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Leber's hereditary optic neuropathy: Update on current diagnosis and treatment

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Leber's hereditary optic neuropathy (LHON) is a fairly prevalent mitochondrial disorder (1:50,000) arising from the dysfunction of the mitochondrial respiratory chain, which eventually leads to apoptosis of retinal ganglion cells. The usual presentation is that of a young male with a sequential reduction in visual acuity. OCT has been used to study the pattern of optic nerve involvement in LHON, showing early thickening of the inferior and superior retinal nerve fibre layer and ganglion cell layer thinning corresponding with the onset of symptoms. Of the three primary mutations for LHON, the m.14484T>C mutation has the best visual prognosis. Recent emerging therapeutic options for LHON include idebenone and the introduction of genetic vector therapy, which is currently in phase III clinical trials. Screening of family members and adequate advice to avoid environmental triggers, such as smoking and alcohol consumption, are also cornerstones in the management of LHON.

KEYWORDS

idebenone, genetic vector therapy, mitochondrial disorder, diagnostics, Leber's hereditary optic neuropathy

Introduction

Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disorder that manifests as subacute, sequential, and painless bilateral vision loss, typically in young males (1, 2). Von Graefe initially recognized the condition in 1858; however, it was later named after Dr. Theodore Leber (3), who reported the condition in several patients across different families and described its unique clinical characteristics (4). LHON was initially thought to be an x-linked disorder, but with later understanding of mitochondrial inheritance, it became clear that mitochondrial mutations are the underlying cause (5).

LHON is one of the most prevalent mitochondrial disorders in specific populations (6, 7). We review the recent developments in the understanding of the pathophysiology of LHON and the latest updates in the diagnostic and therapeutic strategies of LHON.

Epidemiology

The worldwide prevalence of LHON is estimated at 1 in 50,000, with some variability across different countries and continents. In a molecular genetic epidemiological study of LHON in the UK, the prevalence was 1 in 31,000 (6). Another study carried out in Finland suggests the local prevalence to be closer to 1 in 50,000 (8). In Denmark, the prevalence of LHON was reported as 1 in 54,000 (9). 1 in 68,000 was the prevalence of LHON reported in Australia (10). A recent nationwide questionnaire survey carried out in Japan estimates the prevalence LHON to be 1:50,000 (11).

LHON has been widely regarded as a disease of young males peaking at the age of 14-26 years, with a male-to-female ratio of 5:1. However, recent studies have shown that the ratio is closer to 3:1, and approximates 1:1 after the 3rd decade of life (12). Moreover, although the disease is more prevalent in young adults, it can manifest at any age, and 10% of disease onset occurs after the age of 50 (12).

Genetics

Mitochondrial DNA (mtDNA) is a double-stranded circular molecule with a genome containing 37 genes (13). Oxidative phosphorylation is a process mediated by the enzyme complexes (I–V) on the inner mitochondrial membrane. Subunits of complex II are encoded entirely by nuclear DNA, while complexes I, III, IV, and V are encoded by a combination of nuclear and mtDNA. Complex I, the site of all the primary LHON mutations, is a multimer of 7 mitochondrial-encoded subunits and a minimum of 36 nuclear-encoded subunits (14).

Mitochondrial mutations in LHON were first discovered by Wallace et al. in 1988 (5), and are therefore inherited strictly through a maternal lineage. The three primary point mutations in the mitochondrial genome (m.11778G>A, m.14484T>C, m.3460G>A) constitute 95% of all LHON mutations (15). The m.11778G>A mutation, which involves the MT-ND4 gene, accounts for approximately 70% of LHON cases and has the worst prognosis for visual recovery (15). The m.14484T>C, which affects the MT-ND6 gene, is responsible for 14% of LHON cases and has the best prognosis for visual recovery (16–18). Finally, the least prevalent primary LHON mtDNA mutation is the m.3460G>A (13% of cases), which involves the MT-ND1 gene. The rate of partial visual recovery (0.3 LogMAR change in visual acuity) in m.11778G>A, m.14484T>C, and m.3460G>A, is 4-25%, 37-58%, and 20%, respectively (6, 19–21).

In the majority of LHON pedigrees, the primary mutation responsible for LHON is homoplasmic (mutation is present on all inherited mtDNA) (19); however, heteroplasmy (mutation is present in a fraction of the mitochondria DNA) is found in about 10-15% of LHON cases (22). The mutation load appears to be correlated with penetrance and the phenotypic expression of the disease and with the risk of disease manifestation significantly reduced if the mutational load is less than 60% (23). However, LHON with heteroplasmic inheritance does not necessarily manifest as a milder form of the disease (24).

The incomplete penetrance of LHON is not well understood, but some factors affect the expression of LHON mutations. The association of LHON with certain haplogroups (haplogroup J) might have a role in modifying the risk of phenotypic expression of the disease. Mitochondrial haplogroups can be defined as a group of similar haplotypes (a group of alleles inherited in combination from a single parent) with single nuclear polymorphisms inherited from a common ancestor. Sequential accumulation of mutations through maternal lineages is responsible for the development of these haplogroups (25).

Haplogroup J, which is associated with the mutations m.4216T>C, m.13708G>A, m.15257G>A, and m.15812G>A, has been classically thought to enhance the penetrance of m.11778G>A and to a lesser extent m.14484T>C (26). However, this has been challenged by the finding that the presence of haplogroup J with other primary mutations does not seem to further impair mitochondrial oxidative metabolism, nor influence the age of onset or the final visual outcome of LHON (26). Finally, less common secondary mutations (m.11696G>A, m.14502T>C, m.3497C>T, m.3394T>C, m.12811T>C, m.11696 G>A, and m.3316G>A) have been associated with LHON, and they are postulated to act in synergy with the three primary mutations responsible for the disease (27, 28).

Gender has been recognized as an important modifier for the risk of penetrance of LHON. Approximately 10% of females and 50% of males with an underlying LHON mutation will experience vision loss (15). The gender predilection has been linked to the protective effects of estrogen *via* the activation of mitochondrial biogenesis and increasing the mitochondrial load, decreasing the production of reactive oxygen species, and reducing apoptosis in retinal ganglion cells (RGC) (29). In addition, x-linked modifier genes, such as PRICKLE3, encode for mitochondrial proteins linked to the biogenesis of ATPase. In experimental animal modes, PRICKLE3-deficient mutants had a greater rate of conversion to LHON (30).

