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TREATMENTS FOR LEBER'S HEREDITARY OPTIC NEUROPATHY

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CONTENTS

SUMMARY

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disease characterized by devastating visual loss, usually in young adults. The typical presentation involves vision loss in one eye, due to a dense central scotoma, followed weeks later by a similar event in the fellow eye. Characteristic optic nerve changes include telangiectatic capillaries and thickening of the peripapillary retinal nerve fiber layer. Asymptomatic carriers have demonstrated subclinical manifestations of the disease on examination and testing. Mitochondrial point mutations at one of three loci are primarily involved in most cases, although other factors are implicated in disease penetrance. The primary mutations all involve complex I in the mitochondrial respiratory chain. There are no proven treatments for LHON, although many are being investigated. One such promising medication is idebenone, which mimics coenzyme Q_{10} in the oxidative phosphorylation pathway. Investigations into medical and genetic treatments of LHON are ongoing.

INTRODUCTION

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disease characterized by severe vision loss, usually in young adults. Almost universally bilateral, the condition typically subacutely affects one eye initially and then involves the second eye weeks to months later. Although it demonstrates a predilection for young men, LHON may occur later in life and affects women as well. Mitochondrial DNA (mtDNA) mutations identified at nucleotide positions 3460, 11778 and 14484 account for about 95% of cases, but research is ongoing into inciting environmental factors that result in certain individuals being symptomatic while others remain asymptomatic (1, 2). As these investigations continue, novel therapies for the severe visual loss are being suggested. This review will highlight treatments for LHON that have been tested and will also consider therapies that may appear on the horizon.

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CLINICAL PRESENTATION

On fundus examination, the optic nerve in LHON typically demonstrates telangiectatic capillaries and pseudoedema from swelling of the surrounding retinal nerve fiber layer. Over time, there is loss of the papillomacular bundle with corresponding temporal atrophy of the optic nerve. Although these findings are characteristic, in up to 50% of symptomatic patients the optic nerve may appear normal during the acute phase of the disease (3).

Loss of vision is usually severe, with typical visual acuity of 20/400 or worse. Visual field testing may reveal large and dense central or cecocentral scotomas. The absence of true edema of the optic nerve head is evident on fluorescein angiography, given the absence of dye leakage at the disc (3). Optical coherence tomography demonstrates thickening of the retinal nerve fiber layer around the optic nerve and later thinning of the retinal nerve fiber layer, especially temporally (4, 5). This objective and quantifiable assessment corresponds to the clinical examination findings noted above.

The vision loss in LHON is usually permanent, although rarely, some patients recover visual acuity. Improvement in visual acuity is usually associated with the 14484 mutation and rarely seen in individuals harboring the 11778 or 3460 mutation (2, 3). Spontaneous visual recovery with each mutation is more likely to occur if the onset of visual loss occurred before the age of 20 years, and even more so if it began before 10 years of age.

One remarkable aspect of LHON is its tissue specificity. The optic nerve is singularly involved, with preferential loss of the smallest fibers that constitute the papillomacular bundle (2, 6, 7). While in

theory a mitochondrial mutation should affect all tissues in the body, vision loss is commonly the only clinical manifestation, notwithstanding reports of patients with abnormalities of cardiac, skeletal or neurological function. Indeed, an electrocardiogram is sometimes indicated to evaluate the potential problems along the cardiac conduction pathway. A subset of patients has also been identified with both symptoms of LHON and clinical and radiological evidence of multiple sclerosis, although these cases may reflect the coexistence of separate disease entities in common pedigrees with or without one disease predisposing to the other (3).

