Introduction

This article includes discussion of Leber hereditary optic neuropathy, Leber optic atrophy, Leber's hereditary optic neuropathy, and LHON. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Leber hereditary optic neuropathy is a maternally inherited bilateral optic neuropathy that typically affects teenage males with acute vision loss first in one eye and then the other within days or weeks. The etiology involves a point mutation in the mitochondrial DNA at 1 of 3 main loci: 11778, 14484, or 3460. There are some distinctive changes in the ocular fundus appearance at various stages of the process that make specific diagnosis possible clinically. At the time the patient presents with vision loss, there is apparent swelling of the optic disc but there is no leakage of fluorescein dye as is usually present with other forms of optic nerve head swelling. Other distinctive changes include small peripapillary telangiectatic vessel changes that go away shortly after the acute phase and retinal venous tortuosity that may persist indefinitely as a marker. The author updates progress on developing a virus vector delivering DNA restorative therapy for patients with Leber hereditary optic neuropathy, citing a phase I clinical trial that demonstrated safety and even some visual improvement in a few subjects. He also reviews an OCT-based imaging study in which thinning of the retinal ganglion cell layer and the retinal nerve fiber layer were demonstrated prior to vision loss, which may provide a basis for early intervention to prevent vision loss when it becomes available.

Key points

- Leber hereditary optic neuropathy is a disease caused by various mutations in the mitochondrial genome and, as such, is inherited only via the maternal ovum as spermatozoa do not have mitochondria.
- It is usually manifest as sequential binocular acute painless vision loss in sons of carrier mothers.
- There is preferential involvement of retinal ganglion cells in the papillo-macular bundle producing a dense central scotoma on visual field exam with relative sparing of peripheral visual field.
- The optic disc appears swollen in the acute phase but typically does not leak fluorescein on fluorescein angiography.
- Peripapillary retinal telangiectasia is typical during the acute phase but regresses within days to weeks after onset of vision loss in the affected eyes.
- Retinal venous tortuosity can persist as a lasting marker for the disease on fundus exam.

Historical note and terminology

In 1871, Theodor Leber (1840-1917), Professor of Ophthalmology at the University Göttingen, described 55 patients in 16 families with a hereditary optic neuropathy of rapid onset (Leber 1871). The vast majority of his patients was male, had visual loss beginning in the late teens or early 20s, and did not recover. Although his was not the first description of such patients, it was the most complete at that time. Ensuing decades saw the description of several pedigrees with similar clinical findings, almost all of which had a peculiar mode of inheritance from mother to affected son or mother to carrier daughter. Initially thought to be a sex-linked recessive disorder, the greater-than-expected occurrence in women and less-than-expected occurrence in maternal grandfathers of affected males suggested an alternate mechanism for transmission (Russell 1931). In retrospect, many apparent cases of transmission from father to child were probably other hereditary optic neuropathies. Cytoplasmic transmission was suggested in 1936 (Imai and Moriwaki 1936), and the fact that mitochondrial DNA inheritance is maternal (Giles et al 1980) eventually led to the discovery by Wallace and colleagues that many cases of Leber hereditary optic neuropathy are due to a mutation at position 11778 of the mitochondrial genome (Wallace et al 1988). Subsequently, mutations at positions 3460
(Huoponen et al 1991) and 14484 (Johns et al 1992) have been shown to be associated with Leber hereditary optic neuropathy in multiple pedigrees.

Leber was one of the preeminent ophthalmologists of his time. Unfortunately, several disorders described by him, all of which are eponymous, have names similar to Leber hereditary optic neuropathy. Leber congenital amaurosis is a severe bilateral retinal disease that is present at birth, transmitted as an autosomal recessive trait, and diagnosed by a permanent absence of retinal electrical activity. Leber idiopathic stellate neuroretinitis is an acute sporadic inflammation of the optic nerve and macula, characterized by both disc and macular edema, the resolution of the latter leading to a macular "star," hence the name. Leber miliary aneurysms are a milder variant of congenital retinal telangiectasia (Coats disease), a unilateral disease of mostly young boys. Retinal vessels are telangiectatic and may have localized aneurysmal outpouchings. Exudative leakage from these abnormal vessels may lead to visual loss.

Because of this possibility for confusion, it is inadequate to designate a patient with Leber hereditary optic neuropathy a "case of Leber's."

**Clinical manifestations**

**Presentation and course**

Leber hereditary optic neuropathy is a maternally inherited optic neuropathy typically characterized by decreased visual acuity, a visual field defect involving the blind spot and central fixation (ceccocentral scotoma), and a characteristic pseudoeedema of the optic disc, which does not leak on fluorescein angiography. Fine telangiectatic vessels are often present at the disc margins. Acute bilateral disease is seen in about one fourth of patients; more commonly, one eye is involved, with involvement of the other eye occurring from weeks to months later (Harding et al 1995b). The degree of visual loss may be particularly severe, with most patients seeing 20/200 or worse (Newman and Wallace 1990; Newman et al 1991). Visual loss is typically rapid, progressing over days to weeks. Although Leber hereditary optic neuropathy is usually painless, some patients may have discomfort reminiscent of optic neuritis (Harding et al 1995b). Occasional patients may spontaneously recover vision after a variable interval, especially those with the 14484 mutation.

As clinical experience with the disease has increased, it has become apparent that many patients may lack the clinical features described above (Weiner et al 1993). For example, the visual loss may be indolent. Instead of disc swelling, there may simply be optic atrophy, or even cupping (Jacobson and Stone 1991; Ortiz et al 1992). The visual fields may be atypical, eg, bitemporal hemianopsia (Weiner et al 1993).

Male predominance is strong in patients with Leber hereditary optic neuropathy (Newman et al 1991), the degree depending on the specific mutation. The age of onset is usually in the second or third decade, but has been reported as early as 4 years of age (Meire et al 1994) and as late as 73 years of age (Ajax and Kardon 1998). In fact, Leber hereditary optic neuropathy must remain a consideration in patients with optic neuropathy and visual loss onset after the age of 60 years. Pfeiffer and colleagues at the University of Texas identified 5 patients with onset of vision loss after age 60 years in their cohort of genetically confirmed Leber hereditary optic neuropathy, and their search of the literature revealed 14 other such cases (Pfeiffer et al 2013). Also, from a cohort of 251 affected and 277 unaffected Leber hereditary optic neuropathy carriers, Dimitriades and colleagues identified 20 patients (8%) with onset of vision loss later than age 60 years (Dimitriadis et al 2014). The age of onset does not differ significantly between the different mutations (Harding et al 1995b).