Environmental risk factors associated with an increase in LHON penetrance include smoking, heavy alcohol consumption, chemical toxins, as well as antiretroviral and antituberculosis medication (31, 32). Cigarette smoking, in particular, is the most established risk factor, and it has been shown to reduce the mtDNA load in the blood cells of LHON patients as well as reduce the mtDNA load and ATP levels in fibroblast models of LHON patients (33). Smoking also has a deleterious effect on the bioenergetic compensation of LHON carriers, and in animal models, cigarette smoking did not reduce ATP levels in non-mutant control fibroblasts (33).

Pathophysiology

Polypeptide complexes I-V are situated in the inner mitochondrial membrane and are responsible for ATP production through the process of oxidative phosphorylation. In the respiratory chain, electron donors such as NADH and $FADH_2$ contribute electrons to complexes I and II, respectively. Shuttling of electrons through the rest of the chain is aided by co-enzyme Q_{10} and cytochrome *c*. The energy produced by electron shuttling allows protons to be pumped from the mitochondrial matrix to the intermembrane space. The final step in the oxidative chain involves the utilisation of the electrochemical proton gradient by complex V (ATPase) to catalyse the conversion of adenosine diphosphate (ADP) into adenosine triphosphate (ATP) (34).

Dysfunction of the respiratory chain caused by LHON mutations of complex I subunits leads to defects in energy production and downstream accumulation of reactive oxygen species (ROS) that ultimately leads to RGC apoptosis (Figure 1).

Under normal intracellular conditions, the presence of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), counteract the build-up of ROS. In LHON, net build-up of free electrons from poor electron shuttling and the resultant generation of large amounts of ROS leads to RGC death, even without a significant reduction in ATP production (35). Additionally, reduced SOD activity was found in animal models exhibiting optic neuropathy with a pattern similar to that of LHON, which emphasizes the importance of ROS in the pathophysiology of the LHON (36). The build-up of ROS causes damage to various intracellular membranes and the

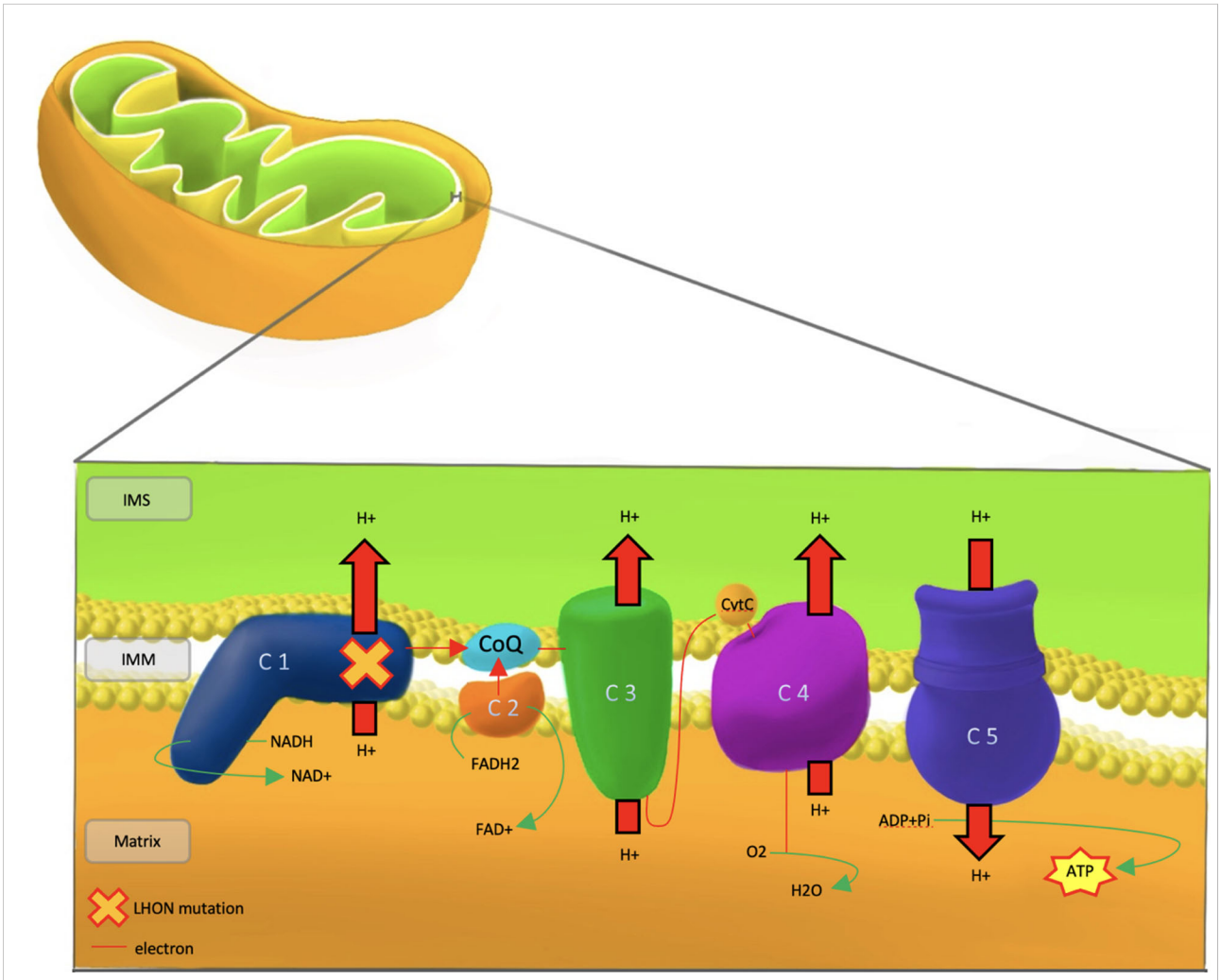

FIGURE 1
Pathophysiology of LHON, showing the mutational defect in Complex 1 of the respiratory chain. IMS, Inter Membrane Space; IMM, Inner Mitochondrial Membrane; LHON, Lebers Hereditary Optic Neuropathy; C 1-5, Complex 1-5; CoQ, co-enzyme Q10; CytC, cytochrome c; NADH/NAD+, Nicotinamide adenine dinucleotide; FADH2/FAD+, flavin adenine dinucleotide; ADP, Adenosine Diphosphate; ATP, Adenosine Triphosphate; Pi, Phosphate; H+, Hydrogen; O2, Oxygen; H20, water.

release of calcium from intracellular stores. The rise of intracellular calcium contributes to mitochondrial permeability transition pore opening and the release of intrinsic apoptotic triggers such as cytochrome c (37). Furthermore, low energy production arising from dysfunctional oxidative phosphorylation leads to a net influx of axonal calcium due to the altered function of membrane channels, namely the Na +-Ca2+ exchanger (38).

