Leber's Optic Atrophy

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

Leber's hereditary optic atrophy is a disease of mitochondria. There is usually 1 of 3 point mutations of DNA. These 3 are: G11778A, T14484C and G3460A. Clinical molecular genetic testing for these mutations is available. More recently, new mutations have been identified (G10680A, T3394C) but these are much less common. 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. It seems likely that the aetiology is multifactorial.

Epidemiology

A study of North East England found that 11.8 per 100,000 had the LHON gene but the incidence of the disease was 3.22 per 100,000. The incidence of blindness due to LHON was 1 in 14,000.

Mutation of the G11778A gene represents 70% of cases worldwide. There are 17 different phenotypes that have been assessed but 3 account for 95% of cases. Up to 40% give no family history.

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.

Clinical features

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 2 years but most people are severely impaired by 3 or 4 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 blind 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.

Investigations

- Visual acuity is usually reduced to counting fingers.
- Visual field testing shows an enlarging central scotoma.
- 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.
- 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 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.

Differential diagnosis

- 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.
- 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.
- Leber’s congenital amaurosis (LCA) was described by the same doctor but is a different disease with several variants.

Associated diseases
Further reading & references

1. Leber Optic Atrophy; Online Mendelian Inheritance in Man (OMIM)
5. Muhr-Transneurag Syndrome, MTS; Online Mendelian Inheritance in Man (OMIM)
7. Leber Congenital Amaurosis 1, LCA; Online Mendelian Inheritance in Man (OMIM)
11. Theodor Karl Gustav von Leber; whonamedit.com