One of the most peculiar features of Leber hereditary optic neuropathy is that the expected relative afferent pupillary defect (Marcus-Gunn pupil) is not as prominent in patients with unilateral disease. This may reflect preservation of W-like retinal ganglion cells, which are thought to mediate the pupillary response, whereas the X-like and Y-like ganglion cells responsible for visual processing are affected by the disease (Ishikawa et al 1995; Wakakura and Yokoe 1995).

Other work has shown that in primates there are intrinsically photosensitive retinal ganglion cells that contain melanopsin, and that these project to the pupillary control center in the pretectum (Dacey et al 2005). Persistence of the pupillary light reflex was demonstrated in behaving macaques after pharmacologic blockade of retinal rod-cone pathways, indicating that melanopsin-containing intrinsically photoreceptive retinal ganglion cells contribute significantly to a sustained component of the pupillary light reflex independent of rod and cone pathways (Gamlin et al 2007). A pupillographic study comparing 10 severely affected Leber patients with 16 healthy age-matched controls...
demonstrated relative preservation of the pupillary light reflex in the Leber hereditary optic neuropathy patients compared to controls, despite an estimated loss of over 90% of the retinal ganglion cells by optical coherence topography retinal nerve fiber layer thickness determination (Moura et al 2013).

**Prognosis and complications**

The prospect for visual improvement in Leber hereditary optic neuropathy is low, with the specific rate highly dependent on which mitochondrial DNA mutation is present (Johns et al 1993a). The most dismal prognosis is for patients with the 11778 mutation, in which the rate of recovery of vision is approximately 5%. The best prognosis is for those with the 14484 mutation, in which partial or full recovery may be seen in as many as 71% of patients (Riordan-Eva et al 1995). An intermediate recovery rate of approximately 22% is seen with the 3460 mutation. In all of these mutations, there may be a latency period of months to years until visual improvement (Stone et al 1992).

Serum neuron-specific enolase is a biomarker for neuronal stress. Serum neuron-specific enolase levels from 74 members of a pedigree with Leber hereditary optic neuropathy and homoplasmic 11778/ND4 mitochondrial DNA mutation demonstrated significantly higher levels in 46 asymptomatic carriers (27.17±39.82 µg/L) than in 14 symptomatic “affected” members (5.66±4.19 µg/L; p=0.050) and 14 “off-pedigree” controls (6.20±2.35 µg/L; p=0.047) (Yee et al 2012). Among the carriers, levels were much higher in males (40.65±51.21 µg/L) than in female carriers (15.85±22.27 µg/L; p=0.034).

In patients with unilateral visual loss, the fellow eye becomes involved in days to weeks (Newman et al 1991). There may be disparity in visual function between the 2 eyes. As of yet, no therapy has been shown to increase the likelihood of visual recovery in affected patients or decrease the likelihood of second eye involvement in those with unilateral disease.

The likelihood that those genetically at risk will develop visual loss depends on gender. The likelihood of symptomatic disease affecting matrilineal first-degree relatives of affected individuals is approximately 20% to 46% for male relatives and 4% to 10% for female relatives (Mackey and Buttery 1992; Harding et al 1995b).

As experience with Leber hereditary optic neuropathy has increased, it has become apparent that other neurologic abnormalities may be seen. Most commonly, patients have a syndrome indistinguishable from multiple sclerosis (Harding et al 1992; Flanigan and Johns 1993; Olsen et al 1995; Jansen et al 1996), particularly in female patients (Harding et al 1995a). However, in a study of 31 unrelated Iranian patients with clinically definite multiple sclerosis with optic nerve involvement and 25 patients with clinically definite multiple sclerosis but no optic nerve involvement showed that none of the patients in either group had mitochondrial DNA point mutations at np 11778, 3460 or 14484 (Houshmand et al 2004).

Patients with the mitochondrial mutation at np 14484 have associated migraine with or without aura commonly, possibly as a manifestation of abnormal oxidative phosphorylation that has been demonstrated in migraineurs (Cupini et al 2003).

Other specific disturbances include cerebellar ataxia (Funakawa et al 1995; Murakami et al 1996), tremor (Nikoskelainen et al 1995), spastic dystonia (Meire et al 1995), peripheral neuropathy (Nikoskelainen et al 1995), thoracic kyphosis (Nikoskelainen et al 1995), and primary degeneration of spinal cord dorsal columns (Jaros et al 2007). The association of spastic dystonia and Leber hereditary optic neuropathy has been documented with a novel mitochondrial mutation, 3697G>A/ND1, a mutation that has also been associated with MELAS syndrome (Spruijt et al 2007). As mentioned previously, the 14459 mutation is characterized by hereditary dystonia (Jun et al 1994; Jun et al 1996). Microscopic abnormality of normal-appearing brain tissue was demonstrated using MRI measures including magnetization transfer ratio and mean diffusivity histogram analysis in 10 patients with Leber hereditary optic neuropathy and these abnormalities were found to be more pronounced in 4 patients with Leber hereditary optic neuropathy and multiple sclerosis-like illness (Inglese et al 2001).

A relatively uncommon complication of Leber hereditary optic neuropathy is a cardiac pre-excitation syndrome, either Wolff-Parkinson-White or Lown-Ganong-Levine syndrome. This can occur in up to 9% of Leber hereditary optic neuropathy patients in Finland or Japan (Nikoskelainen et al 1994; Mashima et al 1996). Prolongation of the corrected QT interval may also occur (Ortiz et al 1992). A 48-year-old man with Leber hereditary optic neuropathy and Wolff-Parkinson-White syndrome was found to have myocardial thickening and isolated left ventricular abnormal
trabeculation on examination using echocardiography and cardiac magnetic resonance imaging. The patient's brother also had isolated left ventricular abnormal trabeculation. Isolated left ventricular abnormal trabeculation is frequently associated with respiratory chain disorders according to the authors (Finsterer et al 2001).

