Leber’s Hereditary Optic Neuropathy

Leber’s hereditary optic neuropathy (LHON) is a painless, bilateral, acute or subacute optic neuropathy that is maternally inherited from mutations in the mitochondrial DNA. The exact worldwide incidence of LHON is unknown, but it is much less prevalent than other optic nerve disorders, such as optic neuritis and ischemic optic neuropathy. Men are affected two to three times more frequently than women.1–3

Symptoms and Signs

Visual loss usually occurs during the second to third decades,3,4 with a mean age of 27 years and a reported range of 1 to 70 years. Painless unilateral loss of visual acuity develops with color desaturation over weeks and often is severe, decreasing to 20/200, counting fingers, or even no light perception by 6 weeks. The eyes can be affected simultaneously or sequentially, with an average interval between eyes being affected of about 2 months and a range of 6 to 22 weeks, and rarely 8 years or longer.3,4 Monocular or subclinical involvement is even more rare.5 Both eyes are affected sequentially in 78% of cases and simultaneously in 22%.5 Sudden, complete blindness can occur in about 3.7 months, and then may worsen over a period of about 2 years. The final visual acuity can range from 20/50 to no light perception, depending on the type of mutation. The most severely impaired bp (base pairs) 11778 patients may have no light perception; the most severe bp 3460 patients may retain light perception; the severe bp 15257 patients will perceive hand motions; and the severe bp 14484 patients will be able to count fingers.

As visual loss progresses, a red-green color defect develops. Pupillary light reflexes are relatively spared. The central or cecocentral scotoma may be relative and then later may become large and absolute. During the acute stages, the optic disc is hyperemic. Capillaries, medium-sized arteries, and venules become more tortuous with arteriovenous shunting in the peripapillary vasculature.7 The classic triad of acute LHON signs includes (1) circumpapillary telangiectatic microangiopathy in 30% to 60% of eyes, (2) swelling of the nerve fiber layer around the disc (pseudoedema), and (3) absence of fluorescein leakage from the disc or papillary region, which distinguishes LHON from a swollen optic disc (Figure 7.1).7–10 Only 58% of patients with the bp 11778 mutation show telangiectatic vessels in the acute phase1 and 33% with the bp 14484 mutation.3 The telangiectatic vessels and pseudoedema of the disc resolve over several months. Optic atrophy develops with the most severe atrophy in the papillomacular nerve fiber layer. Microangiopathy is uncommon after 6 months.3 Optic atrophy has been reported to be seen as early as 1 month from the onset of visual symptoms, but it is universally seen after 6 months.3 Nonglaucomatous cupping of the optic disc and arteriolar attenuation may also develop.
The characteristic funduscopic findings are not always present in affected persons with LHON who present with visual loss. Abnormal funduscopic findings may also be seen in presymptomatic patients and in asymptomatic maternal relatives who carry mitochondrial mutations associated with the disease. Swelling in the peripapillary retinal nerve fiber layer, increased tortuosity of capillaries, medium arteries and venules, and arteriovenous shunting have been reported in presymptomatic individuals and asymptomatic carriers. Presymptomatic at-risk patients may show color defects on Farnsworth–Munsell 100-hue test and even mild abnormalities in the pattern-reversal visual evoked responses.

Other ocular manifestations have been observed in LHON patients. LHON may also be a neuroretinopathy with a broad spectrum of genotype-specific phenotypes. Mann et al. reported peripheral retinal phlebitis has been observed in a patient with LHON who harbored the 11778 mutation. In addition to bilateral central visual loss associated with headache, the patient had vitritis, vasculitis, and optic neuritis. Multiple sclerosis and other causes of vasculitis were ruled out.

Diagnostic Testing

The diagnosis of LHON can be confirmed by genetic testing on whole blood for the main primary mutations: 11778, 3460, 15257, and 14484. If these tests are unremarkable, then the secondary mutations of LHON can be tested.

Although magnetic resonance imaging (MRI) of the brain and orbits is typically normal in patients with LHON, two LHON patients were reported to have abnormal enhancement of the optic nerves and chiasmal enlargement on MRI. MRI of the orbits in some patients can also show increased T2 signal in the affected optic nerve. The optic nerve is affected in the mid- and posterior intraorbital sections, with sparing of the anterior portion. Cerebral mitochondrial dysfunction and damage in LHON patients has also been shown on phosphorous-31 magnetic resonance spectroscopy and magnetization transfer imaging.

Optical coherence tomography (OCT) studies have shown that the retinal nerve fiber layer (RNFL) in patients with LHON is thickened in the early stages of the disease of less than 6 months duration. Beyond 6 months, the RNFL is thinned, and some may be partially preserved in patients with atrophic LHON who have some visual recovery. The temporal fibers, which correspond to the papillomacular bundle, are usually the first and most severely affected, whereas the nasal fibers appear to be partially spared in the later stages of the disease. Patients with subclinical LHON have preferential involvement of the papillomacular bundle. On OCT, unaffected carriers with the 11778 muta-