

Leber's hereditary optic neuropathy

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Creation Date: August 2002

Update: November 2003

Scientific Editor: Professor Jean-Louis Dufier

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Abstract

Leber's hereditary optic neuropathy (LHON) refers to an optic nerve dysfunction due to mutations in the mitochondrial DNA (mtDNA) and is transmitted in a non-mendelian or maternal pattern. However, sporadic forms and singleton cases of LHON are numerous. The prevalence is estimated to 1:50,000. LHON begins generally in young adult patients, with a mean age of onset between 18 and 35 years. Vision loss starts usually in one eye, and is either sudden, leading to acuity lower than 20/400 in less than a week, or progressive over 2 or 3 months. The fellow eye can be affected, either almost simultaneously in nearly 50 % of the patients, or sequentially with sometimes an interval as long as 9 months. Fundus examination often reveals disc pseudooedema and hyperemia, arteriolar dilatation, vascular tortuosity and peripapillary telangiectasias. Although visual loss is usually the only manifestation, LHON associations with cardiac, neurological or skeletal abnormalities have been reported. The optic atrophy seems to be linked to the respiratory chain dysfunction caused by mutations in mtDNA. More than 18 mtDNA mutations have been observed in LHON, and at least four correspond to "primary mutations" as they are sufficient to induce the disease. The major primary mtDNA mutations involve genes encoding different subunits of the complexes I and III of the mitochondrial respiratory chain. Other mutations, known as "secondary mutations", are usually associated with primary mutations. Epigenetic or toxic factors could also be involved in the pathogenicity. There is currently no effective treatment for LHON.

Keywords

Leber's hereditary optic neuropathy, inherited optic atrophies, mitochondrial DNA, primary mutations

Disease name and synonyms

-Leber's hereditary optic neuropathy
-Optic atrophy, Leber type

-Leigh syndrome
-Wolfram syndrome
-Normal tension glaucoma
-Acquired optic atrophies
-Behr syndrome

Excluded diseases

-Autosomal dominant optic atrophy, type Kjer
-Autosomal recessive optic atrophy

Definition/Diagnosis criteria

The "Leber's hereditary optic neuropathy" (LHON) is a distinct type of "inherited optic atrophies" or "hereditary optic neuropathies". LHON refers to an optic nerve dysfunction due to mutations in the mitochondrial DNA (mtDNA) and is transmitted in a non-mendelian or maternal pattern. However, sporadic forms and singleton cases of LHON are numerous.

Differential diagnosis

Other conditions of inherited optic atrophies, especially the dominant [optic atrophy \(type Kjer, OPA1\)](#), as well as many other inherited optic atrophies, such as Wolfram syndrome (caused by mutation in the *WFS1* gene on chromosome 4), and all etiologies of acquired optic atrophies, must be differentiated from LHON. It is particularly important to exclude toxic optic neuropathies, since toxic factors are sometimes considered as risk factors promoting vision loss in subjects harboring LHON mutations. Cullom *et al.* (1993) proposed that the diagnosis of LHON should be considered in all patients diagnosed as having tobacco-alcohol amblyopia, but Kerrison *et al.* (2000) failed to observe any significant deleterious association between tobacco or alcohol consumption and vision loss among individuals harboring LHON mutations. In the early stage of the disease, multiple sclerosis (MS) must be ruled out as both pathologies can first manifest as an acute visual loss. In addition, LHON-MS associations have been reported and "Leber-plus" refer to MS-like neurological manifestations in LHON patients.

Frequency

The prevalence of the LHON is not clearly defined. However, it is generally accepted to be approximately 1:50,000.

The sporadic forms or singleton cases are frequent, since a family history is only observed in 43 % to 65 % LHON cases, depending on the mutation harbored. This suggests *de novo* occurrence of LHON mutations. In Europe and North America, LHON occurs predominantly in males. This male predominance seems to vary according to the mtDNA mutation involved, ranging from 33-67% for mutations 3460, to 80-100% for mutations 11778 or 15257. In Japan and Asia, only 58% of LHON occur in males.

Clinical description

LHON begins generally in young adult patients, with a mean age of onset between 18 and 35 years. However, it can also affect children as young as one year or patients over 60 years.

A painless vision loss occurs usually in one eye. This vision failure can either be sudden, leading to acuity lower than 20/400 in less than a week, or progressive over 2 or 3 months. Slower rates of decrease of vision have been reported. The fellow eye can be affected, either almost simultaneously in nearly 50 % of the patients, or sequentially with sometimes an interval as long as 9 months. But, the mean delay between vision loss of each eye is 2 months. Strictly unilateral forms of LHON have been reported. Final visual acuity ranges from 20/400 to no light perception, depending on the severity of the mutation harbored.

