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Letters to the Editor: New Observation

Automated perimetry in diagnosing acute Leber's hereditary optic neuropathy

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We describe a case of a 62-year-old woman with sudden severe painless unilateral vision loss to counting fingers (CF) without relative afferent pupillary defect (RAPD) or conclusive abnormality on Humphrey 24-2 automated perimetry testing. Humphrey 10-2 perimetry though revealed bilateral cecocentral scotomas and genetic work-up was positive for 3460 mutation in the mitochondrial genome, confirming the diagnosis of Leber's Hereditary Optic Neuropathy (LHON).

A 62-year-old woman presented with 6-day history of sudden awareness of visual loss in the right eye (RE) while driving. She had no systemic symptoms and specifically no symptoms of giant cell arteritis. She was seen in an emergency department 2 days ago where erythrocyte sedimentation rate and C-reactive protein were within normal limits and non-contrast CT head was normal. Her medical history was significant for hypertension, dyslipidemia as well as smoking five cigarettes and consuming 2–3 alcoholic drinks per day. On examination, vision was CF and 20/40. There was no RAPD. Both optic nerves appeared very slightly hyperemic with mild elevation of peripapillary retinal nerve fiber layer (average thickness 126 in RE and 123 microns in LE) on ocular coherence tomography (OCT) (Figure 1A, B). Retinal examination and OCT of the macula were normal (Figure 1C). Visual field (VF) testing using Humphrey 24-2 SITA Fast algorithm with acceptable reliability indices was performed twice and demonstrated only a few scattered depressed points in each eye, more pronounced in the better seeing left eye (LE) (Figure 1D). Foveal sensitivity was normal in RE (38 dB) and decreased (29 dB) in LE.

As her central acuity was not in keeping with the results of VF testing, perimetry was repeated using Humphrey 10-2 algorithm which tests 68 points within central 10 degrees compared with only 12 in 24-2 algorithm. This demonstrated clear bilateral cecocentral scotomas (Figure 1E) with dense involvement of fixation in RE. The presumptive diagnosis of LHON was made. Magnetic resonance imaging was not performed as the differential diagnosis of severe unilateral visual loss without the presence of RAPD and normal retinal examination is very short and includes non-organic visual loss, subtle maculopathies and, very rarely, LHON which is typically accompanied by mild hyperemia and elevation of optic discs and presence of cecocentral scotoma on VF testing.

Patient denied any family history of vision loss. When questioned further regarding the use of alcohol and tobacco, she disclosed that due to the stress of the pandemic, she had recently increased her smoking from 5 to 12 cigarettes per day with the concurrent increase in alcohol consumption from 2 to 5 drinks per day. Treatment with oral idebenone 900 mg daily commenced. She was able to stop all alcohol consumption and stopped smoking with the aid of nicotine patch. Genetic testing confirmed 3460 mutation in mitochondrial ND6 gene at near 100% homoplasmy. Unfortunately, 6 weeks later, her visual acuity declined to 20/200 in LE. Both optic nerve heads remained mildly elevated with now bilateral nasal thinning of the macular ganglion cell complex (Figure 1F). Electrocardiogram was normal.

Acute central vision loss with bilateral hyperemia and mild elevation of the optic nerves with peripapillary telangiectasia is a classic presentation of acute LHON[1] which is caused by mutation in the mitochondrial genome affecting the electron transport chain and leading to increased generation of intracellular reactive oxygen species. Damage occurs preferentially to highly energy-dependent and mitochondria-rich retinal ganglion cell axons of the papillomacular bundle (PMB) resulting in severe impairment of central acuity and cecocentral scotomas on VF testing. Penetrance is approximately 50% in men and 10% in women and conversion from a carrier to symptomatic state is usually triggered by external stressors, most commonly cigarette smoking followed by alcohol consumption.[2] Conversion in this case occurred when pre-existing moderate smoking and alcohol consumption dramatically increased during the COVID-19 lockdown, an unfortunate unexpected consequence of current pandemic.[3] The 3460 mutation has been particularly closely linked to tobacco and alcohol use and carries a slightly better prognosis than the more common 11,778 mutation with higher chance of spontaneous visual recovery.[4]

Acute optic neuropathy is almost always associated with RAPD as even in bilateral cases the involvement is rarely symmetric. In this case, absence of RAPD at presentation was likely explained by the

