Leber Hereditary Optic Neuropathy

Leber hereditary optic neuropathy (LHON) is a genetic disorder that causes optic neuropathy and can lead to severe visual disability. LHON was the first disease discovered to be caused by a point mutation in mitochondrial DNA, and recent developments now make LHON the first mitochondrial disorder treatable with gene therapy.[1]

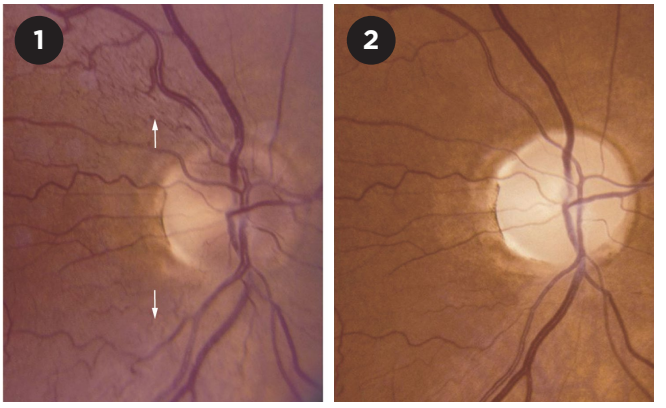
Epidemiology

The prevalence of vision loss due to LHON has been estimated to be between 1 in 30,000 and 1 in 65,000 in Northern Europe, Asia, and Australia. Between 70% and 90% of individuals with vision loss due to LHON are male, and the onset of vision loss in males typically occurs between the ages of 20 and 30 years. Women affected by LHON tend to be older. Although epidemiological data are limited, there are no known overt racial, ethnic, or geographic disparities.

Genetics and Pathophysiology

LHON is caused by mutations in mitochondrial DNA (mtDNA). More than 90% of LHON patients worldwide carry one of three primary mtDNA point mutations: G11778A, T14484C, or G3460A (approximately 70%, 13%, and 14% of cases, respectively). These mutations affect proteins located in mitochondrial membranes that are involved in cellular respiration through the process of oxidative phosphorylation.

Intriguingly, only approximately 50% of males and 10% of females who carry a LHON mutation manifest optic neuropathy. This incomplete penetrance and sex imbalance imply the presence of modulatory factors beyond mtDNA mutations that affect disease phenotype. It has been suggested that environmental factors or genetic factors encoded by nuclear DNA (possibly on the X-chromosome) play a role in disease pathophysiology. Another theory suggests that individuals with LHON mutations harbor variable percentages of unmutated mtDNA—known as heteroplasmy—and that a patient's phenotype may be determined by the balance of normal and mutated mtDNA.



TYPICAL FUNDUS SIGNS. *(1) Optic nerve pseudoedema and circumpapillary telangiectasias (arrows) in a LHON patient early in the disease process. (2) Optic nerve pallor and atrophy in the same patient late in the disease course.*

Clinical Features, Presentation

Classic presentation. The classic presentation of LHON is a young adult male who develops acute or subacute, painless, severe unilateral vision loss, followed by similar vision loss in the fellow eye two or three months later (though rarely the delay may be much longer).

Less commonly, patients may be female or of older age, or they may present with simultaneous bilateral involvement.

LHON Plus. Occasionally, patients exhibit extraocular manifestations, including neurologic, psychiatric, and cardiac conduction abnormalities. Cases with such features are termed LHON Plus.

Disability varies. The severity of visual disability is widely variable, even within affected families and among patients who share the same causative genetic mutation. Because the cause of such marked phenotypic variability remains unclear, it is difficult to predict if, when, or how a genetically affected individual will manifest disease in their lifetime.

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Diagnosis

Differential diagnosis. LHON should be considered in the differential diagnosis of any case of painless, unexplained optic neuropathy, regardless of laterality, patient sex, age, or family history. Other diagnoses to consider in the setting of acute unilateral or bilateral central vision loss with signs suggestive of acute optic neuropathy are optic neuritis, retrobulbar compression due to an intracranial mass, and toxic or nutritional optic neuropathy. The differential diagnosis for chronic vision loss resulting in papillomacular retinal nerve fiber layer (RNFL) damage and temporal optic atrophy include late presentations of the diagnoses listed above as well as dominant optic atrophy. Patients with vision loss but no other overt examination findings may be initially misdiagnosed with functional vision loss disorder.

