

Leber's hereditary optic neuropathy

Synonyms: Leber's optic atrophy, Leber's hereditary optic atrophy, optic atrophy, Leber's optic neuropathy and hereditary optic neuroretinopathy

What is Leber's hereditary optic neuropathy?

Leber's hereditary optic neuropathy (LHON) is a disease of mitochondria. There is usually 1 of 3 point mutations of DNA. These three are: G11778A, T14484C and G3460A. Clinical molecular genetic testing for these mutations is available. Overall, about 45 mutations have been discovered, (eg, G10680A, T3394C) but these are much less common.^[1] It may be inherited or, more rarely, a spontaneous mutation. Inheritance is entirely from the maternal side. This has sometimes led to the erroneous belief that it is an X-linked condition but inheritance is not Mendelian.^[2]

It seems likely that the aetiology is multifactorial. A complex interplay between genetic, hormonal and environmental factors may modulate the risk of a carrier losing vision.^[3] Heavy smoking may be a significant risk factor.^[4]

How common is Leber's hereditary optic neuropathy? (Epidemiology)

Leber's hereditary optic neuropathy (LHON) is estimated to be the most frequent mitochondrial disease with a prevalence ranging from 1 in 27,000 in North East England to 1 in 45,000 in a meta-analysis of reports in the European population. It has a strong male preponderance (80% to 90%), and the usual age at onset is between 15 to 35 years.^[5]

A nationwide Japanese survey reported 120 cases of newly developed LHON during 2014, of whom 93.2% were males.^[6]

Genetics

Mutation of the G11778A gene represents 60% of cases worldwide. There are 18 different phenotypes that have been assessed but 3 account for 95% of cases.^[2] Up to 40% give no family history.^[7]

Penetrance is about 50–60% in males and 10–15% in females. Many, if not most, cases with no family history are due to incomplete penetrance rather than new mutation.^[2]

Clinical features^[8]

The mean age of onset is between 27 and 34 years with a range of 1 to 70 years.

- It usually presents in young adults as painless subacute bilateral visual failure, affecting men more than women (3M:1F). Women tend to present a little later but the disease can be more severe.
- It starts with blurring of central vision and desaturation of colour in both eyes simultaneously in about half of cases. If it is asymmetrical, both eyes are usually affected within 2–15 months.
- The rate of progression can vary from rapid to over two years but most people are severely impaired by three or four months.
- Central vision deteriorates to counting fingers in 80%. There may be temporary improvement before the atrophic phase.
- Optic atrophy develops and clinical investigations are unhelpful in distinguishing it from other causes.
- Visual acuity remains static thereafter. Most will be registered as severely sight impaired for the rest of their lives, with a permanent large scotoma.
- Occasionally there is also dystonia and spasticity or a multiple sclerosis-like illness, especially in affected females.
- A subgroup with onset in childhood has been identified in Italy.^[9]

Diagnosing Leber's hereditary optic neuropathy (investigations)^[5]

- Visual acuity is usually reduced to counting fingers.

- Visual field testing shows an enlarging central scotoma.
- ECG may reveal cardiac conduction abnormalities.
- Fluorescein angiography may be useful in the acute phase. The disc swells due to pseudo-oedema of the nerve fibre layer; peripapillary telangiectasias appear and there is increased tortuosity of the retinal vessels. Not everyone shows the full picture.
- Optical coherence tomography; in childhood disease, measuring the optic disc vertical diameter on OCT indicates prognosis. Larger diameter may be associated with a better visual prognosis.
- Electrophysiology studies, including pattern electroretinogram and visual evoked potentials, may demonstrate optic nerve dysfunction even without retinal disease.
- CT scan or MRI scan of the brain is necessary (particularly when there are extra-ocular features) to exclude other inflammatory and structural causes of an acute optic neuritis if there is no family history. MRI scan is often normal but may show a high signal within the optic nerves.
- Biochemical mitochondrial studies may show respiratory chain defects.^[7]
- Molecular genetic testing.

Differential diagnosis^[5]

- There are many causes of acute bilateral visual failure that must be excluded during the acute phase, including tobacco amblyopia.
- In the phase of optic atrophy, the inherited deafness-dystonia-optic neuropathy (Mohr-Tranebjaerg syndrome) must be considered.^[10]
- Optic neuropathies can result in similar changes at the optic disc, particularly in late-stage disease, making it difficult to differentiate from glaucoma based on disc assessment alone.^[11]
- Leber's congenital amaurosis (LCA) was described by the same doctor but is a different disease with several variants.^[12]

Associated diseases^[13]

A number of studies have found associated conditions. The most common are cardiac pre-excitation syndromes, usually [Wolff-Parkinson-White syndrome](#) but also [Lown-Ganong-Levine syndrome](#). A multiple sclerosis-like disease has also been described.