The predilection of LHON to involve the papillomacular bundle fibers of the optic nerve axons suggests that the diameter of the axons and myelination play a role in the pathophysiology. The unmyelinated axons of RGCs exist in the pre-laminar segment and are myelinated in the post-laminar segment (39). The lack of myelin in the pre-laminar segment renders them less efficient in propagating action potential and, therefore, especially vulnerable to damage in LHON due to the higher energy needs (31).

RGCs are classified into midget, parasol, and small bistratified ganglion cells. Midget RGCs carry the smallest calibre axons and are the primary type of RGCs affected in LHON. In addition, midget cells are the most prominent subtype in the papillomacular bundle mediating visual information and red-green chromaticity (40). In the early pre-symptomatic phase of the disease, temporal macular RGCs and peripapillary nerve fibres are initially damaged.

Natural history, examination, and diagnostic evaluation

LHON classically presents with bilateral sequential vision loss, with the interval between the two eyes varying from weeks up to years apart. Visual acuity is often severely affected due to the early involvement of the papillomacular bundle, which results in a dense central or centro-cecal scotoma that enlarges over time (41, 42). The pupillary light reflex is often brisk and preserved, with the absence of a relative afferent pupillary defect, even with early unilateral involvement. This has been attributed to the preservation of melanopsin-containing RGCs early in the clinical course of LHON (43). Melanopsin RGCs constitute one percent of all the RGCs and are sensitive to sustained and strong blue light, contributing to autonomic functions like the circadian rhythm and pupillary constriction (44).

The natural course of LHON generally follows a pre-symptomatic phase, an acute phase, and a chronic phase. The duration of each phase can vary from patient to patient, but a general timeline is 12-24 weeks for the acute phase and a transition to the chronic phase after the initial 6 months (45). The acute phase is characterised by the deterioration of central vision and is usually when patients first present.

The clinical findings in a patient with LHON in the pre-symptomatic phase include peri-papillary telangiectatic vessels (peripapillary microangiography) and mild zones of disc pseudo-oedema (retinal nerve fibre layer swelling around the optic disc without leakage of fluorescein angiography) (Sadun et al., 2004). Spectral-domain OCT at this stage will demonstrate dynamic inferior-temporal retinal nerve fibre layer (RNFL) thickening and no significant changes in the ganglion cell layer (GCL) (46). Swelling of the RNFL may reflect a compensatory aggregation of mitochondria in the nerve fibres. This may be attributed to enhanced mitochondrial biogenesis, which is activated as a compensatory strategy to mitochondrial dysfunction in LHON (47).

In the acute phase, patients present with symptoms of a central or ceco-central scotoma, and visual acuity can deteriorate significantly with dyschromatopsia and reduced contrast sensitivity (48). Specifically, protan and tritan colour sensitivity are affected early on in LHON (49). Fundus examination may show vascular tortuosity, pseudo-edema, optic disc hyperemia, or peripapillary telangiectasis (50). However, it is not uncommon for the fundus examination to be normal (20-40% of patients), which can delay the diagnosis (Yu-Wai-Man et al., (51)) (Figure 2). Spectral-domain OCT at this stage will show thickening of the inferior and superior RNFL, which is synchronous with thinning of the inferior-temporal RNFL. At the onset of visual deterioration, the GCL and the inner plexiform layer undergo significant reduction in thickness, which later correlates with further deterioration in vision (46, 52). As the acute phase progresses, RNFL swelling normalises (45) (Figures 3, 4, 5). Furthermore, early abnormalities after the onset of symptoms can be detected using visual evoked potentials (VEPs), including an absent response, decreased amplitudes, and delayed latency (40). ERG can show reduced cone-responses and N50-90 amplitudes (53). Furthermore, MRI findings have been reported in the early stages of LHON and include optic nerve enhancement in post-contrast MRI images (54).

The chronic phase is characterised by optic atrophy, which can develop as soon as six weeks from initial clinical presentation (55, 56). Patients at this stage reach a plateau of visual deterioration, and their chance for visual recovery is diminished. OCT will show GCL thinning, which is well established in the chronic phase, and RNFL thinning is also evident (Figure 5) (45). The progression in OCT findings from the pre-symptomatic phase to early and late acute, and eventually the chronic phase, is essential in following up patient progression in LHON.

Patients with LHON may manifest extraocular features (LHON plus syndromes), including cardiac arrhythmias, such as Wolff-Parkinson-White syndrome. Therefore an EKG is recommended in the comprehensive clinical evaluation of LHON patients (57) (58). Neurological features may include peripheral neuropathy, postural tremors, clonus, dystonia, non-specific myopathy, and movement disorders. Therefore, a complete neurological exam and a brain MRI may be warranted in some cases of LHON (59, 60). In addition,