Clinical vignette

PS was a 22-year-old man who awoke on April 19, 2000, with hazy vision in both eyes and special difficulty seeing in bright illumination. The vision had been worsening gradually since about 1 month after onset, prior to which he could still drive a car. The blur was greater in the central field of either eye than in the periphery. He had not experienced any positive visual symptoms.

He also had been having frequent unilateral headaches for the past 8 to 9 months. It was most often on the left side and was usually worse when on the right side. It felt like pressure that starts behind the eye and in the temple and spread to the back of his head and neck. He could feel the muscles of his neck tighten when that area is involved. The headache lasted about 2 hours and occurred 3 to 4 times weekly. Being in the sun or watching TV for a long interval seemed to precipitate the headache. The pain was steady in quality, and there was some globe tenderness with the headache.

He had a long history of headaches, but these seemed to him different than past headaches. The differences included greater localization around his orbit and temple and the high frequency. His past headaches were more holocephalic and somewhat less frequent. He never had nausea or vomiting with any of his headaches (past or present). He remembered having a headache when he awoke with the first vision symptoms, but he could not recall which side it involved.

When this started, he saw a local optometrist. He had trouble getting an appointment with an ophthalmologist, so the first ophthalmologic evaluation was May 14, 2001, at which time the examination was unrevealing. He was referred for retinal evaluation, and once again a normal dilated fundus examination was described. His measured visual acuity was 20/60 for either eye. Fluorescein angiogram was normal. He was referred for neuro-ophthalmologic examination on May 29, 2001.

The neuro-ophthalmologist diagnosed optic nerve damage most likely related to alcohol use. The patient reported a pattern of drinking 5 to 7 drinks in the evening 2 to 3 nights per week. He never missed meals and did not experience vomiting or diarrhea.

Evaluation included brain and orbit MRI with and without gadolinium that was read as normal. Blood work included complete blood count, B12, folate, thiamine, liver function tests, erythrocyte sedimentation rate, and 24-hour urine collection for heavy metals. All were normal. The hematocrit was slightly low, but the hemoglobin level was normal. The erythrocyte indices were normal. The available reports do not include Leber mitochondrial gene testing.

He had a general physical examination by an internist and this was said to be normal. Past medical history is unremarkable. Past ocular history is negative. Medications include only thiamine 50 mg twice a day and B-complex vitamins. Social history is significant for the increased drinking (alcohol) pattern since last semester at college. He had smoked cigarettes and cigars “occasionally.” Family history was extensively known, and there was no history of unexplained poor vision.

Examination

Visual acuity:
- Right eye: 20/200
- Left eye: 20/400
  Uncorrected

Manifest refraction:
- Right eye: -1.00 + 0.75 x 105 --> 20/200
- Left eye: -0.50 + 1.25 x 075 --> 20/400

Color vision:
- Right eye: 11/11
- Left eye: 10/11

Ishihara plates
Done with +4.00 sphere in both eyes
Pupils:

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* Pupil measurements in mm

+ Scale of 0 to 4+

There is no relative afferent pupillary defect. The pupils were measured using an infrared video pupillograph and neutral density filters.

Motility:

Versions and ductions are full. Saccades and pursuit are normal into all fields of gaze. There is no significant nystagmus and there are no dissociated eye movements.

Palpebral fissures (mm):

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<td>MRD2</td>
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Applanation tonometry:

- Right eye: 14
- Left eye: 14
- Done at: 11AM

Exophthalmometry:

- Base: 94
- Right eye: 21
- Left eye: 21

Visual fields:

Using the Goldmann perimeter, the central and peripheral isopters are normal in either eye. There are dense central scotomas in both eyes; the maximum density in the right eye was I4e and for the left eye, V4e. Also, the diameter of the scotoma was larger for the left eye.

Humphrey 24-2 central threshold examination also demonstrated highly circumscribed central scotomas in both eyes.

Slit lamp examination:

- Unremarkable

Dilated fundus examination:

- The optic discs are a little full in contour, but normal in color and capillary content. There are somewhat dilated “telangiectatic” vessels on and around the optic discs, particularly the left one.
- The retinal arterioles and veins are normal, and the maculae are unremarkable. The retinal periphery is normal in either eye. The veins are not tortuous.

Impression.

This appears to correspond most closely to a phenotypic Leber hereditary optic neuropathy, possibly triggered by metabolic stresses related to alcohol consumption. The lack of eye pain bilaterality and circumscribed nature of the papillomacular bundle involvement seems unlikely to represent an inflammatory optic neuropathy.

Biological basis

Etiology and pathogenesis

The etiology of Leber hereditary optic neuropathy is unclear. Because it is associated with mutations in mitochondrial DNA coding for elements of the oxidative phosphorylation chain (Complex I), it has been presumed that abnormal energy production or oxidative damage in retinal ganglion cells is responsible for the optic neuropathy, resulting in the
clinical and pathological findings. Similarities between Leber hereditary optic neuropathy, vitamin B12 deficiency, and nutritional amblyopia have suggested that abnormalities of ATP levels might be causative (Rizzo 1995). However, abnormalities of retinal ganglion cell energy production or free radicals have not been demonstrated in an in vitro or in vivo model of Leber hereditary optic neuropathy; thus, it remains the subject of active laboratory investigation. In a study of various nonenzymatic antioxidants and lipid peroxides in the blood of patients with Leber hereditary optic neuropathy carriers with homoplasmic DNA mutation at 11778, it was found that these carriers had lower levels of the alpha-tocopherol/cholesterol + triglyceride ratio than controls without these mutations. It was suggested that alphatocopherol may be the primary scavenger molecule against the free radicals induced by complex I deficiency. The authors also suggested that the reduced alpha-tocopherol levels resulted from consumption of the antioxidant by the affected tissues (Klivenyi et al 2001).

Howell has suggested that respiratory chain dysfunction might lead to axoplasmic flow stasis at the level of thecribriform plate, with secondary damage from swelling of axons in that confined space, which he calls a “chokepoint” (Howell 1998).

