NANOS Patient Brochure

Hereditary Optic Neuropathy

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A hereditary optic neuropathy is caused by a genetic variant (or mutation) that causes dysfunction of the neurons (nerve cells) which form the optic nerve. The optic nerve sends information from the back of the eye to the vision center in the brain. The two most common types of hereditary optic neuropathies are dominant optic atrophy (DOA) and Leber hereditary optic neuropathy (LHON). In both of these conditions, the genetic variant affects the mitochondria, where energy is produced inside of the neurons and their axons.

Dominant Optic Atrophy (DOA)

Dominant optic atrophy is the most common of the hereditary optic neuropathies, with prevalence being in the range of 1 in 10,000 to 1 in 50,000 in the overall population. It is inherited in an autosomal dominant fashion. In DOA, premature degeneration of the optic nerve leads to vision loss.

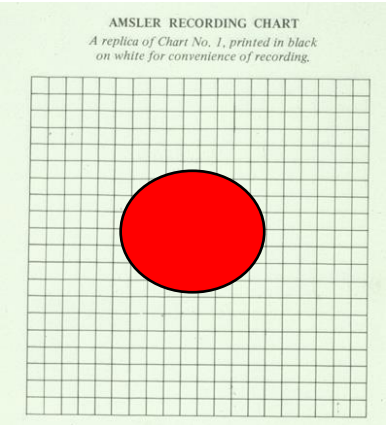
The onset is typically in the 1st decade of life. Children may fail their school vision screening, thus leading to the diagnosis. The course of vision loss is slowly progressive, typically one line on the eye chart per decade of life. Both eyes tend to be affected equally with painless central vision loss, as seen in Figure 1. The optic nerve becomes pale, as seen in Figure 2. Though DOA may cause significant visual impairment, it does not cause complete blindness.

Most patients with dominant optic atrophy have no associated neurologic abnormalities, although nystagmus ("jiggling" of the eyes) and hearing loss have been reported. Occasionally there are associated cardiac or neurologic abnormalities.

The diagnosis of dominant optic atrophy is mainly clinical, based on history and exam findings. The OPA1 gene is responsible for most cases of DOA. However, although genetic testing is available, results can be falsely negative because other mutations may exist for which testing does not yet test. Though hereditary, not all cases of DOA have a prior family history, as spontaneous mutations can occur. Genetic testing for DOA may be expensive and also may not be covered by all insurance carriers.

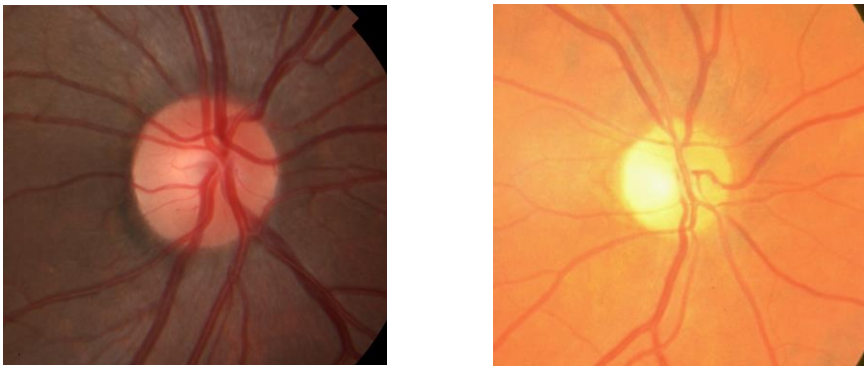
There is no effective treatment to date for DOA. Low-vision evaluation is recommended to determine if visual aids (i.e., magnifiers, large-font devices, talking watches) may be helpful. Genetic counseling is suggested.

Figure 1- Visual field test showing
central loss from hereditary optic neuropathy



Central area missing or blurred

Figure 2- Normal optic nerve (left) and Pale optic nerve (right)



Leber Hereditary Optic Neuropathy (LHON)

Leber hereditary optic neuropathy is inherited in a mitochondrial pattern, which means that the condition can be passed down only from mother to child. The prevalence of LHON in a European study was estimated to be 1 in 30,000 to 1 in 50,000. In LHON, one of the mitochondrial genes that regulates the production of energy in the optic nerves is abnormal. Over time, the waste products of that energy production begin to damage the optic nerves.

LHON typically begins with painless vision loss in one eye, followed by similar vision loss in the other eye weeks to months or years later. The amount of vision loss may be mild, or it may be severe. Central vision tends to be affected more than peripheral vision, as seen in Figure 1.

Although the vision loss is typically permanent, there are some people with LHON who may recover some vision. The chance for visual recovery may depend on the exact mutation.