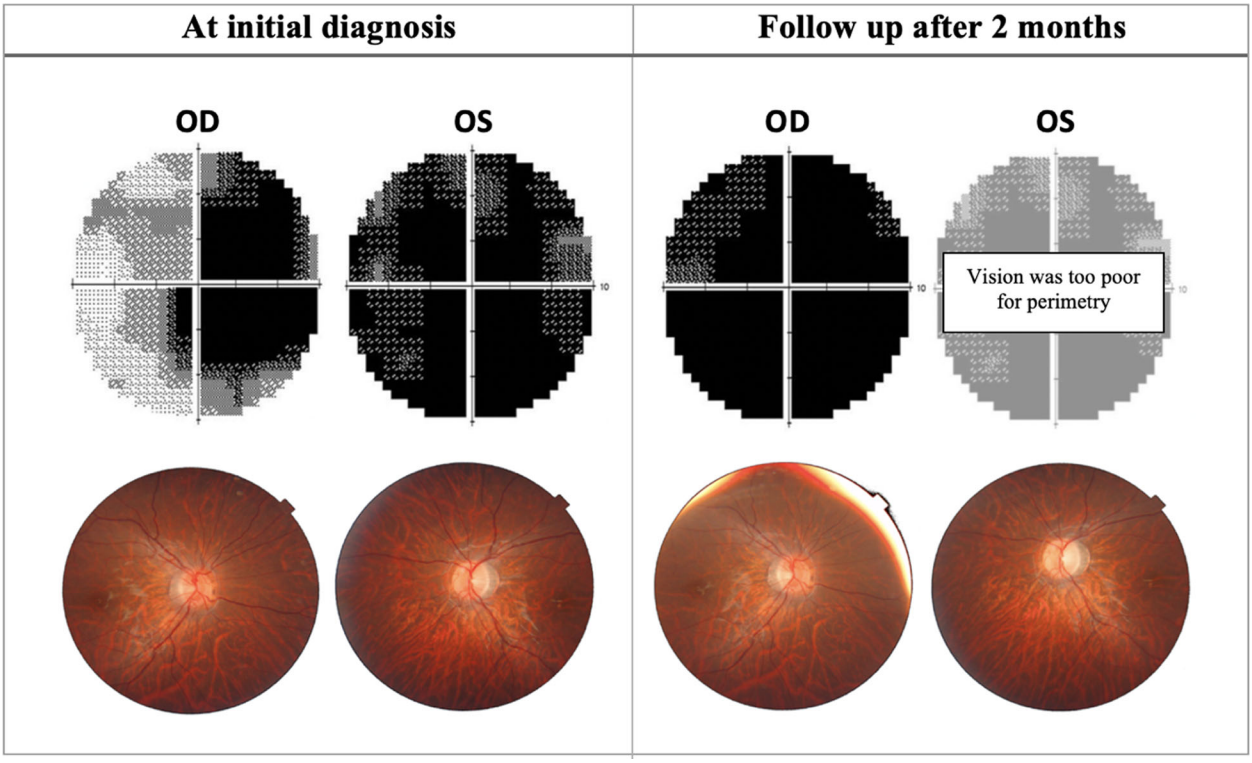

FIGURE 2
Progression of perimetric and fundoscopic findings in patient A, an 18-year-old LHON patient. The patient presented with poor visual acuity at initial diagnosis: 20/400 OD & CF OS. Right eye later progressed to CF after 2 months. *OD, Oculus dexter; OS, Oculus sinister; CF, Counting fingers*.

neuro-psychiatric disturbances, spastic dystonia, ataxia, and juvenile-onset encephalopathy have been reported in some cases of LHON (61, 62). Furthermore, the LHON-Multiple sclerosis phenotype (Harding syndrome) is a LHON-plus syndrome that can be difficult to distinguish from multiple sclerosis. This syndrome can present with an optic neuritis-like picture (ocular pain with bilateral vision loss), disseminated central nervous system demyelination, periventricular white matter lesions, and positive oligoclonal bands in the cerebrospinal fluid (63).

Leigh syndrome is a rare neurodegenerative mitochondrial disorder most commonly affecting children aged three to twelve months, but it can infrequently be observed in adulthood (64). It is characterized by psychomotor regression, peripheral neuropathy, cerebellar ataxia, spasticity, and hypotonia (65). Ocular manifestations include nystagmus, ophthalmoparesis, and optic atrophy (66). Leigh syndrome has been reported in association with LHON-phenotype through MT-ND6 mutations, which include G14459A and T14484C point mutations (67).

The diagnosis of LHON is based on clinical presentation with the exclusion of alternative etiologies (optic neuritis, compressive, or toxic optic neuropathy), the results of ancillary tests (visual field, OCT, VEP, ERG), and confirmation by molecular genetic testing. Genetic testing can be initially targeted at the three common pathogenic types of LHON, followed by a multi-gene panel for mitochondrial diseases, including NADH dehydrogenase. Finally, if both yield negative results, complete mtDNA sequencing is performed (51, 68). In a patient with a positive family history of LHON with typical symptoms, genetic testing may not be required for diagnosis, but confirmation of the underlying mutation may be prognostically valuable (51). In addition, *de novo* mutations can possibly arise in coherence with an established pedigree.

Management and therapeutic approach

As with the majority of mitochondrial disorders, the therapeutic options for LHON remain only supportive. It is essential to counsel patients about the deleterious effects of smoking, the consumption of large amounts of alcohol, and certain medications and toxins that can adversely affect mitochondrial function. Furthermore, low vision rehabilitation