Regardless of the mechanisms involved, Kirkman and colleagues have shown that oxidative stress is strongly associated with the onset of symptomatic vision loss in a study of 196 affected and 206 unaffected members of 125 pedigrees that harbor 1 of the 3 primary mitochondrial DNA mutations. They found a strong and consistent association between vision loss and smoking, with penetrance of 93% among males who smoked. There was a lesser trend toward increased vision loss with alcohol ingestion but only with very heavy intake (Kirkman et al 2009).

Inheritance of Leber hereditary optic neuropathy susceptibility is maternal, consistent with a mitochondrial genome abnormality as the cause (Newman 1993). Each mitochondrion contains 2 to 10 copies of a closed circular double-stranded DNA coding for 13 of the 67 proteins making up the mitochondrial respiratory chain, as well as the transfer RNA and ribosomal RNA needed for mitochondrial protein synthesis. In most pedigrees, mutations at positions 11778, 3460, or 14484 of the mitochondrial genome are found, and these mutations are not found in pedigrees of unaffected individuals. In general, these mutations involve mitochondrial DNA complex I, or NADH:ubiquinone oxidoreductase (ND) genes (G11778A in ND4, G3460A in ND1, T14484C in ND6). Two additional pedigrees have been described with a novel point mutation in the mitochondrial DNA ND6 gene, A14495G (Chinnery et al 2001b). In addition, a mutation at position 14459 is associated with Leber hereditary optic neuropathy and hereditary spastic dystonia (Jun et al 1994; Jun et al 1996; Shoffner et al 1995). Study of families with the 14459 mitochondrial mutation have emphasized the wide variability of clinical expression in various family members, ranging from no disease to infancy onset dystonia, spasticity, encephalopathy, and anarthria (Gropman et al 2004; Tarnopolsky et al 2004). A case clinically compatible with Leber hereditary optic neuropathy followed by stroke-like episodes in later life has been described as a MELAS overlap syndrome in a single patient with a mutation at G13513 (Pulkes et al 1999). Another Leber hereditary optic neuropathy-MELAS overlap case had a heteroplasmic point mutation at 3376 (G>A) in the MTND1 gene (Blakely et al 2005). These are called primary mutations.

Complete mitochondrial DNA genome sequencing in a family with 2 affected patients but without any of the 3 primary mutations has identified a point mutation at position 14568 in the ND6 gene. This is the seventh mutation within the highly conserved ND6 gene leading to Leber hereditary optic neuropathy (Fauser et al 2002). Complete mitochondrial DNA sequencing in another patient and his sister, neither of whom had any of the standard primary mutations, were found to have a T to C missense mutation at 11253 in the ND4 gene, causing replacement of a highly conserved isoleucine by a threonine residue (Leo-Kottler et al 2002). None of 100 controls showed this mutation. Interestingly, this patient had spontaneous recovery of vision.

A mutation at position 15257 has been suggested to cosegregate with the disease, but the presence of this mutation in normal subjects has led to controversy about whether this is actually a primary mutation (Johns et al 1993c; Oostra et al 1994; Brown et al 1995; Leuzzi et al 1997). However, the fact that subjects may harbor any given mutation but not develop clinical Leber hereditary optic neuropathy makes it difficult to determine whether there is a causal relationship between the genotype and phenotype for this and similar mutations. Mutations at other points in the mitochondrial genome may be associated with Leber hereditary optic neuropathy in conjunction with one of the primary mutations. These include 3394, 4160, 4216, 4917, 5244, 7444, 13708, and 15812 (Brown et al 1992; Brown et al 1995). It is controversial whether the presence of secondary mutations affects the prognosis of the disease (Nikoskelainen et al 1996). The fact that genetically identical monozygotic twins may be discordant for long periods of time for Leber hereditary optic neuropathy implies that epigenetic factors affect the susceptibility to the disease (Johns
Although most patients with Leber hereditary optic neuropathy are homoplasmic for a primary mitochondrial DNA mutation, some patients (4% to 14%) may have heteroplasmy or a variable proportion of mutant and wild-type mitochondrial DNA (Harding et al 1995b; Mashima et al 1995). The degree of heteroplasmy probably influences the likelihood of developing symptomatic Leber hereditary optic neuropathy in those at risk (Smith et al 1993; Harding et al 1995b; Mashima et al 1995; Tanaka et al 1998), but not necessarily the degree of visual loss (Smith et al 1993). In an analysis of 17 independent pedigrees harboring the G117678A mutation, it was found that the frequency of blindness in males was related to the mutation load in blood cells and that mothers with 80% or less mutant mtDNA in their blood cells were less likely to have clinically affected sons than mothers with 100% mutant mtDNA in the blood (Chinnery et al 2001a). A study of 167 genealogically unrelated Leber hereditary optic neuropathy families revealed that the prevalence of heteroplasmy was 5.6% for the 11778 mutation, 40% for the 3460 mutation, and 36.4% for the 14484 mutation. The authors conclude that this significant variance in prevalence of heteroplasmy between the different primary Leber hereditary optic neuropathy mutations suggests genotypical differences in disease expression (Jacobi et al 2001).

Another factor affecting susceptibility to clinical manifestations may be the possibility of adaptive change in the mtDNA in the presence of point mutations. One study investigated the quantitative ratio of mtDNA to nuclear DNA in peripheral circulating leukocytes from 13 asymptomatic carriers and 18 family noncarriers related to 11 patients with Leber hereditary optic neuropathy due to the 14486 mutation. Significant increase in the mtDNA relative to nuclear DNA was found only in asymptomatic carriers, indicating that those who had not increased the mtDNA had become symptomatic (Nishioka et al 2004).

Mitochondrial haplotype grouping reveals that haplogroup J is more often seen in patients with the 14484 and 11778 mutations, suggesting a polygenic effect on disease penetrance (Brown et al 1997; Lamminen et al 1997). In a study of 3613 subjects from 159 Leber hereditary optic neuropathy pedigrees, it was found that vision loss was more prevalent when the primary mutations were found on specific haplotype subgroups—J2 for 11778G to A, J1 for 14484T to C and haplotype K for 3460G to A (Hudson et al 2007).