Typical presentation

While there is variance in age, gender and particulars, LHON presents itself in most patients in a fairly stereotypical fashion. The following would be a classical example:

> An 18-year-old man went off to college without any prior history of problems with vision, neurological or systemic disease. He had been a good athlete in high school and had no problems with physical endurance. A few months into his freshman year in college, he noted painless loss of vision in one eye that occurred over a few days. The initial diagnosis was optic neuritis and workup, including magnetic resonance imaging (MRI) scan, was entirely negative. However, a month later, similar loss of vision occurred in the fellow eye. This led to a referral to neuro-ophthalmology, where visual acuity in both eyes was recorded using the semiquantitative scale "counting fingers" and large, dense central scotomas were revealed in his visual fields. A careful examination of the family history revealed that an uncle on his mother's side had gone blind in both eyes without a diagnosis. This and aspects of the eye examination described above led to a tentative diagnosis of LHON. Blood testing confirmed an 11778 mtDNA mutation. The patient eventually developed optic atrophy in both eyes and his visual acuity never improved.

This describes the conversion of this young man from a carrier state to being affected. His mother remains an asymptomatic carrier with good vision, as do his siblings, who remain at risk. His uncle went blind in his early twenties, reflecting conversion to the affected state as well. Unlike nuclear genetics, in mitochondrial mutations a carrier and an affected patient are genetically indistinguishable. Something, however, tips the carrier into the devastating loss of vision that characterizes the conversion.

Clinical presentation in asymptomatic carriers

Carriers of the LHON mutation have traditionally been regarded as having normal vision (1). However, asymptomatic carriers were recently shown sometimes to exhibit subclinical manifestations of the disease upon physical examination (8-10). Examination and testing of 75 asymptomatic carriers in a large Brazilian family with the 11778 mutation revealed microangiopathy of the optic nerve in 13% of eyes and swelling of the retinal nerve fiber layer in 14% (11). Most of the patients exhibiting these changes in the fundus examination had corresponding central visual field defects revealed by Humphrey visual field tests. Carriers also had deficits in tests of color vision and contrast sensitivity when compared with controls (12, 13). Optical coherence tomography testing showed that some carriers also had thickening of the retinal nerve fiber layer, particularly prominent in the inferotemporal region (4).

GENETICS

Although many mtDNA point mutations have been described as primary mutations causing LHON, three are responsible for 95% of the cases around the world: 3960, 11778 and 14484 (1, 3). The prevalence of each mutation depends somewhat upon the region in which the disease is studied. For example, 11778 is the predominant mutation in patients in Japan and China, whereas 14484 is the most common mutation in French Canadians exhibiting the disease (3). The clinical characteristics seen with each mutation appear to be indistinguishable. The only distinctive feature appears to be visual prognosis, which, as mentioned previously, is best in patients with the 14484 mutation.

Secondary mutations have also been associated with LHON, although their significance in the etiology of the disease is not clear. One thought is that these variants are DNA polymorphisms that may affect the expression –and perhaps disease penetrance– when primary mutations already exist (3).

Other effects on LHON disease expression include heteroplasmy, nuclear mutations and environmental factors. Heteroplasmy occurs when mutant mtDNA and wild-type mtDNA coexist in the same cell. During replication and in the process of development, copies of mtDNA may be distributed unevenly within each cell. One consequence is that mutant mtDNA may be more prevalent in certain tissues, which causes the disease to manifest there and not in tissues containing predominantly wild-type mtDNA (1, 3). Another consequence is that the fetus may have a different mtDNA mixture (heteroplasmy) than the mother. Heteroplasmy rates below 70% are never symptomatic (1). However, 10-15% of LHON patients are 70-99% heteroplasmic for their mutation. Heteroplasmy may be one factor in the variability of disease expression (3).

Complexes in the respiratory chain are encoded by many nuclear as well as mitochondrial genes. Hence, nuclear mutations are relevant in many diseases affecting mitochondria. Nuclear mutations have been investigated in LHON in search of an explanation as to why men are disproportionately affected. One hypothesis is that affected patients also inherit an X-linked recessive mutation. Indeed, a susceptibility locus to LHON was identified on the X chromosome (Xq25–27.2) in a large Brazilian family harboring the 11778 mutation (14).