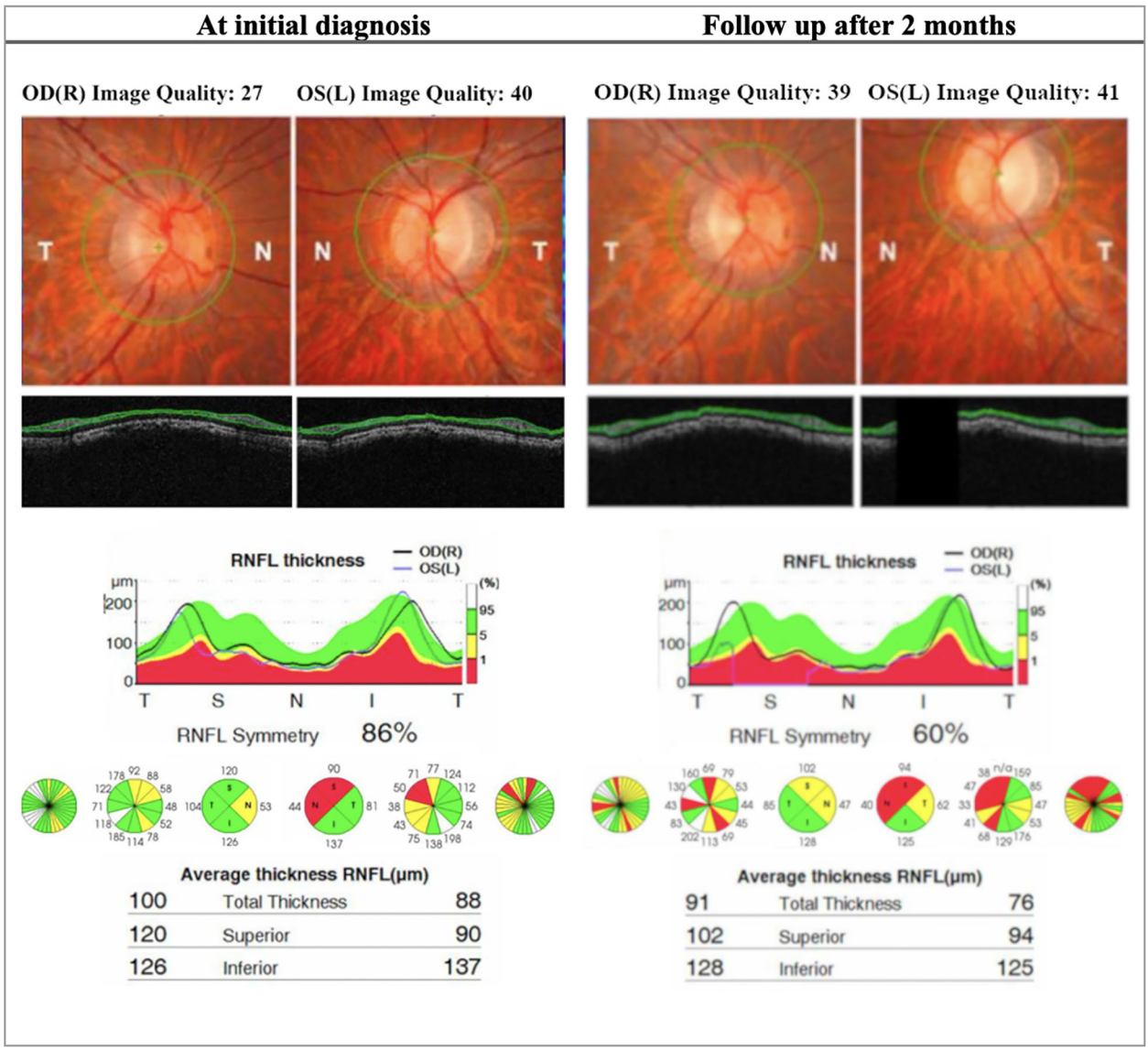

FIGURE 3
OCT (Topcon 3DOCT-3000) findings in patient A, an 18-year-old LHON patient. The patient presented with poor visual acuity at initial diagnosis: 20/400 OD & CF OS. The right eye later progressed to CF after 2 months. This patient was homoplasmic for the mutation m.10663T>C p.ND4L: (Val65Ala). At initial diagnosis the patient presents with thinning of the RNFL in the left eye in the superior and nasal quadrant. At follow up there is significant reduction of RNFL thickness bilaterally, more seen in the superior and nasal quadrant and is more evident in the left eye. *OD, Oculus dexter; OS, Oculus sinister; CF, Counting fingers; RNFL, Retinal nerve fiber layer.*

and aids can be an option in patients with intact peripheral vision (69). Younger patients with the onset of disease at the age of less than 20 years have been reported to have a better visual prognosis (70). In addition, a subacute course of vision loss, as well as a larger optic disc, are both favourable prognostic indicators for visual recovery (71, 72).

Ubiquinone analogues such as co-enzyme Q10 function as carriers of electrons from complex I to complex II of the respiratory chain. However, evidence for the clinical benefits of co-enzyme Q10 in LHON patients is lacking. In addition, the lipophilic nature of the compound makes it poorly absorbable across the intestinal tract (73, 74). On the other hand, idebenone is a short-chained water-soluble ubiquinone that is easily absorbed through the oral route. It provides protection by bypassing complex I, maintaining ATP production, and protecting against mitochondrial oxidative damage (75). Idebenone has been found to be beneficial in promoting vision recovery in LHON patients, particularly in the early stages of the disease and in younger patients (49, 76–78). Currently, idebenone is approved by the European Medicines Agency for

