Leber Hereditary Optic Neuropathy

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Synonyms of Leber Hereditary Optic Neuropathy

- Leber's optic atrophy
- Leber's optic neuropathy
- LHON

General Discussion

Leber hereditary optic neuropathy (LHON) is often characterized by bilateral, painless subacute loss of central vision during young adult life. In most cases, symptoms begin with one eye first, followed a few weeks later by visual failure in the other eye. Extremely rarely there may be neurologic abnormalities, such as peripheral neuropathy, postural tremor, nonspecific myopathy, and movement disorders. LHON is caused by mutations in mitochondrial DNA and it is strictly transmitted by maternal inheritance. The prevalence of visual loss from LHON is approximately 1:50,000 people. Many carriers never suffer significant visual loss; males are about four to five times more likely than females to lose vision and be affected.

Signs & Symptoms

Individuals with LHON typically display symptoms in their young adult years. If vision is lost, then it usually occurs before 40 years of age.

The acute phase of LHON is characterized by a loss of central vision, including blurring and reduced perception of color. Individuals usually lose vision in one eye first and then lose vision in the other eye after two to three months. The atrophic phase is characterized by bilateral optic atrophy, resulting in lifelong blindness.

Depending on the mutation and pedigree, most female carriers do not lose vision but up to half of males do.

Causes

LHON is caused by genetic mutations in the mitochondrial DNA (mtDNA). Some mothers with a LHON gene mutation do not show symptoms, but family history often reveals female relatives with visual loss at an early age.

Mutations in mitochondrial DNA can only be inherited maternally because mitochondria derive from ova, not sperm. All of the offspring of a mother with an mtDNA mutation will inherit the gene. A male with a mitochondrial DNA mutation cannot transmit the mutated gene to any of his children.

The three primary mitochondrial DNA LHON-causing mutations are mt.3460G>A, mt.11778G>A, and mt.14484T>C, which account for over 90% of LHON patients. The most

common LHON-causing mutation is mt.11778G>A. The greatest penetrance (chance of a carrier to lose vision) is for mt.3460G>A and the least is for mt.14484 T>C.

Affected Populations

The prevalence of visual loss from LHON is approximately 1:50,000 people. Many carriers never suffer significant visual loss; males are about four to five times more likely than females to lose vision and be affected.

Related Disorders

Symptoms of the following disorders are similar to LHON. Comparisons may be useful for a differential diagnosis:

Autosomal dominant optic atrophy (DOA) is related to the OPA1 family of genes that has an effect on mitochondrial biogenesis and function. The family pedigree is autosomal dominant. The symptoms tend to come on earlier than in LHON and to do so in a more insidious and milder way. Generally, before puberty the child develops slowly progressive loss of vision and central scotomas a mild optic atrophy that progresses until young adulthood to a moderate loss of vision and optic atrophy. This difference in tempo and symmetry as well as the different genetics allows for the distinction with LHON.

Toxic or nutritional deficiencies that produce bilateral mitochondrial optic neuropathy: There are several problems with metabolism that can lead to mitochondrial dysfunction that produces an acquired optic neuropathy that seems very similar to these two genetic conditions (LHON, DOA).

Diagnosis

LHON is diagnosed based on ophthalmologic findings, which include specialized visual testing. The testing involves dilated fundus examination to identify characteristic changes in the optic disc and vascular changes during the acute phase, visual fields, electrophysiologic studies, and imaging, particularly OCT. Molecular genetic testing for mitochondrial genes associated with LHON can be used to confirm diagnosis. Most affected individuals know if their family members also are affected by LHON.

Standard Therapies

Treatment

Affected individuals should receive supportive management and treatment through the usage of visual aids, occupational rehabilitation, and local social services. Small studies have shown that therapies involving ubiquinone and idebenone may provide possible benefits during the acute and chronic phases of the disorder. Affected individuals should avoid smoking and excessive alcohol consumption, which generate reactive oxygen species (ROS) producing mitochondrial impairments.

Clinical Testing and Work-Up

Consistent monitoring and surveillance of asymptomatic individuals with LHON-causing mutations is not necessary. However, if visual disturbance is experienced, affected individuals should immediately seek medical attention from an ophthalmologist or neuro-ophthalmologist.

Individuals should follow-up frequent to their own circumstances and availability of local healthcare.

Genetic counseling is recommended for patients and their families. However, the key to understanding is that female carriers always transmit the gene and male carriers never do.

Investigational Therapies

Several other modalities of treatment are being tested in clinical trials. These include gene therapy (for mtDNA 11778) and MTP-131 as eye drops or subcutaneous injection.

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov . All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

Some current clinical trials also are posted on the following page on the NORD website:
https://rarediseases.org/for-patients-and-families/information-resources/info-clinical-trials-and-research-studies/

For information about clinical trials sponsored by private sources, contact:
www.centerwatch.com

For more information about clinical trials conducted in Europe, contact:
https://www.clinicaltrialsregister.eu/

Contact for additional information about Leber hereditary optic neuropathy:

Alfredo A. Sadun, MD, PhD
Flora Thornton Chair, Doheny Eye Institute
Vice-Chair Ophthalmology, UCLA
800 Fairmont St. suite 215
Pasadena, CA 91105