While most people with LHON are affected in young to mid-adulthood (20-50 years old), it can affect anyone of almost any age. LHON affects males more than females. Patients may have the mutation and be a carrier, but never develop any symptoms or signs visual loss. It is possible that habits and activities that increase the body's energy and waste-removal needs (such as smoking, drinking alcohol, etc.) may trigger the onset or may worsen the vision.

Some people with LHON will also have other problems, which may include heart rhythm problems. If LHON is suspected, an EKG should be done. LHON may also be associated with other neurologic conditions and patients with any type of neurologic symptom should receive a formal and full neurologic evaluation.

The diagnosis of Leber hereditary optic atrophy is originates through clinical

suspicion, based on the history and findings on examination. The eye exam can look completely normal at first, which can make the diagnosis very challenging. In the chronic stage, the optic nerves will look pale, as seen in Figure 2.

Genetic testing is available. The three most common mutations are G11778A, T14484C, and G3460A. However, genetic testing results can be falsely negative because other mutations may exist for which testing does not yet test. Though hereditary, not all cases of LHON have a prior maternal family history, as spontaneous mutations can occur. Genetic testing for LHON may be expensive and also may not be covered by all insurance carriers.

Until very recently, there were very few treatments available for LHON. Researchers had looked at many different treatments, with most notably antioxidants such as ubiquinone and idebenone (a derivative of coenzyme Q). Idebenone has shown some promising initial results. A large study looking at brimonidine, a drop typically used for glaucoma, did not show any significant improvement in outcome.

There are currently several clinical trials looking at forms of gene therapy as a method of treating LHON in its first few months of symptoms. These studies are studying different medications targeting the defective gene by an injection into the eye. There is also a clinical trial doing further study on idebenone.

The search for a cure is far from over; the clinical studies are currently testing for safety (the FDA requires multiple tests of safety and efficacy before approving it for general use in the U.S.). Additionally, not everyone is eligible to participate in these studies. Talk with your neuro-ophthalmologist to see if you may be a candidate for any of these trials.

In the meantime, recommendations for LHON patients include a low vision evaluation or visiting visual rehabilitation services. Low-vision aids (i.e., magnifiers, large-print devices, talking watches) and lifestyle modifications may help maximize vision which is remaining. Genetic counseling is suggested.

Suggestions to avoid agents that might stress mitochondrial energy production (i.e., tobacco and alcohol, particularly if excessive) have no proven benefit but are theoretically reasonable. Patients with cardiac and neurologic abnormalities should be referred to a specialist.

There are also support groups available for people with LHON. A link to one of the major support groups is listed below.

Frequently Asked Questions

1. *Will my vision loss progress to blindness?*

   Both dominant optic atrophy and Leber hereditary optic neuropathy may cause

significant visual loss. Though the vision loss may meet the criteria for legal blindness, that does not mean complete blindness. Patients with hereditary optic neuropathy tend to lose central vision, which can impair reading, face recognition, watching television and driving. However, peripheral vision may be intact, which allows for some useful vision.

2. *Can I pass the genetic defect along to my offspring? What is their risk of visual loss?*

   Dominant optic atrophy may be passed down from an affected parent (either mother or father) to the child with a 50% chance of the offspring receiving the gene, but the disease can be variable in different individuals. All patients with the mutation will have some degree of vision loss, but not to the level of complete blindness.

   Leber hereditary optic neuropathy is passed down through the mother, so fathers cannot pass the disease on to their children. All children of a mother with the LHON genetic defect will be carriers. However, not all will be affected by vision loss. Estimates are that 50% of male children and 85% of female carriers will *never* be affected.

3. *If there is a metabolic problem, should I limit exercise or other activities?*

   There is no data thus far to suggest that physical exercise or visual activities such as reading or computer use will worsen vision.

Other Resources

- https://rarediseases.info.nih.gov/diseases/11972/dominant-optic-atrophy
- Autosomal Dominant Optic Atrophy Association
  Website: http://www.adoaa.org/
- National Library of Medicine (patient-oriented article on LHON):
  https://ghr.nlm.nih.gov/condition/leber-hereditary-optic-neuropathy
- GeneReviews (textbook article on LHON - very technical):
  http://www.ncbi.nlm.nih.gov/books/NBK1174/
- GeneTests (list of centers that perform LHON genetic testing):
  https://www.genetests.org/search/tests.php?locations%5B%5D=USA&user_submitted=1&search=LEBER+HEREDITARY+OPTIC+NEUROPATHY+TEST&filter_status=1
- LHON.org (support group): http://www.lhon.org