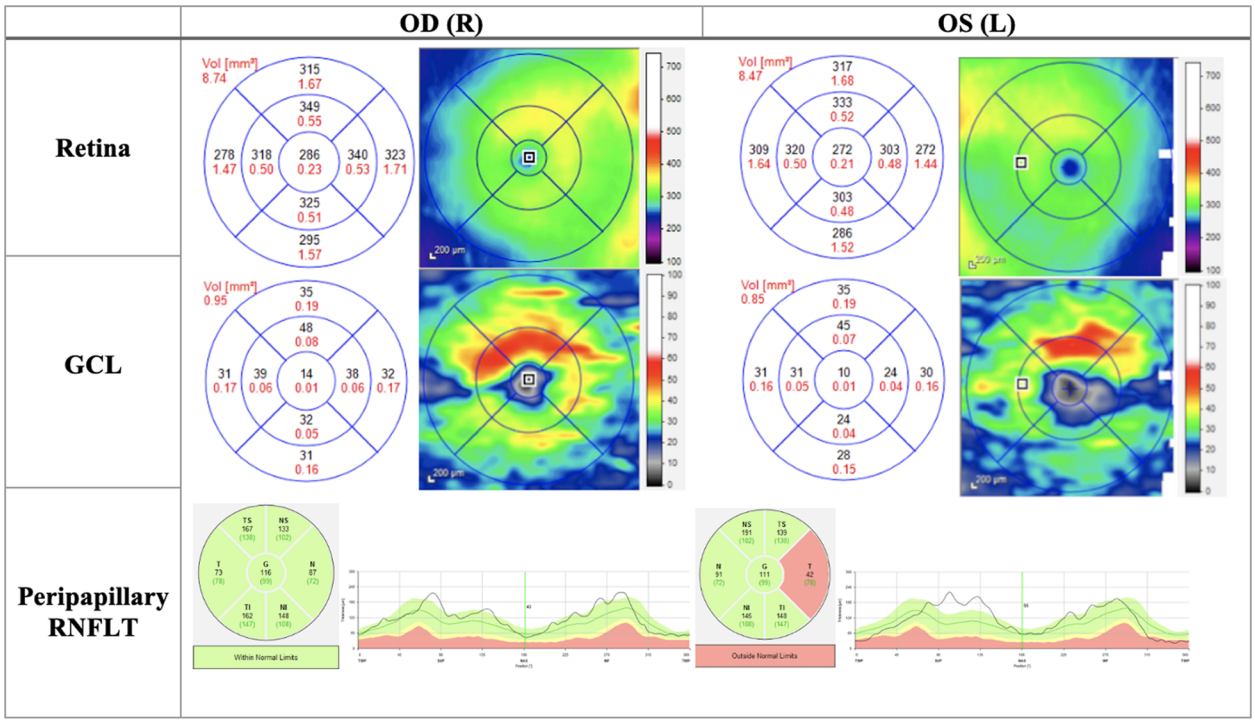

FIGURE 4
OCT (Heidelberg, Spectralis) findings of patient B, a 20-year-old male patient presenting to the clinic with bilateral vision loss and bilateral central scotomas of 3-month duration. The thickness map shows thinning of GCL despite normal RNFLT in OD, and thinning of the temporal RNFT with corresponding GCL thinning in OS. *OD, Oculus dexter; OS, Oculus sinister; GCL, Ganglion cell layer; RNFLT, Retinal nerve fiber layer thickness.*

the treatment of LHON in adolescent and adult patients at a dose of 900mg/day divided into three doses. Treatment should be continued for at least a year or until a plateau of vision improvement is reached (79) (Table 1). The "Post-Authorisation Safety Study with Raxone® in LHON Patients" was completed in 2021 (NCT02771379). Another ubiquinone analogue with *in vitro* activity superior to idebenone, EPI-743, is in the experimental phase and has shown potential benefits in LHON visual recovery (80).

Various vitamins and supplements, such as vitamin B_{12}, vitamin C, vitamin E, thiamine, riboflavin, L-carnitine, L-arginine, and creatine, have been used in LHON patients.

The presence of vitamin B_{12} deficiency was statistically significant for LHON mutation carriers in the general population, and excess alcohol consumption was a significant predictor of such deficiency (81). However, despite the safety profile of these various vitamins and supplements, there were no proven clinical benefits for promoting visual recovery in LHON patients (82).

Brimonidine, a topical α2-agonist used to manage glaucoma patients, has shown protective anti-apoptotic value in RGCs in animal models (83). Unfortunately, when used in LHON patients, brimonidine did not appear to be efficacious (84). Nonetheless, its use in LHON patients with concurrent glaucoma may be justified.

Gene therapy is the latest therapeutic strategy for LHON that has shown some promising results. Currently, gene therapy in LHON aims to deliver the un-mutated MT-ND4 gene into RGC nuclei with the goal of producing functioning proteins/complex I subunits that can be embedded into the mitochondrial respiratory chain. Recombinant adeno-associated viral vector rAAV2, which encodes human wild-type MT-ND4, has been used in multiple trials and proved to be a valuable contribution to LHON treatment.

The use of the viral vector rAAV2-ND4 was first introduced in a trial by Wan et al. in 2010. Nine patients were enrolled in a phase 1 trial (NCT01267422). Eight of those enrolled received an intravitreal injection of the vector in one eye, while one patient received the vector in both eyes. Six of the nine patients exhibited an improvement in BCVA of at least 0.3 logMAR after a period of nine months (85). In 2017, a group of 149 patients was recruited by the same Wuhan research group for an interventional trial where they received a single unilateral intravitreal injection of rAAV2-ND4 (NCT03153293). Within three days, 54 patients exhibited significant improvement in VA of more than 0.3 logMAR in at least one eye (86). Furthermore, a single unilateral injection was found to result in bilateral visual acuity improvement (0.21 logMAR treated eye; 0.24 logMAR untreated eye)12 months post-therapy (87).

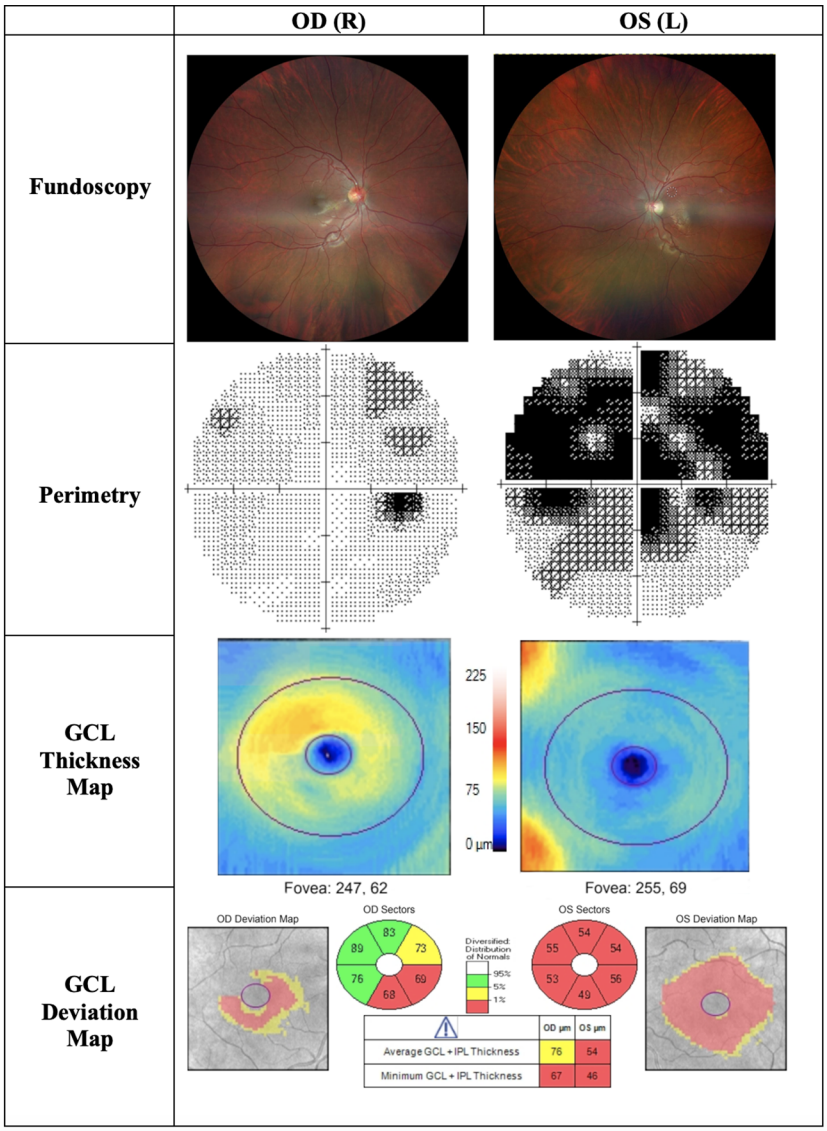

FIGURE 5
Findings of patient C, a 22-year-old male patient presenting to the clinic with progressive central visual loss OS for the duration of 5 months. His visual acuity was 2/200 OS and 20/400 OD. Fundoscopy showed a pale disc OS and peripapillary telangiectasias OD. The thickness map shows marked GCL thinning OS and early thinning of GCL OD, corresponding with deterioration of visual acuity. *OD, Oculus dexter; OS, Oculus sinister; OU, Oculus uterque; GCL, Ganglion cell layer.*