Diagnostic features. The exam, visual function testing, imaging, and genetic testing can help determine the diagnosis.

Exam signs. Certain exam signs favor a diagnosis of LHON (see "Early and Late Features of LHON," below). Typically, a relative afferent pupillary defect is minimal or absent, which is unique among asymmetric optic neuropathies. Notably, pupillary light reflexes are largely preserved throughout the disease course, even after optic atrophy has occurred. It is thought that melanopsin-containing intrinsically photosensitive retinal ganglion cells—which contribute to the pupillary response—may be spared in LHON, and that their persistent activity may maintain pupillary responses.[2]

The optic disc in acute LHON classically exhibits "pseudoedema," also described as "nerve fiber layer prominence" or "fullness." The disc margin may be hyperemic with telangiectatic and tortuous vessels; together, these subtle vascular changes have been described as circumpapillary telangiectatic microangiopathy (Fig. 1).

Approximately six weeks after the onset of vision loss, disc pseudoedema and peripapillary vascular changes resolve, and the optic nerve takes on a more atrophic appearance. At this stage, temporal pallor of the optic disc is common, reflecting permanent loss of the papillomacular nerve fiber bundle (Fig. 2). As with other aspects of LHON, the fundus examination is inconsistent. In some patients, early exam signs may be evident preceding any vision changes, whereas others with active vision loss may initially have a fundus that appears normal.

Visual function testing. The tempo and course of vision loss is also an important diagnostic feature. Visual dysfunction typically progresses until a nadir is reached three to six months after symptom onset. Visual function testing demonstrates a dense central vision defect with poor VA, typically 20/200 or worse. Extremely poor vision (e.g., light perception or worse) or only slightly decreased vision (except in very early disease) should prompt evaluation for alternate diagnoses. Typically, the earliest finding on visual field testing is a cecocentral scotoma, corresponding to early loss of the papillomacular nerve fiber bundle, which later evolves into a central scotoma. Dyschromatopsia in proportion to the decline in VA is almost invariably present.

Imaging. Ocular imaging in the diagnosis of LHON is of indirect utility but can be helpful to diagnose and follow patients. Classically, fluorescein angiography was used to prove optic nerve pseudoedema by demonstrating a lack of true disc leakage despite the presence of disc congestion on fundus exam. Early in the disease course, OCT of the RNFL may be normal or thickened in the setting of edema of retinal ganglion cells (RGCs). Later in the disease process, RGC axons atrophy and the RNFL thins. This thinning is typically evident earliest and most severely in the temporal quadrant along the course of the papillomacular RNFL bundle.[3] OCT evaluation of the macular RGC complex also shows thinning within a few weeks of presentation, a finding that usually precedes RNFL thinning. It may therefore be clinically useful to monitor both parameters. There are no reliable or specific findings with brain or orbital MRI, but neuroimaging may be necessary to exclude alternate diagnoses such as retrobulbar optic nerve compression by tumors or to evaluate for LHON Plus syndromes.

Genetic testing. Genetic testing for causative mtDNA mutations can provide definitive diagnosis in individuals with suggestive clinical features. In patients suspected to have LHON, it is recommended to first pursue a targeted mtDNA sequencing approach probing for the three most common mutations (approximately 90% of LHON patients).[4] If such targeted analysis is unrevealing, subsequent sequencing can be performed using a larger, more comprehensive multigene panel. If necessary, sequencing of the entire mitochondrial genome can be performed.

Early and Late Features of LHON

	Early Features	Late Features
Visual Acuity	Subacute decline, usually asymmetric	20/200 or worse bilaterally
Visual Field	Cecocentral scotoma	Dense central scotoma
Disc Appearance	Pseudoedema, telangiectatic microangiopathy	Pallor/atrophy
OCT RNFL	Normal or thickened	Thinning/atrophy
OCT Macula	Early thinning	Thinning/atrophy

Management

Current therapies. Idebenone, the only medication approved by the European Medicine Agency to treat LHON, is a synthetic form of coenzyme Q_{10}, a molecule that acts as an electron shuttle in the electron transport chain during mitochondrial respiration. No treatments have been approved for use in the United States. Other medications,

including steroids, cyanide antagonists, brimonidine, cyclosporine, and hydroxycobalamin, do not appear to be effective.