Environmental factors may also play a role in the expression of LHON. A large number of small affected families have been described and there have been conflicting reports on the effects of smoking and drinking. One case-control study failed to demonstrate these habits as risk factors (15), although analyses on one homogeneous, very large, 332-patient pedigree in Brazil showed a doubling of the risk for LHON with either alcohol or tobacco use (2). A subsequent multicenter survey of a more heterogeneous mix of 402 patients (196 affected and 206 unaffected carriers) with 1 of the 3 primary LHON mutations found a statistically significant difference between the extent of both tobacco and alcohol use in affected and unaffected carriers (16). These authors noted, however, that the difference in alcohol consumption between each group was no longer statistically significant as a risk factor when isolated from the male gender.

Exposure to smoke unrelated to tobacco use may also provoke conversion and blindness in LHON. Several families have collectively gone blind in association with exposure to smoke from tire fires and malfunctioning stoves (17).

Several agents have been implicated in the induction of visual loss in carriers with the LHON mtDNA mutation. In addition to possible tobacco and alcohol effects, there have been reports of LHON conversions in association with the use of antibiotics such as ethambutol (18, 19). It is difficult, of course, to ascertain with certainty whether these patients would have lost vision anyway, as they had LHON, or whether they suffered from nutritional deficiencies or toxic effects. The consensus seems to be that environmental effects such as these can lead to decompensation and hence to the conversion from the status of carrier to affected (1).

BIOCHEMISTRY

Oxidative phosphorylation is the process through which mitochondria synthesize adenosine triphosphate (ATP), thereby supplying energy to cells. This reaction depends upon complexes I–V in the respiratory chain, as well as the cofactors coenzyme Q_{10} (also called ubiquinone) and cytochrome *c*. In the first step of the chain, complex I transfers electrons from nicotinamide adenine dinucleotide (NADH) to coenzyme Q_{10}, forming ubiquinol. This compound transports the electrons to complex III, which sends them to complex IV via cytochrome *c*. An electrochemical gradient created by the proton transfer fuels complex V, part of which is located in the mitochondrial membrane. While complex V phosphorylates adenosine diphosphate (ADP) to ATP, complex II is involved in a pathway parallel to that of complex I. Complex II is the only complex encoded entirely by nuclear DNA (nDNA); all other respiratory chain complexes are composed of subunits encoded by both mtDNA and nDNA (1). This partly explains why all LHON mutations involve complex I subunits. Mutations in complexes III, IV or V might be fatal, but complex II allows for an alternate pathway around complex I.

A byproduct of oxidative phosphorylation may be reactive oxygen species (ROS), which are produced when electrons are released from complex I or III and subsequently react with molecular oxygen. The result is the superoxide anion, which may in turn generate other free radicals. It is thought that excessive ROS production may occur in LHON, causing further damage to respiratory enzymes (1).

TREATMENTS

There are no proven treatments to retard, much less reverse, the progression of optic neuropathy or the associated visual loss in LHON. Although many proposed treatments have been studied and shown to be without merit, a few do show promise.

Topical brimonidine tartrate, an α_2-adrenoceptor agonist, was tested as a prophylactic agent to protect against involvement of the fellow eye in LHON (20). There is evidence that this medication, commonly used to reduce intraocular pressure in patients with glaucoma, prevents loss of retinal ganglion cells in rat models of mechanical and ischemic injury (21). It is thought that brimonidine, by upregulating the apoptosis regulator Bcl-2, can block the mitochondrial permeability transition pore, thus forestalling mitochondrially induced apoptosis (22). It was theorized, therefore, that the compound might protect against the death of retinal ganglion cells in LHON. The study was halted early due to insufficient enrollment (9 patients aged 13-54 years were enrolled between May 2002 and February 2004) and because none of the patients achieved the target of vision loss of fewer than 15 letters (20). This trial was not ideal, however, as eight of the nine unaffected eyes in the study already had optic nerve hyperemia and telangiectatic vessels upon clinical examination. It is likely that these patients were already developing the disease in the second eye at the time of enrollment and that the treatment was initiated too late in the course of the disease.