GS010, which is a recombinant adeno-associated viral vector serotype 2 (rAAV2) that encodes human wild-type MT-ND4, has shown improved visual acuity when injected into the vitreous cavity of a single eye during clinical trials carried out by GenSight Biologics (88). In 2017, in two phase III clinical trials *rescue* (NCT02652767) (LHON patients with vision loss <6 months) and *reverse* (NCT02652780) (LHON patients with vision loss >6 months to 1 year), GS010 was randomly injected into one eye, while the other eye received a sham injection. In these trials, patients experienced significant improvement in visual acuity in the treated eyes as well as the sham eyes, raising the possibility of possible vector transfer from the GS010 eye to the sham eye (39). 71% of *rescue* and 76% of *reverse* patients had at least 0.3 gain of logMAR VA in at least one eye. In addition, a clinically relevant recovery at week 96 post-treatment was seen in 71% of *rescue* and 81% of *reverse* patients (89). In the ongoing phase III *reflect* trial (NCT03293524), GS010 was injected bilaterally in subjects with LHON exhibiting the m.11778G>A mutation when vision loss was present for less than one year and showed greater efficacy in visual recovery of +5 ETDRS when compared to GS010 injected in a single eye (90) (Table 2).

TABLE 1 Idebenone in the treatment of LHON.

Study design	End-points	Summary Points
RHODOS Trial NCT00747487 (78) *24-week double-blinded RCT.* *Idebenone 900mg/day, n=55.* *Placebo, n=30.*	-Primary: Best recovery of visual acuity between baseline and Week 24. -Secondary: Change from baseline to Week 24 in best visual acuity. Change in visual acuity of the best eye at baseline. Change in visual acuity for both eyes in each patient. Acuity assessed with: ETDRS charts.	Main Findings: -Statistical significance not reached in the primary end point. -Beneficial effect of idebenone over placebo present when assessing all secondary end-points. Supplementary Findings: -Largest treatment effects in m.11778G>A and m.3460G>A mutations.
Idebenone Treatment In Leber's Hereditary Optic Neuropathy (76) *Retrospective evaluation of idebenone therapy.* *Idebenone cohort, n=44* *Untreated control cohort, n=59*	-Primary: Recovery of visual acuity defined as a gain of at least two lines on Snellen acuity or a change from 'off chart' to 'on chart'.	Main Findings: -Increased frequency of recovery was significant with the use of idebenone in m.11778G>A patients. -Early start of therapy was the most predictive factor for visual recovery. Supplementary Findings: -Trend for earlier onset of visual recovery in treated patients compared with untreated.
RHODOS–OFU NCT01421381 (77) *Single visit observational follow-up study 30 months following the end of the RHODOS trial.* *Idebenone 900mg/day, n=39.* *Placebo, n=19.*	-Primary: Change in best visual acuity assessed at this study visit compared with baseline and Week 24 of RHODOS.	Main Findings: -Beneficial effects from 24 weeks of treatment with idebenone during RHODOS persisted despite discontinuation of therapy for a median time of 30 months.

TABLE 2 GS010 in the treatment of LHON.

Study design	End-points	Summary Points
RESCUE Trial NCT02652767 (89) ***Double-blinded RCT.*** ***LHON patients (m.11778G>A) with vision loss of 6 months or less.*** ***Each participant had one eye randomly selected to receive GS010 and the other eye received a sham injection.*** ***Intravitreal injection of a single dose of GS010 in one eye.*** ***n=39.*** ***Sham injection in the other eye.*** ***n=39.***	-Primary: Difference in change from baseline in ETDRS Visual Acuity at Week 48 between GS010 and sham. -Secondary: Difference in change from baseline in ETDRS visual acuity at Week 72 & 96 between GS010 and sham. Number of eye responders (15 letter ETDRS improvement vs baseline) to treatment. Number of Subject Responders (15 letter ETDRS improvement compared to sham in same patient) to treatment.	Main Findings: - 71% of subjects had an improvement of at least -0.3 logMAR (15 ETDRS letters equivalent) from the nadir in at least one eye. -Improvement from nadir is significant ($P < 0.0001$) and occurred at similar magnitude in both eyes. -Bilateral improvement in vision occurred after a nadir of deterioration at week 24. -Primary end point of -0.3 logMar (15-letter) was not met due to bilateral improvement.
REVERSE Trial NCT02652780 (91) ***Double-blinded RCT.*** ***LHON patients (m.11778G>A) with vision loss of more than 6 months and up to 1 year.*** ***Each participant had one eye randomly selected to receive GS010 and the other eye received a sham injection.*** ***Intravitreal injection of a single dose of GS010 in one eye.*** ***n=37.*** ***Sham injection in the other eye.*** ***n=37.***	-Primary: Difference in change from baseline in ETDRS Visual Acuity at Week 48 between GS010 and sham. -Secondary: Difference in change from baseline in ETDRS visual acuity at Week 72 & 96 between GS010 and sham. Number of eye responders (15 letter ETDRS improvement vs baseline) to treatment. Number of Subject Responders (15 letter ETDRS improvement compared to sham in same patient) to treatment.	Main Findings: - 76% of subjects had an improvement of at least -0.3 logMAR (15 ETDRS letters equivalent) from the nadir in at least one eye. -Bilateral improvement in vision occurred after a nadir of deterioration at week 12. -Primary end point of -0.3 logMar (15-letter) was not met due to bilateral improvement.

