LEBER HEREDITARY OPTIC NEUROPATHY. CLINICAL CHARACTERISTICS, DIAGNOSIS AND MANAGEMENT

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Abstract

Leber hereditary optic neuropathy (LHON) is a rare, maternally inherited mitochondrial disorder, which affects the retinal ganglion cells. LHON usually presents in young males with progressive visual decline due to optic neuropathy. Visual acuity decrease progresses to legal blindness in a large number of patients. The diagnosis of LHON is based on history, visual acuity, perimetry, fluorescein angiography, optical coherence tomography, electrophysiology, and on the molecular confirmation of a pathogenic mtDNA mutation. Currently, the treatment of LHON includes genetic counseling, avoidance of certain environmental risk factors, and medical treatment with idebenone for subacute and dynamic cases. Recently, gene therapy using adeno-associated virus (AAV) vectors and mitochondrial replacement therapy are also showing promising results. This review will address the pathophysiology, clinical presentation, diagnostic procedures and current management of LHON.

Key words: leber hereditary optic neuropathy, LHON, mitochondrial disease, optic atrophy, gene therapy, idebenone, adeno-associated virus vectors

1. Introduction

Leber's hereditary optic neuropathy (LHON) is the most common primary mitochondrial DNA (mtDNA) disease [1-4]. LHON is a maternally inherited condition, which is associated with defective cellular energy production by the retinal ganglion cells. More than 90% of LHON patients harbor one of the three mtDNA point mutations. The prevalence of LHON is 1 in 30.000-50.000 in North Europe, with an estimated incidence of 1 in 1.000.000 in Japan [3, 5, 6]. LHON affects mainly males (80%-90%), usually between 15 to 35 years [7]. In most cases painless acute or subacute central visual loss occurs in both eyes within a few weeks to months. Most patients remain legally blind with visual acuity less than 20/200 for the rest of their lives. LHON is characterized by a preferential loss of retinal ganglion cells within the papillomacular bundle, which results in dense central scotomas [8]. In severe cases, the entire visual field can be affected [3, 5, 6]. In the last few years, advances in molecular medicine have led to substantial understanding of the genetic basis of LHON. Gene therapy trials have shown promising results in reducing the impact and progression of LHON. Idebenone, which is a synthetic analog of coenzyme Q_{10} has been recently implement in clinical trials for treatment of LHON. However, optimal management of LHON still remains a major challenge in the field of inherited mitochondrial diseases.

This review will address the pathophysiology, clinical presentation, diagnostic procedures and current management of LHON. A PubMed search of all articles published from January 1991 to September 2021 on etiology, clinical characteristics and treatment of LHON was performed. Searches included a combination of the following terms: "Leber's hereditary optic neuropathy", "visual field", "LHON mutations", "natural history", "electrophysiology", "retinal ganglion cell function", "prognosis", "LHON treatment", "gene therapy", "idebenone". The resulting references were then reviewed for pertinent articles. Selected key papers of historical importance published before 1991 were also included.

2. Etiology

2.1. *Genetics*

Three primary point mitochondrial mutations, m.3460G>A (MTND1), m.11778G>A (MTND4), and m.14484T>C (MTND6) are detected in approximately 90% of all LHON patients in multiple and ethnically divergent pedigrees. The remaining 10% of LHON cases are due to less common pathogenic mtDNA mutations, which have been documented in single case reports. The 11778G>A mutation is the most common cause of LHON worldwide, and is associated with a severe phenotype of LHON and the poorest visual recovery rates between 11-14% [3, 8]. It is detected in 70% of LHON cases in Northern Europe

Table 1. The 3 main LHON mutations; Phenotypic correlation and lifetime risk for visual loss

Mutations	Phenotypic correlation	Risk for visual loss		Median age at onset	M: F Ratio	Visual recovery	References
		M	F				
m.3460G>A	Intermediate course	32%-49%	15%-28%	20-22 y	1.7-4.3:1	15% - 25%	[11-14, 17]
m.11778G>A	Severe clinical form of LHON-poorest visual recovery rates The most common mutation	43%-51%	9-%11%	22-24 y	3.7-5.1:1	14% of persons of all ages; 11% of those aged ≥15 y	[12, 15, 17]
m.14484T>C	The most optimal visual outcome	47%	8%	20 y	7.7:1	37% - 64%	[13, 16, 26]

F = female, **M** = male, **y** = years

and 90% in Asia. The 14484T>C mutation is associated with the most optimal prognosis and best long-term visual outcome. In 37-64% of patients, some degree of visual recovery is achieved after reaching a visual "nadir". This mutation has been commonly described in French Canadians [9, 10]. The mutation 3460G>A presents with an intermediate course and the visual recovery rates between 15-25% [9, 10]. Phenotypic correlation and lifetime risk for vision loss for each of the three main mitochondrial mutations are summarized in Table 1.

2.2. *Sex*

LHON is characterized by incomplete penetrance. Sex and age are major risk factors for visual loss. A mtDNA mutation exists in all maternal related relatives of LHON patients, however most of the patient's relatives will never experience any symptom. Although wide variability exists across different families, the average lifetime risk of optic neuropathy and visual loss in male carriers is 50%, and in females it is only 10%.