Fundus examination can be strictly normal at the onset of LHON. However, it often reveals disc pseudoedema and hyperemia, arteriolar dilatation, vascular tortuosity and peripapillary telangiectasias. Fluorescein angiography confirms the absence of a true disc oedema. The peripapillary telangiectasias are also observed in about half of the asymptomatic relatives harboring the mtDNA mutation. Huoponen has reported that peripapillary telangiectasias appear at the pre-clinic stage of the disease and disappear as LHON progresses toward the end stages, suggesting that this disorder is primarily a vascular disease of the optic disc. At the end stages, the whole optic disc or its temporal portion became atrophic. In addition, disappearance of the optic fibers of the papillo-macular bundle can be observed.

A maculopathy identical to Stargardt disease has been reported in LHON associated with mtDNA mutations 11778 and 15257. Such maculopathy can be responsible for the alterations of the electroretinogram (ERG) sometime observed in LHON.

Visual loss is usually the only manifestation in LHON patients. However, some associated systemic abnormalities have been reported; Cardiac pre-excitation syndromes (Wolff-Parkinson-White syndrome or Lown-Ganong-Levine syndrome), are often observed in families harboring mutation 11778 especially in Finnish or Japanese patients, with an approximative frequency of 8 to 9%. Minor skeletal changes (thoracic kyphosis, ...) or neurological abnormalities (deafness, ataxia, tremor, dystonia, ...) have been also reported. The neurological manifestations are usually asymptomatic, being only observed on MRI. These include putamen calcification or vertigo. In some patients, the neurological manifestations are indistinguishable from those observed in MS. The term of "Leber plus" is used to define this association between LHON and MS-like syndrome. The relations between these two pathologies are still unclear.

Although there is no association between MS and mtDNA mutations, the mtDNA haplogroup J might be a risk factor for optic neuritis, when associated with MS.

All of the mtDNA mutations involved in LHON can be associated with these neurological manifestations. However, manifestations of dystonia in “Leber plus” are related to mutation 14459. In opposition to other neurological mitochondrial diseases, muscle biopsies rarely exhibit typical red ragged fibers.

Visual loss is often permanent. However, spontaneous improvement can be observed. The delay between onset and improvement of LHON, as well as its frequency seems to depend on the mtDNA mutation of the patient. Most studies report that mutation 11778 is associated to the lowest frequency of visual recovery (4%), whereas the probability of visual improvement is 22% with the mutation 3460, and reaches over 35% with mutation 14484. This visual improvement is often unilateral but can be asymmetrical. The intensity of the visual recovery is often limited. However, molecular studies have confirmed that the vision can be restored to an almost normal value during the evolution of a true LHON. Patients often perceive a reduction of the surface or the depth of the central scotoma with its fenestration or a clearing of vision within the central scotoma. Other parameters of visual function can improve, such as static perimetry, flicker. In addition, patients often describe a Uhthoff phenomenon, which is not specific to LHON and causes a temporary decrease in vision.

Etiology

Pathophysiology

At histological examination, the optic nerve displays signs of optic atrophy with axonal reduction and degeneration, and modifications of the axoplasmic morphology. These abnormalities predominate in the P-cells, which are the fibers with the smallest caliber in the central part of the nerve. The involvement of these small fibers is not specific to LHON, as it is encountered in all genetic and acquired optic neuropathies. In addition, myelin abnormalities (changes in myelin thickness or myelin constitution) have been observed in the myelinated post-laminar portion of the optic nerve. A dramatic reduction in the number of retinal ganglion cells and fibers of the papillo-macular bundle is also usually observed during the course of LHON. However, it seems that the respiratory chain dysfunction caused by mtDNA mutations blocks the function of the optic nerve axons and ganglion cells, before the degeneration starts. The delay before the occurrence of degeneration varies, leading to a

stage of “viable but inactive neurons” as described by Howell (1998).

The major primary mtDNA mutations associated with LHON are all missense mutations. They involve genes encoding different subunits of the complexes I and III of the mitochondrial respiratory chain. Defects in the respiratory chain was demonstrated in platelet mitochondria, as well as in muscle or lymphoblast mitochondria. Reduction of complex I activity seems to be marked when associated with the mutation 3460, less severe with mutation 11778 and mild with mutation 14484. However, mtDNA mutations can not fully account for the onset of LHON, as not all individuals harboring a pathogenic LHON mutation express the disease. In addition, although mtDNA is present in all cells, the clinical manifestations of the disease are usually limited to the optic nerve. This may be due to the high concentration of mitochondria in the optic disc, but this hypothesis has not yet been demonstrated.