Although there are no reports of vitamin B_{12} administered in isolation as a treatment for LHON, one case series noted three patients (two with the 14484 mutation and one with the 11778 mutation) who were vitamin B_{12}-deficient upon presentation of visual loss and therefore treated with the supplement (23). Interestingly, the only patient who showed visual improvement was a 28-year-old woman who did not have a history of tobacco or alcohol use. The authors suggest that vitamin B_{12} deficiency may precipitate vision loss in LHON (23).

One area of research in the treatment of LHON has targeted the excessive production of ROS during oxidative phosphorylation. Antioxidants such as glutathione, trolox (a vitamin E derivative) and decylubiquinone (a coenzyme Q_{10} analogue) have demonstrated protective effects in vitro. In one study, LHON cybrids treated with rotenone demonstrated a marked decrease in viability. When incubated with exogenous glutathione, however, these cybrids showed a significant increase in viability (24). Another study cited that a decrease in glutamate transport was correlated with an overproduction of mitochondrial ROS. The authors found that both trolox and decylubiquinone could partially rescue the glutamate transport rate in LHON cybrids (25). Lastly, researchers at Mahidol University in Thailand are currently conducting a clinical trial to investigate the efficacy of curcumin (250 mg twice daily) in LHON patients with the 11778 mutation. Curcumin is a component of turmeric and is thought to have antioxidant properties (26).

Research has also focused on supplying exogenous coenzyme Q_{10}. Ubiquinone is readily available as a nutritional supplement. Case reports of treatment with ubiquinone have been published, one in a 21-year-old patient with a known 11778 mutation who had marked improvement in visual acuity with a dose that was gradually increased to 200 mg/day. The medication was prescribed for a year and then stopped, but the visual recovery continued to persist over a 4-year follow-up period (27). Although spontaneous visual recovery in patients with the 11778 mutation is extremely rare, it has been reported (28). It is possible, therefore, that the natural history of this patient's disease would have resulted in visual recovery even in the absence of ubiquinone. The lack of subsequent success stories has contributed to most neuro-ophthalmologists' skepticism regarding this treatment.

One likely limitation of treatment with exogenous coenzyme Q_{10} is that it has a long membrane-binding phospholipid tail that prevents it from entering the mitochondrion. Idebenone is identical to coenzyme Q_{10}, except that it has a shorter tail. Its delivery characteristics allow it to enter mitochondria in much higher concentrations, but it is less efficient in the role of shuttling electrons from complex I to complex III along the respiratory chain (G. Miller, personal commu-

nication). Furthermore, idebenone crosses the blood–brain barrier more easily than coenzyme Q_{10}. Efforts are under way in the development of a new molecule with a tail length between that of ubiquinone and idebenone.

Successful treatment with idebenone has been described in several case reports and retrospective studies. A 24-year-old Tunisian man with the 14484 mutation had improvement in both visual acuity and in his central scotoma after treatment with idebenone (270 mg/day) and vitamin B_{12} (5000 IU/day) (29). Although spontaneous visual recovery is most common with this mutation, the authors noted that the patient's improvements occurred more rapidly than would be expected without treatment. A recent report of 2 patients (a 30-year-old man and a 19-year-old woman) with the 11778 mutation demonstrated no improvement in visual acuity after treatment with idebenone (270 mg/day), vitamin C and riboflavin (30). Each patient received different doses of vitamin C and riboflavin. A possible confounding factor, however, is that each patient was treated with "megadoses" of methylprednisolone prior to the idebenone treatment regimen. Since no ancillary testing data from before and after treatment were available for these patients, it is not known if treatment had any effect on their visual fields.