(Continued)

TABLE 2 Continued

Study design	End-points	Summary Points
REFLECT Trial **NCT03293524** (90) ***ONGOING TRIAL*** ***Double-blinded RCT.*** ***LHON patients (m.11778G>A) with vision loss of up to 1 year.*** ***Each participant received GS010 in their first-affected eye, and either gene therapy or placebo in their second-affected eye.*** ***Intravitreal GS010 in both eyes.*** ***n=48.*** ***GS010 in one eye and placebo intravitreal injection in the other eye.*** ***n=50.***	-Primary: BCVA in 2nd affected eye reported with LogMar from baseline at 1.5 years. -Secondary: BCVA in 2nd affected eye reported with LogMar from baseline at 2 years.	Main Findings: -Average final visual acuity was reported in subjects treated bilaterally, compared to subjects treated unilaterally was +5 ETDRS letters. Supplementary Findings: -BCVA improvement between second-affected eyes was equivalent to +3 ETDRS letters in favor of GS010 at 1.5 years. -2nd affected eyes treated with GS010 showed +19 ETDRS letters improvement over nadir ($p<0.0001$) at 1.5 years. -2nd affected eyes receiving placebo showed +16 ETDRS letters improvement over nadir ($p<0.0001$) at 1.5 years.

An expert panel consensus on the therapeutic management of LHON recommended the use of idebenone at a dose of 900mg/day for at least one year as the first-line treatment for patients with less than one year since the onset of the disease. However, there was no evidence to recommend treatment for chronic cases (more than one year since the onset of symptoms in the second eye) (Figure 6). Gene therapy was not included in the panel's recommendation (39).

Screening and genetic counselling

If a primary LHON mutation is detected in a proband, screening of other family members can be offered to exclude the possibility of a *de novo* mutation (92). Given that LHON is maternally inherited, all males should be reassured that none of their offspring will inherit the mutation. On the other hand, homoplasmic females will transmit the mutation to all their

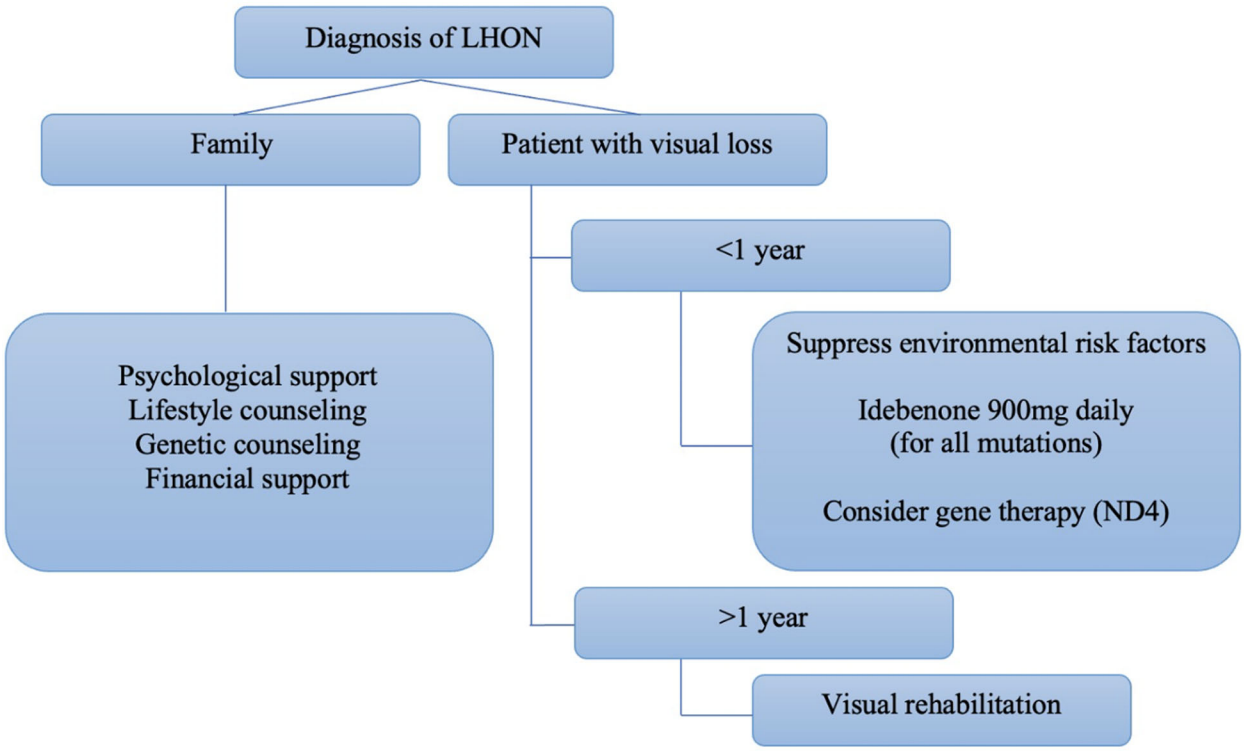

FIGURE 6
Algorithm proposed by Hage and Vignal-Clermont considering the statements of the Milan panel and gene therapy as part of a treatment guide for LHON (Hage & Vignal-Clermont, (39)).

offspring. In heteroplasmic mothers, varying levels of mutant mtDNA is transferred to offspring, with approximately 60% mutant mtDNA required as a threshold for disease manifestation (23). This, however, should be cautiously discussed with patients as the presence of a clear threshold is variable.

Children of homoplasmic mothers need to be aware that the penetrance of LHON is variable, and not all carriers develop the disease. Risk stratification for penetrance in carriers can be assessed by considering their age, gender, and other prognostic factors (10). Age and gender appear to be the most critical factors in evaluating the risk of penetrance: however, patients must be aware that these predictions are still estimates. Carriers should also avoid smoking and heavy alcohol consumption, as well as possible triggers for the disease.

Conclusion

LHON is a mitochondrial optic neuropathy that affects young males but is also not uncommon in females. Recently, advancements have been made in understanding the pathophysiology of LHON and developing new therapeutic strategies, such as gene therapy through the use of viral vectors in clinical trials. However, further studies are required to incorporate gene therapy as a universally approved treatment for LHON.

Author contributions

AE contributed to the literature search and writing of the manuscript and abstract. AA contributed to writing of the manuscript and illustrations. RB contributed by supervising the review, providing appropriate modifications to the manuscript, and providing expert opinion. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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