Management of Leber's hereditary optic neuropathy^[14]

Currently, there is no value in monitoring asymptomatic people with the gene, as no effective prevention exists. In the last few years, clinical trials for gene therapy as well as idebenone, a synthetic analog of coenzyme Q10, have sought to reduce the impact and progression of LHON after its onset.^[15] So far, these trials have received most attention. Though encouraging however, the results have been mixed.^[16]

In vitro studies have highlighted oestrogen's role in preserving vision by increasing mitochondrial biogenesis and recent work suggests oestrogen may also have a therapeutic role in restoring vision.^[17]

Support, advice about jobs and visual aids will be required.^[18]

It is noted that the optic neuropathy associated with vitamin B12 deficiency is very similar to Leber's congenital optic neuropathy and therefore some have advocated that known carriers of the gene defect should take care to have an adequate dietary intake of vitamin B12.

Mitochondrial replacement therapy is also being explored as a possible option.^[19]

Genetic counselling

The disease is inherited from the mother and not the father. An affected mother invariably passes on the gene although there is limited penetrance. De novo mutations are presumed rare and the 40% with no family history are largely accounted for by incomplete penetrance or failure to know the family. If the mother has the gene, so too will all siblings. It will be passed to all children by mothers and none by fathers.

Genetic testing is not useful in predicting age of onset, severity, or rate of progression in asymptomatic carriers. Age and sex are important. An 18-year-old male has a lifetime risk of around 50% for developing the disease after a positive test result but this falls as years go by without manifestation. However, the risk never vanishes, as it can present late in life. If the mutation is heteroplasmic, it may not be present in every family member. Heteroplasmy occurs in 12%.^[20]

Intrauterine testing is not applicable, as no children of carrier fathers will be affected, although all children of carrier mothers will have the gene. However, it will be manifest in only 50% of male offspring and 15% of females with the risk of severe sight impairment being 40% and 10% respectively.

General wisdom holds that children who are at risk of a disorder that strikes in adulthood and for which there is no treatment, should not have testing unless there are symptoms. It is argued that asymptomatic testing removes the choice to know or not know this information, and it raises the possibility of stigma within the family and society, which could have serious implications for education and career. However, this strategy may change if gene therapy and mitochondrial replacement therapy fulfil their potential as a prophylactic treatment for asymptomatic patients.

Prognosis^[21] ^[22]

- In the acute phase, patients describe a loss of colour vision in one eye, followed by a painless subacute decrease in central visual acuity, accompanied by an enlarging central scotoma.
- The second eye usually follows a similar course within three months, and significant improvements in visual acuity are rare for patients with G11778A or G3460A mutation. However, despite the severe visual impairment, some will gain some recovery of sight, particularly with the T14484C mutation.
- In the chronic phase, patients usually have a bilateral visual deficit that is symmetrical and lifelong. Most remain legally severely sight impaired, are unable to drive a motor vehicle, and are unable to find employment.

It is hoped that the ongoing studies of gene therapy in animal experiments and clinical trials in humans will translate into an improvement in the prognosis of this condition in the future.^[23]

History

Theodor Karl Gustav von Leber (pronounced LAY-ber) was born in 1840 and died in 1917.^[24] He trained as a chemist but turned to medicine on the advice of Robert Bunsen of burner fame. He studied under Carl Ludwig and Albrecht von Graefe. He has lent his name to Franceschetti-Leber phenomenon, LCA, Leber's military aneurysm, Leber's plexus and LHON.

He described the disease in 1868 but little progress was made until the 1980s. Many different pedigrees have been described. Wallace and co-workers demonstrated that human mtDNA was maternally inherited and suggested that maternally transmitted diseases might be due to mtDNA mutations.

Further reading

- [LHON Society](#)
- [Theodorou-Kanakari A, Karampitanis S, Karageorgou V, et al; Current and Emerging Treatment Modalities for Leber's Hereditary Optic Neuropathy: A Review of the Literature. Adv Ther. 2018 Oct;35\(10\):1510-1518. doi: 10.1007/s12325-018-0776-z. Epub 2018 Sep 1.](#)

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