One retrospective study evaluated 28 Japanese LHON patients aged 14 to 45 years. The authors divided the subjects into two cohorts: an untreated group and a group treated with a combination of idebenone (180 mg/day), riboflavin (60 mg/day) and ascorbic acid (750 mg/day). The distribution of primary mitochondrial mutations was fairly equivalent between the two cohorts. A statistically significant difference in visual recovery favoring those who were treated was seen only in the patients harboring the 11778 mutation. It is worth noting that the visual recovery was often limited to fenestrations in the central visual field defects. The time to visual recovery, when it occurred, was also significantly shorter in the treated patients. The components of this medication cocktail, however, were not evaluated individually. It is therefore unknown if the statistically significant improvements noted were attributable to the three compounds acting in concert or just to one component (31).

Recently, a case series was reported of seven LHON patients who were treated with idebenone alone (about 450 mg/day), one of whom had the 14484 mutation. Most eyes showed recovery of visual acuity, color vision and visual fields (32). One LHON patient with the 11778 mutation improved from "counting fingers" vision in both eyes to respective visual acuities of 20/20 and 20/30 in the right and left eye.

FUTURE DIRECTIONS

As in other areas of medicine, the exploration of genetic treatments for LHON is an exciting prospect. The nature of this mitochondrial defect, however, increases the challenges faced by researchers in the quest for successful LHON therapies. For example, although various manners of substituting nDNA have been developed, methods of transporting genes or their products into the mitochondria are problematic and are still being explored. In one technique, allotopic rescue, the nuclear genome expresses a protein usually expressed by the mitochondrial genome via a virus vector. A polypeptide is attached to this new protein to enable it to be transported into mitochondria (3). This gene transfer technique has worked via intravitreal injection in a mouse model (33), but further studies will be required before this method can be applied to human patients.

WHAT WE DO

After diagnosing LHON, we manage the patient with at least eight elements:

- We have a frank discussion with the patient regarding the nature of the disease, the involvement of the optic nerve and the poor prognosis for the recovery of vision.
- Genetic counseling is given, whereby it is emphasized that affected men cannot transmit their defect to their offspring and that their children will therefore have the same minimal risk for LHON as the general population. It is also emphasized that affected women and carriers are certain to transmit the mtDNA mutation to their children, who will be carriers at a fairly high risk of becoming affected.
- We advise patients to refrain from smoking tobacco products, including cigarettes, cigars and pipes.
- We recommend that patients minimize their consumption of alcohol.
- We advise patients that caution should be taken with any exposure to smoke, including fires, exhaust fumes and second-hand cigarette smoke.
- We recommend that patients consume a healthy diet, including vitamin B_{12}, folate and high-quality proteins. Some patients choose to take vitamin supplements to ensure adequate intake.
- We have a discussion regarding novel and unproven modalities. Currently, patients are being informed of idebenone as possibly effective.
- Patients are advised that there are a number of optic nerve regeneration scams that they should identify and avoid. There are unsanctioned private groups in China, India and Germany that intrathecally inject stem cells (embryonic in China and India, autologous in Germany) and claim success based on subjective anecdotal testimonies. No scientific measures or controls are used in these procedures and most testimonies originate from cases of optic nerve hypoplasia that often show spontaneous partial recovery. There is no logical reasoning to support the travel of intrathecally placed stem cells to the interior of the eye where the retinal ganglion cell layer is situated.

CONCLUSIONS

LHON is a maternally inherited disease with variable penetrance. Investigation into potential treatments for the devastating visual loss is complicated by two issues. Firstly, there are genetic, environmental and possibly epigenetic factors to consider. Secondly, patients are unlikely to benefit from therapy after optic atrophy occurs. Fortunately, great progress has been made in recent years in understanding the natural history of LHON. As the pathological mechanisms are becoming clear, several new avenues for promising therapies are presenting themselves.

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DISCLOSURES

The authors state no conflicts of interest.

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