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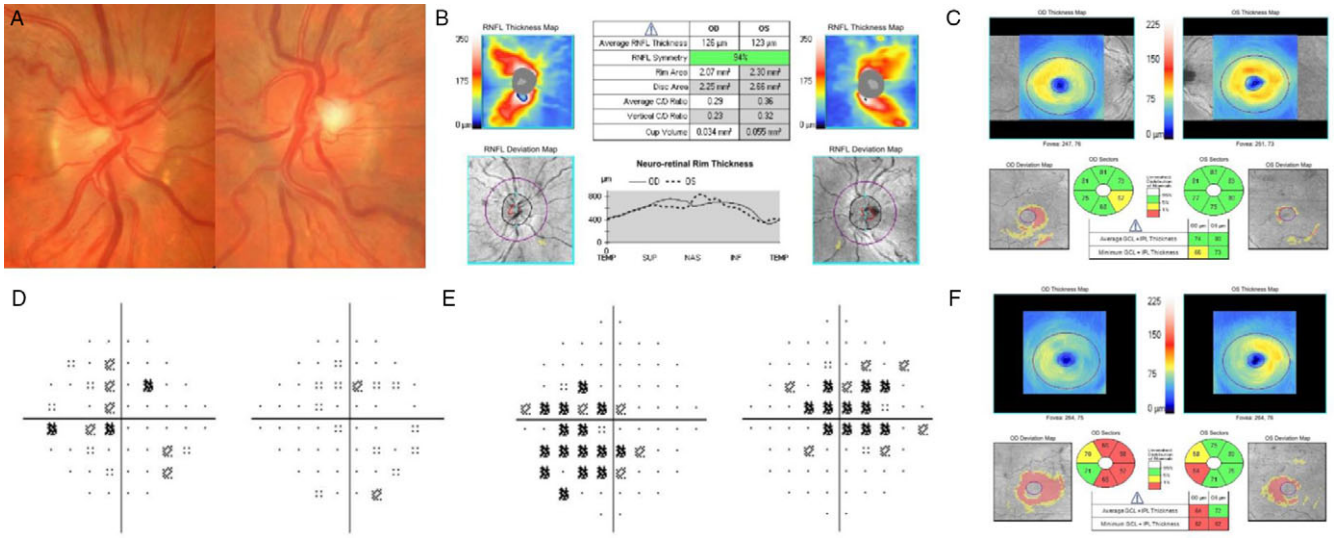

Figure 1: Acute Leber's hereditary optic neuropathy. (A) Bilateral, hyperemic optic nerves with mild elevation of the peripapillary retinal nerve fiber layer, (B) and normal macular ganglion cell layer thickness, (C) on optical coherence tomography, (D) 24-2 Humphrey visual fields showing nonspecific depressed points bilaterally, (E) 10-2 Humphrey visual fields revealed bilateral cecocentral scotoma with dense involvement of fixation in the right eye. Six weeks after initial presentation bilateral, right greater than left thinning of the macular ganglion cell complex was present, consistent with involvement of retinal ganglion cells in the papillomacular bundle.

similar extent of VF loss in each eye with sparing of fixation in LE explaining preserved acuity there.[5] Mean deviation values on VF testing were nearly identical in each eye with the denser central scotoma in RE affecting central acuity earlier. Pupillary responses have also been suggested to be uniquely spared in cases of LHON compared to other optic neuropathies with one study reporting that video pupillography of constriction and escape rates was similar to controls in most patients with LHON, compared with obvious abnormalities in patients with similar impairment in central acuity due to ischemic or inflammatory optic neuropathy.[6] The pupillary light reflex is driven by melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs). Post-mortem analysis has shown that these ipRGCs are relatively preserved in LHON which could be another reason for the absence of RAPD in patients with acute LHON.[7] While the reason for this is not known, the hypothesis is that melanopsin itself may protect axons from damaging blue light exposure. There is also a relative concentration of these cells in the peripheral nasal retina, outside the PMB.

In summary, we describe a case of an older woman with sudden severe painless vision loss in RE without RAPD. Despite CF vision in RE, 24-2 Humphrey VF was normal. Presence of subtle mild bilateral optic nerve head elevation prompted VF testing using Humphrey 10-2 algorithm which revealed clear bilateral cecocentral scotomas involving fixation in RE only. Diagnosis of Leber's Hereditary Optic Neuropathy (LHON) was suspected and confirmed on genetic testing. Conversion was related to increased alcohol consumption and smoking during the current pandemic. This case emphasizes the importance of employing an algorithm specifically evaluating central VF when there is discordance between central acuity and peripheral VF testing. Early diagnosis is key to counsel patients on the importance of avoiding tobacco and other toxins. While randomized trial studying idebenone in LHON demonstrated only a trend toward an improved vision, further longitudinal data demonstrated increased proportion of patients with visual recovery and magnitude of recovery with increased treatment duration thus the current recommendation is to start idebenone treatment early and maintain it for 24 months to maximize efficacy.[8,9]

Conflict of Interest. The authors have no conflict of interest to disclose.

Statement of Authorship. Both authors contributed equally to preparation, writing, editing and finalizing this manuscript.

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