Epigenetic or toxic factors might play an important part in the onset of LHON in predisposed subjects harboring a mtDNA mutation. Among toxic factors, alcohol or tobacco are often suspected to promote LHON, although their association with LHON is controversial (see in “differential diagnosis”). Additional factors that may contribute to the onset of LHON, such as anaesthesia, traumatism, have been investigated. Susceptibility to the epigenetic/toxic factors depends on the mutation of mtDNA harbored by the patient. Thus, patients with mutations at positions 3460 and 14484 are at higher risk of developing LHON in presence of these factors.

Genetics

More than 18 mtDNA mutations have been observed in LHON. At least four of these mutations correspond to “primary mutations”. Two characteristics are necessary to qualify a mutation as “primary mutation”. This mutation must be the only one observed in a LHON patient and it must be different from a mtDNA polymorphism. Majority of LHON cases are due to one of the three following mtDNA mutations: G11778A (subunit 4 of complex I of the respiratory chain), G3460A (subunit 1 of complex I) or T14484C (subunit 6 of complex I). Other mutations, such as mutation 4160, 4171, 14482, 15257, have not yet been demonstrated to act as “primary mutations”. Some of these potential “primary mutations” have only been described in 2001, explaining why some LHON cases can still not be associated with a primary mutation. Other mutations are known as “secondary mutations”, as they are usually associated with

a primary mutations. It seems that they are unable to modify the evolution and clinical expression of LHON. Some of these "secondary mutations" are mutations 3394, 4160, 4216, 4917, 5244, 13708 or 15812. According to their various combinations, these "secondary mutations" could be associated with different mtDNA haplogroups commonly observed in Caucasians, especially the J or T haplogroups. Primary mutations 11778 and 14484 are more specifically associated with the J haplogroup, whereas mutation 3460 is not related to any specific haplogroup.

No gene located on X chromosome has yet been linked to LHON. In particular, *NDUFA1*, a gene located on X chromosome and coding for a subunit of complex I of the respiratory chain and, was found to be not linked to the LHON disease.

About 15% of LHON carriers are heteroplasmic for the mtDNA mutation (*i.e.* some mtDNA molecules only carry the mutant allele). It has been suggested that this heteroplasmy for mtDNA mutation is at the origin of the mutational threshold, which seems necessary for disease expression. Patients with greater amount of mutated mtDNA may be at greater risk of developing LHON. On the other hand, homoplasmy (*i.e.* every mtDNA molecule harbors the mutant allele) does not necessarily lead to the phenotypic expression of the disease. But, this hetero- or homoplasmy ratio is measured in blood cells and does not correspond to the mtDNA hetero- or homoplasmy value in the optic nerve. Depending on the degree of hetero- or homoplasmy, the risk of developing LHON varies from 50 to 82% in males and 8 to 32% in women. In addition, women with a level of mtDNA heteroplasmy less than 80% are at low risk of transmitting the disease.

Paraclinical testing and diagnosis

When a papillitis or a pseudoedema is observed, the absence of diffusion of the optic disc at the acute stage of the disease can be confirmed using fluorescein angiography. The visual field testing reveals an absolute central scotoma. A red-green dyschromatopsia is observed at color vision testing, as found in most optic nerve diseases. In the acute stage of the disease or in mild cases of LHON, the visual evoked potentials (VEP) can be reduced in size, delayed and desynchronized, but they are absent at the end stage, whereas the ERG are usually normal. However, the photopic ERG can also be altered, even in the absence of any clinically detectable maculopathy.

MRI is only useful to exclude another neurological disease, especially MS, although hypersignals of the white matter can be

observed in both MS and LHON, regardless of the mtDNA mutation involved. In addition, MRI can reveal the reduction in diameter of the optic nerve, a characteristic feature of atrophy. Characterization of one of the primary mtDNA mutations, which are often homoplasmic, is the major diagnostic evidence for LHON. However, diagnosis cannot be ruled out in the absence of this mutation, as all the mutations associated with LHON are unlikely to be identified yet.

Treatment

Although different substances, such as thiamin, coenzyme Q10, vitamin B2, vitamin K, vitamin C have been tested, there is to date no effective treatment for LHON. Mashima *et al* (2000) have reported that Idebenone and vitamin therapy can reduce the time to achieve visual recovery in LHON but do not necessarily promote this visual improvement.

It is thus highly recommended to avoid all risk factors such as alcohol or tobacco, which might play a role in the occurrence of LHON.

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