification of macular ganglion cell layer (GCL) thickness. Compared with the normative data published in the literature among similarly aged Caucasians (Fig. 4A), Ms. Berry's GCL was diffusely and severely thinned bilaterally[1] (Fig. 4B), which pointed us back to an occult optic neuropathy diagnosis. The prominent discordance between GCL thinning and normal RNFL in the presence of rapid-onset central vision loss is a characteristic feature of LHON. Given this information, we ordered mitochondrial point mutation testing for Ms. Berry, which revealed a pathogenic 11778G>A homoplasmic mutation.

Discussion

LHON is a prototypical inherited mitochondrial optic neuropathy, characteristically presenting with sequential or simultaneous bilateral painless central vision loss in young men. Among those who harbor a pathogenic LHON mutation, males are up to nine times more likely to manifest with vision loss, while females tend to remain asymptomatic carriers.[2]

Mutations. Three primary mtDNA point mutations constitute approximately 90% of LHON cases: 11778G>A, 14484T>C, and 3460G>A. The 11778G>A point mutation is the most common in North America and the least likely to show late spontaneous visual recovery compared with the other LHON mutations.

Pathophysiology. Retinal ganglion cells (RGCs) within the papillomacular bundle are selectively affected early in LHON, accounting for the disease's characteristic visual acuity loss, dyschromatopsia, and dense central or cecocentral scotoma. While the underlying pathophysiology remains incompletely defined, it is thought that the small caliber of papillomacular bundle RGC axons makes them more vulnerable to reactive oxygen species and oxidative phosphorylation energy impairment related to mitochondrial dysfunction.[3]

In addition, individual patient factors, including poor nutrition, smoking, and excessive alcohol consumption, may contribute to mitochondrial damage and visual loss.

Signs and symptoms. At the time of acute loss of vision, the optic nerves usually appear normal but may demonstrate mild peripapillary telangiectasias and pseudoedema, which slowly changes to pallor. Similarly, over a variable period of months, OCT shows a transition from either normal or

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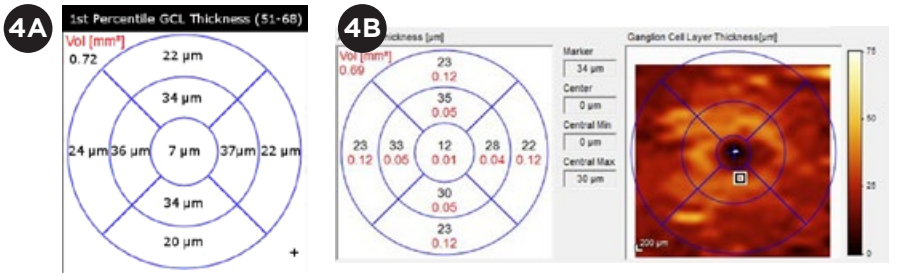

SEGMENTATION DATA. *(4A) Diagram displaying the first percentile normative values of GCL thickness per macular region in Caucasians aged 51 to 68 years based upon published data.[1] (4B) The patient's right eye segmentation data from SD-OCT of the macula displaying the volume and average thickness of the GCL corresponding to each macular region.*

mildly thickened RNFL to thin RNFL. A longitudinal study using high resolution OCT imaging of patients with LHON revealed that thinning of the temporal peripapillary nerve fiber layer typically occurs within three months of the onset of visual loss.[4] Pathological thinning within the macular RGC layer occurs within weeks of onset of vision loss and can even be seen as an early sign of impending vision loss during the presymptomatic phase in patients with LHON mutations. Ms. Berry's normal-thickness RNFL after six months of visual loss was uncharacteristic for LHON and made the diagnosis particularly challenging.

To recap, Ms. Berry's bilateral, severe central vision loss with sparing of the peripheral fields, mild temporal optic nerve head pallor disproportionate to her degree of vision loss, lack of a structural cause for optic neuropathy on MRI, and prominent GCL thinning on OCT segmentation of the macula in the setting of normal RNFL thickness cumulatively implicated LHON. Thus, LHON should be considered in the appropriate clinical context, even among patients who do not fit the typical LHON demographic.

Treatment

There is currently no evidence-based, effective treatment for LHON. Idebenone (a ubiquinone [coenzyme Q10] analog) holds promise for patients with early LHON but is not approved by the FDA. However, several clinical trials are underway to evaluate the efficacy of idebenone, as well as gene therapies, for LHON (see www.clinicaltrials.gov). Ms. Berry enrolled in a multicenter randomized controlled trial of idebenone treatment for LHON.

In LHON patients, it is important to identify and treat any concomitant medical conditions or habits that could contribute synergistically to impairment of mitochondrial function. Among these are poor nutrition and vitamin deficiencies (vitamin B12, thiamine, folate, copper), smoking, and alcohol abuse. These factors may be associated with expression of vision loss among carriers of Leber mutations and/or lead to further progression of vision loss after onset of LHON if not addressed. Ms. Berry's vitamin testing was normal. She was advised to stop smoking and limit alcohol consumption.

Genetic Counseling

Ms. Berry was referred to a genetic counselor for a detailed family pedigree and discussion of risks of vision loss in family members. She had two daughters who were obligate carriers of her homoplasmic LHON mutation, and several of her male grandchildren were carriers. Because they would be at greatest risk for expression of vision loss, all carriers were advised to avoid malnutrition, smoking, and heavy alcohol use for life. The ill-defined vision loss Ms. Berry described in her maternal uncle might have been attributable to LHON. Most patients with LHON (approximately 60%) are aware of a family history of vision loss compatible with the disease.

Conclusion

Clinical features suggestive of LHON include bilateral (sequential or simultaneous), progressive, and painless central visual loss with subtle or no optic nerve findings early. Although LHON is most commonly seen in males aged 10 to 30 years, it can also occur in women and can present at later stages of life. In individuals with unexplained bilateral vision loss of less than three to six months in duration, an OCT demonstrating normal peripapillary RNFL may not be sufficient to exclude optic neuropathy from LHON. A macular segmentation analysis demonstrating thinning of the GCL out of proportion to RNFL thinning can facilitate early diagnosis. Patients can then be educated to optimize their nutritional status and to minimize behaviors that are toxic to mitochondria; beyond that, they may consider enrolling in randomized controlled trials of promising experimental therapies being conducted at large academic centers.

*Patient name is fictitious.

1 Nieves-Moreno M et al. *PLoS One.* 2017;12(7):e0180450.
2 Meyerson C et al. *Clin Ophthalmol.* 2015;9:1165-1176.
3 Sadun AA et al. *Clin Exp Ophthalmol.* 2013;41(7):702-712.
4 Hedges TR et al. *Neuroophthalmology.* 2016;40(3):107-112.

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