In Chinese pedigrees with Leber hereditary optic neuropathy bearing the primary G11778A mutations, secondary mutations at the tRNA{Met} A4435G and the tRNA{Thr} A15951G loci were found to increase the penetrance of clinical disease (Li et al 2006; Qu et al 2006). Cells from matrilinear family members carrying both the G11778A and the secondary A15951G mutation had about a 35% reduction in the level of tRNA{Thr} relative to those carrying only the G11778A mutation (Li et al 2006). The authors speculated that this reduction of tRNA metabolism could cause impaired mitochondrial translation in subunits including ND4 of NADH dehydrogenase (complex I).

Male predominance is strong in Leber hereditary optic neuropathy, the degree depending on the specific mutation. The genetic basis for this is controversial. It was initially believed that digenic inheritance, with the second gene on the X chromosome, could account for the higher proportion of symptomatic males among obligate carriers with a primary mutation. However, detailed genetic studies argue against an X-linked locus for male susceptibility, and this issue remains a topic of investigation (Chalmers et al 1996; Pegoraro et al 1996). At least one pedigree has been described in which 9 patients in 4 generations with the 11778 mutation developed Leber hereditary optic neuropathy, and 8 of the 9 were girls (Thieme et al 1999).

Light and electron microscopic studies of Leber hereditary optic neuropathy eyes and optic nerves demonstrate loss of the retinal ganglion cell layer and optic atrophy (Kerrison et al 1995). However, the nature of pathological study prevents determination of the pathophysiology of the disease, for example, whether axonal loss causes (or is caused by) ganglion cell loss or even whether functional mitochondrial abnormalities in the ganglion cell are responsible, as opposed to another cell type (eg, astrocytes or oligodendrocytes).

Studies of the effects of mitochondrial DNA mutations on mitochondrial function have classically focused on energy metabolism in lymphoblast or platelet mitochondria from affected individuals. In general, mutations at the 11778 position result in minor changes in oxidative phosphorylation but may affect binding of complex I to ubiquinone (Degli Esposti et al 1994). Mutations at the 3460 position result in greatly decreased complex I activity (Majander et al 1991; Smith et al 1994; Cock et al 1998). There is some evidence that nuclear genome variation alters the expression of mitochondrial complex I expression in persons bearing the 3460 mitochondrial mutation (Cock et al 1998). Mutations at the 14484 position result in decreased complex I electron transfer activity and ATP synthesis (Oostra et al 1995). In
vivo imaging using 31P magnetic resonance spectroscopy demonstrates moderately decreased energetics in the skeletal muscle of patients with the 11778 mutation (Barbiroli et al 1995) but less so in patients with other mutations (Lodi et al 1997).

In an attempt to further define the effects of specific mitochondrial DNA mutations on mitochondrial function, several workers have fused rho0206 cells lacking mitochondria with mitochondria from affected individuals, producing cell lines ("cybrids") containing mutated mitochondria. Cybrids with the 11778 mutation have a 40% decrease in NADH dehydrogenase-dependent respiration but not rotenone-sensitive NADH dehydrogenase activity (Hofhaus et al 1996), whereas cybrids with the 14459 mutation have a 39% decrease in complex I activity (Jun et al 1996). In at least one study, however, these metabolic consequences could not be confirmed and studies using cybrids will probably require further study (Carelli et al 2002).

In a study using in vivo phosphorus magnetic resonance spectroscopy to measure oxidative phosphorylation in occipital lobe and calf muscle, it was found that in 3 members of a family with the 3460 mutation indices of brain energy metabolism was abnormal in all 3, but muscle oxidative phosphorylation rate was normal in all. This study indicates that the distribution of the biochemical expression of the mutation can be studied in vivo and that it is not equal in all organs of affected persons (Lodi et al 2002).

It has long been assumed that oxidative stress triggers the onset of symptomatic optic neuropathy in patients with Leber hereditary optic neuropathy. Wang and coworkers assessed free radicals in venous blood from 14 patients, 20 asymptomatic relatives, and 30 control subjects using luminal luminescence after addition of phytohemagglutinin. They found that free radicals increased in the blood of Leber hereditary optic neuropathy patients and their asymptomatic relatives to a much greater extent than in normal controls, indicating reduced antioxidant capacity in members of the affected families (Wang et al 2008).

Some patients with Leber hereditary optic neuropathy go on to develop a remitting, relapsing condition similar to multiple sclerosis (Harding et al 1992). Neuropathologic examination of one such patient with 1448 mutation showed extensive frontal lobe demyelination mixed with cavitary necrosis and CD8-positive T-cell predominant inflammatory infiltrates. Several pathophysiologic possibilities are discussed, one being that Leber hereditary optic neuropathy somehow activates an autoimmune process in the central nervous system with some features of multiple sclerosis (Kovacs et al 2005).

An optic neuropathy that is pathologically similar to that of Leber hereditary optic neuropathy has been produced in a DBA/1J mouse model of oxidative injury by increasing mitochondrial levels of reactive oxygen species (Qi et al 2003).

**Epidemiology**

Leber hereditary optic neuropathy is an uncommon cause of optic neuropathy. Its prevalence is highly dependent on the population studied, as well as which mutation is being analyzed. In Australia 2% of those disabled by blindness have Leber hereditary optic neuropathy as a cause (Mackey and Buttery 1992). The 11778 is the most prevalent mutation, with the proportion varying depending on population. In Japan, approximately 80% to 90% of patients with Leber hereditary optic neuropathy have the 11778 mutation, whereas 40% to 85% of non-Japanese patients have that mutation (Nakamura et al 1992; Ishikawa et al 1995). The male preponderance varies, dependent on mutation studied. In a European population, there were male-to-female ratios of 3.7:1 with the 11778 mutation, 4.3:1 with the 3460 mutation, and 7.7:1 with the 14484 mutation (Harding et al 1995b). In a study comparing 16 women and 66 men with Leber hereditary optic neuropathy, it was found that women were older at presentation (average 31.3 vs. 24.3 years), had more severe vision loss, less tendency to recover vision, and a much higher rate of having an affected mother than did affected men (Leo-Kottler and Christ-Adler 1999).