In 2011, a prospective, randomized clinical trial (RHODOS) randomized patients with LHON diagnosed within the previous five years to treatment with 24 weeks of daily oral ibedenone or placebo.[5] While the initial trial did not meet its primary endpoint comparing improvement in VA between the two groups, there was a trend toward a beneficial, protective effect. Despite a lack of proven efficacy, given the seemingly favorable risk/benefit ratio, idebenone was approved for use in Europe in 2015. Consensus guidelines suggest starting idebenone for LHON patients with vision loss of less than one year in duration.[6] Studies of other potentially neuroprotective agents—including EPI-743, an investigational antioxidant that has shown promise in a small LHON cohort—are ongoing.[7]

Therapies in development. Gene therapy has emerged as one of the most promising approaches to treat inherited ophthalmic diseases. Multiple recent clinical trials have investigated treating LHON patients who have the G11778A mutation with a one-time intravitreal injection of viral-mediated gene therapy. The goal of this approach is for patients to be able to produce a fully functional mitochondrial ND4 protein, which is defective in the presence of the G11778A mutation.[8] Three different therapeutics are currently in development. Trials that have reported safety data have shown the most common side effect of treatment to be mild, self-limiting ocular inflammation, and no serious ocular or systemic adverse effects have so far been observed through multiple years of follow-up. Treatment appears to promote a modest improvement in visual recovery compared to the natural history of the disorder.[9] In general, younger patients and those treated more quickly following the onset of vision loss appear to respond best to treatment. Gene therapy is currently only available within the context of a clinical trial, unless special approval is sought.

Many of these early clinical trials were designed for one eye to receive gene therapy and the other to receive sham treatment so that the sham-treated eye could serve as an internal control. Surprisingly, however, results have consistently shown that not only does the eye receiving gene therapy regain some vision, but also there is improvement in the sham-treated eye (albeit slightly less than the directly treated eye). It has been shown that viral vector DNA is capable of transferring from the treated eye to the contralateral nontreated eye in nonhuman primate experiments,[10] providing a plausible mechanism for the bilateral treatment effect.

Prognosis

Natural history. Most LHON patients develop permanent bilateral central vision loss. However, even without treatment, at least partial spontaneous visual recovery is possible. Natural history studies have shown that among patients with the three most common mutations, patients with the T14484C mutation have the highest rate of spontaneous improvement from visual nadir (35%-60% of patients), those with the G3460A mutation have an intermediate rate (approximately 20%), and patients with the G11778A mutation have the lowest rate of recovery (approximately 5%). Recovery typically begins as small islands of improved vision within the central defect and usually occurs within the first two years after vision loss. Final VA is widely variable. Gene therapy appears capable of increasing the incidence and degree of visual improvement in patients with the G11778A mutation.[9]

Patients should be counseled to avoid environmental toxins and heavy alcohol and tobacco use, which can exacerbate the existing mitochondrial optic neuropathy. Patients often benefit from referral to vision rehabilitation clinics and should be monitored for the development of comorbid depression, which is common in this population due to significant visual disability.

Genetic counseling. Affected patients should be offered formal genetic counseling. They can be counseled with certainty that mutations in mtDNA cannot be inherited paternally but will be passed down from an affected mother to all of her children. However, given the incomplete understanding of all the factors that impact LHON phenotypes, there is significant prognostic uncertainty for individuals harboring a causative mutation.

Conclusion

LHON is a maternally inherited optic neuropathy caused by mutations in mtDNA. For reasons that are not yet clear, the disease exhibits incomplete penetrance and a widely variable phenotype. LHON most commonly presents in young adult males but should be considered in any case of undifferentiated, painless optic neuropathy. Pharmacologic and gene therapy treatment approaches have been shown to be safe and possibly effective in promoting some visual recovery, though no treatment has been approved for use in the United States, and most patients still develop significant permanent bilateral vision loss.

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