Although the vision loss most commonly occurs among patients aged between teens and forties, it has been reported in much older individuals, and testing for the Leber hereditary optic neuropathy mutations should be done in any patient with acute, sequential, bilateral optic neuropathy regardless of age (Shah et al 2008).

In a psychophysical study of 18 asymptomatic carriers of the 11778 mutation versus 18 control subjects, Gualtieri and colleagues demonstrated abnormally high contrast discrimination thresholds among the carriers as compared with normal control subjects. This suggests that even in asymptomatic carriers there are subtle abnormalities of visual processing that may be used to identify them (Gualtieri et al 2008).
Prevention

The most important risk factor for development of Leber hereditary optic neuropathy is the presence of one of the primary mutations (11778, 3460, and 14484). As the mitochondrial DNA are maternally inherited, it can be expected that the children of an affected female, but not of an affected male, will harbor the mutation. Similarly, a cousin linked through a female lineage to an affected subject may be at risk, as would any similar relative. DNA testing can confirm whether or not an individual relative has the relevant mutation.

No prophylaxis has been convincingly shown to be of value in preventing development of Leber hereditary optic neuropathy in those genetically at risk, or in those at risk based on prior involvement of one eye. Topical application of brimonidine purite QID to the unaffected eye in 9 patients with visual loss in 1 eye and a primary mitochondrial gene mutation failed to prevent eventual visual loss in the second eye (Newman et al 2005).

Because of the presumption that mutations in genes coding for respiratory chain subunits result in functional abnormalities of oxidative phosphorylation, some clinicians suggest that their patients take vitamin C, vitamin E, coenzyme Q10, or other antioxidants. For similar reasons, many patients are counseled to avoid use of tobacco or alcohol. Some suggest avoiding foods containing naturally occurring cyanide, which interferes with mitochondrial respiration. A systematic epidemiologic and neuro-ophthalmologic study of a large Brazilian pedigree with 11778 haplogroup J mutation has demonstrated a strong influence of environmental risk factors in the development of phenotypic disease, particularly smoking (Sadun et al 2003).

Chariot and colleagues describe a 37-year-old man with onset of choreiform movements, bilateral lesions in the subthalamic nuclei on MRI, and a history of bilateral optic neuropathy that started when he was 9 years old. Treatment with 250 mg coenzyme Q10 per day and multiple vitamins was associated with recovery of the movement disorder and resolution of the MRI changes but no recovery of vision (Chariot et al 1999). This patient had none of the primary mitochondrial mutations associated with Leber hereditary optic neuropathy and must be regarded as only possibly an example of this disease with an as yet undiscovered mutation.

Differential diagnosis

Leber hereditary optic neuropathy is often confused with other optic neuropathies and may even be misdiagnosed as nonorganic visual loss. The presence of a family history, especially in the maternal lineage, is helpful in making the diagnosis but is not always known or present. Instead, certain clinical observations may help in distinguishing Leber hereditary optic neuropathy from other optic neuropathies. Other hereditary optic neuropathies may be distinguished based on a combination of clinical features and inheritance pattern. Kjer dominant optic atrophy has an autosomal dominant mode of inheritance mapped to chromosome 3q. Typically with onset from 4 to 8 years of age, it is only slowly progressive and rarely results in visual acuity worse than 20/200. Although temporal disc cupping and a tritan (blue-yellow) color defect are typical, these findings may also be seen in Leber hereditary optic neuropathy (Jacobson and Stone 1991). Recessive optic atrophy is a severe, usually congenital hereditary optic neuropathy associated with visual acuity worse than 20/200, nystagmus, and achromatopsia. The age of onset usually distinguishes it from Leber hereditary optic neuropathy. Other hereditary optic neuropathies may be associated with neurodegenerative disorders, such as Charcot-Marie-Tooth disease and Friedreich ataxia.

It is often difficult to distinguish Leber hereditary optic neuropathy from other optic neuropathies when only one eye is involved. In these cases, the visual loss and disc elevation of Leber hereditary optic neuropathy may be mistaken for optic neuritis (papillitis), anterior ischemic optic neuropathy, or anterior compressive, infiltrative, or infective optic neuropathies. Optic neuritis is typically associated with ocular discomfort aggravated by eye movement, which is only occasionally seen in Leber hereditary optic neuropathy (Harding et al 1995b). Recovery of vision from optic neuritis usually begins after 1 or 2 weeks, and substantial improvement is often seen by 6 weeks, unlike the usually persistent visual loss of Leber hereditary optic neuropathy. High signal abnormalities on T2-weighted MRI images of the deep white matter are often seen in patients with optic neuritis, but a multiple sclerosis-like syndrome with corresponding neuroimaging findings can also be seen in Leber hereditary optic neuropathy (Harding et al 1992; Harding et al 1995a; Flanigan and Johns 1993; Olsen et al 1995; Jansen et al 1996).

A United Kingdom-wide prospective cohort study of prevalent cases of multiple sclerosis with Leber hereditary optic neuropathy mitochondrial DNA mutations identified 12 new cases from 11 pedigrees, and 44 cases with this
A combination of existing literature identified a clinical profile that is distinct from that of patients with just Leber hereditary optic neuropathy DNA mutations, and also distinct from that of patients with just multiple sclerosis. The hybrid group had features more like multiple sclerosis than Leber hereditary optic neuropathy disease, including female preponderance, multiple episodes of visual loss, and a long interval before the fellow eye is affected (1.66 years on average), as well as features that are more typical of Leber hereditary optic neuropathy than multiple sclerosis, including painless vision loss and failure of visual recovery. The authors conclude that the co-occurrence of multiple sclerosis and Leber hereditary optic neuropathy mitochondrial DNA mutations is likely due to chance, but the resulting clinical profile has a phenotype distinct from either group alone, suggesting a mechanistic interaction (Pfeffer et al 2013).

The possible genetic and pathogenetic linkage between Leber hereditary optic neuropathy and multiple sclerosis was further investigated in a multinational study group called the MAGNIMS network. They utilized a blinded standardized review of brain MRIs from 30 patients with multiple sclerosis, 31 patients with Leber hereditary optic neuropathy, and 11 patients with symptoms of both whom they dubbed as having "LMS." All of the patients with LMS had white matter lesions by definition, and 25% of patients with Leber hereditary optic neuropathy had similar brain lesions. Many more females with Leber hereditary optic neuropathy had white matter lesions than males (relative risk 8.3), mirroring the gender ratios for patients with multiple sclerosis (Matthews et al 2015).

Nonarteritic anterior ischemic optic neuropathy produces rapid painless visual loss, but is uncommon in patients less than 50 years old and is frequently associated with altitudinal visual field defects corresponding to segmental disc edema. Arteritic anterior ischemic optic neuropathy is seen in elderly patients with symptoms, signs, and laboratory evidence of giant cell arteritis. There is usually pallid disc edema and severe visual loss.

Orbital lesions that compress the optic nerve (eg, extraocular muscle enlargement from Graves disease or orbital tumors), infiltrative disease of the optic nerve (eg, lymphoma, metastatic carcinoma, sarcoid, etc.), or infections of the optic nerve (eg, Cryptococcus or cytomegalovirus) may cause disc edema and visual loss. The time course of these processes is usually less rapid than that of Leber hereditary optic neuropathy, but in some cases, they may overlap. Associated clinical findings, such as proptosis, a history of immunosuppression, or the presence of a known primary cancer, suggest one of these etiologies. However, in some cases the history and examination do not aid in distinguishing these optic neuropathies, and neuroimaging, laboratory studies, and sampling of cerebrospinal fluid are required.

The differential diagnosis of bilateral Leber hereditary optic neuropathy is different. When disc elevation is present without severe visual loss, the possibility of papilledema (ie, disc edema secondary to increased intracranial pressure) should be considered. In papilledema, the visual acuity is initially normal, and the visual field either is normal or demonstrates enlargement of the blind spot. Associated symptoms (headache, vomiting, tinnitus, transient obscurations of vision lasting a few seconds) and signs (unilateral or bilateral sixth nerve palsy, absence of spontaneous venous pulsation at the disc) may suggest the diagnosis. Other causes of bilateral disc edema and visual loss include bilateral presentation of one of the optic neuropathies mentioned above and acute toxic optic neuropathies.

Bilateral Leber hereditary optic neuropathy without disc elevation should be differentiated from nutritional and toxic optic neuropathy, bilateral presentation of a retrobulbar optic neuropathy, low-tension glaucoma (Lauer et al 1985; Mashima et al 2003), and occult retinal dystrophy, particularly a cone dystrophy. All of these may demonstrate decreased visual acuity and central visual field loss. Optic disc pallor may only develop late in the course of the optic neuropathies and may only be present on the temporal disc, where it may be hard to distinguish from normal variation in color. Retrospective surveillance of patients with the diagnosis of tobacco-alcohol amblyopia may yield Leber hereditary optic neuropathy mutations (Cullom et al 1993). Cone dystrophies may only be detected by electroretinography.

Finally, factitious visual loss is a diagnosis of exclusion in a patient with vision loss, no relative afferent pupillary defect, and relatively normal discs. Patients with relatively symmetric vision loss from bilateral optic neuropathy will not have a relative afferent pupillary defect because this test compares conduction in the 2 optic nerves. Because the optic disc pallor of Leber hereditary optic neuropathy may occur late or be difficult to detect, patients should not be diagnosed as having factitious visual loss without considering other possibilities. In some patients, the presence of a constricted “tubular” field (best demonstrated at the tangent screen) instead of the cecocentral scotoma of Leber hereditary optic neuropathy may help in making this diagnosis.
Diagnostic workup

The most reliable way to determine the likelihood of Leber hereditary optic neuropathy is to analyze the patient's mitochondrial DNA for the presence of one of the primary mutations. A peripheral blood sample may be sent to a commercial or research laboratory. Testing usually involves polymerase chain reaction amplification of the appropriate regions of the mitochondrial genome and determination of the presence of a mutation by changes in restriction digest pattern or DNA sequencing, or by allele-specific amplification (Norby et al 1991). Results may take days or weeks to return.

Fluorescein angiography may help determine whether disc elevation represents true edema or the pseudoedema of Leber hereditary optic neuropathy. In the former, but not in the latter, there is leakage of fluorescein from the disc during the late phase of the angiogram.

Changes in the thickness of the retinal nerve fiber layer can now be measured noninvasively using optical coherence tomography and this has shown characteristic changes in the pre-symptomatic stages as well as after the onset of vision loss. In the months prior to symptomatic visual loss, there is characteristic thickening of the retinal nerve fiber layer in the upper and lower arcuate regions and nasal to the disc with relatively little thickening temporal to the disc in the papillo-macular bundle fibers (Savini et al 2005). This correlates with the ophthalmoscopic appearance of pseudo-disc edema in this condition. It is postulated that the thickening relates to dysfunction in energy dependent axoplasmic transport in these ganglion cell nerve fibers. In the acute stage of vision loss, there is rapid thinning in the papillomacular bundle, commensurate with the selective development of central scotoma on visual field examination and with the selective susceptibility of the small diameter axons of the papillomacular bundle (Barboni et al 2005).

Another study examined 6 eyes from 4 patients with Leber hereditary optic neuropathy using spectral domain optical coherence tomography to measure thickness changes in the retinal ganglion cell inner plexiform layer and the macular retinal nerve fiber layer during the presymptomatic stage and at months 1, 3, 6, and 12 after visual loss. Thinning of both the inner plexiform layer and the macular retinal nerve fiber layer was detected in the presymptomatic stage, which may have important implications for therapeutic or preventive interventions even prior to vision loss in 1 eye (Balducci et al 2015).

As the differential diagnosis of Leber hereditary optic neuropathy is large, other diagnostic procedures are frequently performed prior to DNA testing. Magnetic resonance imaging with intravenous contrast and fat suppression may demonstrate abnormal enhancement along the optic nerve, for example, as seen in optic neuritis or infiltrative or infectious optic neuropathies but also occasionally seen in Leber hereditary optic neuropathy (Kermode et al 1989; Borruat and Sanders 1994). Lumbar puncture may detect evidence of central nervous system inflammation, infection, or neoplasm. Serological and radiological studies help in the diagnosis of disorders such as syphilis, vitamin B12 deficiency, and sarcoid. Electroretinography may detect changes consistent with cone dystrophies, although in some cases focal electroretinography may be necessary. Obtaining pattern-shift visual evoked responses (which are abnormal or unrecordable) is usually unnecessary, except in cases of suspected nonorganic visual loss.

Management

No clinical trial has conclusively shown that pharmacological or lifestyle intervention has any effect on the course of Leber hereditary optic neuropathy, whether in terms of recovery of visual function or involvement of the second eye after unilateral disease. Nonetheless, on the basis of clinical experience suggesting that Leber hereditary optic neuropathy may occur in the setting of tobacco or ethanol abuse, many physicians advise their patients to stop smoking and drinking alcohol. Similarly, because the mitochondrial DNA mutations in this disorder affect subunits of the electron transport chain, some clinicians offer their patients the option of taking vitamin C, vitamin E, and coenzyme Q10. Good glucose control may be of help in patients with diabetes mellitus (DuBois and Feldon 1992).

Two therapeutic trials involving patients with Leber hereditary optic neuropathy, one retrospective and the other, prospective, were published in late 2011. The prospective, randomized, placebo-controlled trial involved treatment of 84 patients with Leber hereditary optic neuropathy and 1 of the 3 primary mitochondrial gene mutations (Klopstock et al 2011). Fifty-five patients were treated with idebenone 900 mg/day, and 30 patients received placebo. Idebenone is a synthetic benzoquinone that crosses the blood-brain barrier and mitochondrial membranes. The proposed benefit stems from idebenone’s ability to pass electrons to complex III, bypassing defective complex I in the mitochondrial electron transport chain. Treatment was carried on for 6 months and was initiated at various times in the course of the
To study the effectiveness of allotopic expression, Guy and colleagues created transmitochondrial hybrid cell lines (cybrids) by fusing enucleated patient cells homoplasmic for wild type (11778G) or mutant (G11778A) mitochondrial DNA with neutral nucleated host cells that have permanently lost all mitochondrial DNA after exposure to ethidium bromide (Guy et al 2002). They then showed that in transmitochondrial cybrids with G11778A mutated mitochondrial DNA, ATP synthesis dependent on complex I substrates was substantially reduced and that this deficiency in oxidative phosphorylation can be reversed using allotopic expression of the ND-4 gene and transport of the gene product into the mitochondria that are still homoplasmic for G11778A mutant mtDNA (Qi et al 2007). The protein product of this nuclear ND-4 gene is expressed in the cytoplasm and imported into the mitochondria by appending a mitochondrial transport peptide on the N-terminal and a FLAG tag on the C-terminal by which to identify the gene product.

Taking these techniques another step closer to human intervention, Guy and colleagues injected a nuclear encoded ND-4 subunit fused with a mitochondrial targeting sequence on the N-terminal and a FLAG epitope on the C-terminal for subsequent identification into the right eyes of mice using an adeno-associated viral plasmid vector (Guy et al 2002). They were then able to show that the human ND-4 was effectively integrated into the murine Complex I within mitochondria of the retinal ganglion cells and optic nerve axons and that expression of human ND-4 did not induce loss of retinal ganglion cells, reduction of ATP synthesis, or reduction of pattern electroretinogram.
amplitude. Thus, they did not demonstrate any impediment to further consideration of human treatment using this technique (Koilkonda et al 2014a). This safety study was extended to additional animals, including nonhuman primates, and increased the ratio of mutant to wild-type ND-4 gene administered by intravitreal injection without any reduction in the prevention of optic neuropathy and visual loss (Koilkonda et al 2014b).

The next step in this process was a prospective open-label trial in which the study drug, a self complementary adeno-associated virus vector expressing a normal ND4 complementary DNA, was intravitreally injected unilaterally into the eyes of 5 blind patients with G11778A Leber hereditary optic neuropathy (Feuer et al 2016). Four of these had visual loss for more than 12 months and the fifth patient for less than 12 months. Study subjects were followed for 90 to 180 days with ocular and systemic safety assessments and visual examinations. Visual acuity on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart remained unchanged in the first 3 participants. At 90 days follow up visual acuity, 2 subjects had improved from hand motion vision by 7 letters, and in 1 patient, it had improved by 15 letters, which is the equivalent of 3 lines. No participant lost vision, and no serious adverse events were documented. Additional study of these and other participants is planned over the next 4 years.

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**References especially recommended by the author or editor for general reading.**

**Former authors**

Leonard A Levin MD PhD (original author)

**ICD and OMIM codes**

**ICD codes**

ICD-9:
Leber hereditary optic neuropathy: 377.16

ICD-10:
Leber hereditary optic neuropathy: H47.2

**OMIM numbers**

Leber hereditary optic neuropathy: #535000

**Profile**

**Age range of presentation**

02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance**

male>female, >2:1
male>female, >1:1

**Family history**

family history typical
family history may be obtained

**Heredity**

heredity typical
heredity may be a factor

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

nonorganic visual loss
Kjer dominant optic atrophy
temporal disc cupping
tritan color defect
recessive optic atrophy
nystagmus
achromatopsia
neurodegenerative disorders
Charcot-Marie-Tooth disease
Friedrich ataxia
optic neuritis (papillitis)
multiple sclerosis
anterior ischemic optic neuropathy
anterior compressive optic neuropathies
infiltrative optic neuropathies
infective optic neuropathies
pallid disc edema
Graves disease
orbital tumors
lymphoma
metastatic carcinoma
sarcoid
cryptococcus
cytomegalovirus
papilledema
nutritional optic neuropathy
toxic optic neuropathy
low-tension glaucoma
occult retinal dystrophy
cone dystrophy
optic disc pallor
tobacco-alcohol amblyopia
factitious visual loss
constricted “tubular” field

Associated disorders

Acute bilateral disease
Cerebellar ataxia
Multiple sclerosis
Peripheral neuropathy
Spastic dystonia
Thoracic kyphosis
Tremor

Other topics to consider

Amblyopia
Mitochondrial disorders
Molecular diagnosis of neurogenetic disorders
Optic neuritis
Toxic and nutritional deficiency optic neuropathies
Vitamin B12 deficiency