The predominance of vision loss in male LHON patients is explained by a vision loss susceptibility allele on the X-chromosome. Patients with the 11778 and 14484 mutations at Xp21 chromosome were 35-fold more likely to lose their vision than patients without such mutations [7].

2.3. *Age*

Regarding age, more than 95% of male patients are affected before the age of 50 years, for all three main mutations. Consequently, a 50-year-old male without symptoms has <5% chances of vision loss [3].

2.4. *Heteroplasmy*

An additional factor that may influence the phenotypic expression of LHON is heteroplasmy, i.e. each cell contains many mitochondria and some of them with pathogenic mtDNA that cause LHON are mixed with other mutated and wild-type forms of mtDNA [17]. According to some studies, individuals with a "mutation load" less than 60-75%, may never experience vision loss. Tissue heteroplasmy leads to a variety in phenotypes in patients with similar mitochondrial genotypes, as subjects at risk may have different amounts of mutant mtDNA in their optic nerves [18]. Furthermore, due to heteroplasmy, the right and left eye may have different amounts of affected mtDNA [19]. Presymptomatic testing for quantifying the level of heteroplasmy is not widely used, because mtDNA in peripheral blood cells might not predict the mutation load of the retinal ganglion cells (RGCs). Additionally, most LHON individuals are homoplasmic, i.e. they have 100% of mutant mtDNA. Only 10%-15% of subjects carrying a LHON mutation are heterosplasmic [3, 9, 20].

2.5. *Other genetic factors*

Additionally, polymorphisms in nuclear genes related to mitochondrial regulation likely explain the variable penetrance and phenotypic expression of LHON. The correlation between LHON and multiple sclerosis (LHON-MS, known as "Harding disease") has been explained on the basis of immunologic factors explain [21]. The HLA-DR locus is not a main factor for the development of vision loss, however the resulting pathological condition has a characteristic phenotype, suggesting a mechanistic interaction. The course of LHON-MS is more aggressive and prognosis and management should be guarded [22].

2.6. *Environmental factors*

Finally, it has been suggested that environmental factors could be associated with the primary mtDNA

Table 2. Extraocular manifestations of LHON

Extraocular manifestations of LHON	
Cardiac abnormalities	Cardiac arrhythmias Wolff-Parkinson-White (WPW)
Neurologic abnormalities	Dystonia Postural tremor Peripheral neuropathy Movement disorders Multiple sclerosis-like illness Nonspecific myopathy

pathogenic mutation and affect the course of the disease which varies from optic nerve dysfunction to total visual failure. Factors that may affect phenotypic expression of the disease are systemic illnesses, nutritional deficiencies, trauma, medications, smoking, alcohol, and drug-induced mitochondrial toxicity [2].

3. Molecular Pathophysiology

Retinal ganglion cells of the papillomacular bundle are the main target tissue of damage, resulting in degenerated cell bodies and axons. The ensuing demyelination extends to the lateral geniculate bodies. Retinal pigment epithelium and photoreceptors are not affected [23]. In LHON, complex I subunit genes in the respiratory chain are affected from mitochondrial mutations hence RGCs are degenerated selectively. Specifically, the majority of mutations in LHON involve a single subunit of mitochondrial NADH dehydrogenase (MTND), an enzyme partially responsible for the oxidative phosphorylation pathway, causing impairment of complex I of the electron transport chain (ETC) [7, 8]. Therefore, the mitochondrial respiratory chain produces less ATP, the reactive oxygen species increase, the glutamate transport is affected, and these factors synergistically contribute to retinal ganglion cell apoptosis and optic atrophy within a year of disease onset [24]. Though the genetic phenotype is well-described, the pathophysiology of selective damage of the retinal ganglion cell layer in LHON is not fully clarified yet [2].

4. History/Clinical Presentation

Patients with LHON usually present with unilateral, painless, subacute, central visual loss, with the fellow eye being affected within the following 6 months, and in more than 97% of patients within one year [25]. In approximately 25% of cases, both eyes are affected on initial presentation. Symptoms begin between 15-35 years of life, with an average onset age at 22-24 years for the 11778A mutation, and at 20 years for the 14484C mutation [3, 21, 26]. However, LHON has been reported in patients from 2-87 years of age [27-30].

LHON is four to five times more common in males than females. However, the timing and severity of the initial vision impairment is not significantly influenced by either sex or mutational status [23]. The disease is transmitted strictly by maternal inheritance.

A history of trauma, alcohol-tobacco abuse, drug intake, systemic illnesses and increased intraocular pressure are potential precipitating factors for vision decline in subjects at risk for LHON. LHON Plus disease refers to coexisting neurologic or cardiac deficits, hence correlated symptoms or signs, such as arrhythmias, cardiac conduction abnormalities, tremor, dystonia, movement disorders, nonspecific myopathy, weakness, and multiple sclerosis-like illness, should be investigated (Table 2). Leigh syndrome may also correlate with LHON [31].

5. Physical Examination

The course of LHON has been divided into three clinical stages, depending on the duration of vision loss: the subacute stage (less than 6 months), the dynamic stage (6-12 months) and the chronic stage (>12 months) based on both structural and functional changes [32].

Visual acuity loss may be mild in early stages, but typically deteriorates to acuities worse than <20/200, or counting fingers [33]. Usually, the unaffected eye becomes involved within weeks to months, however the interval between initial and fellow eye involvement may be longer, with the longest interval between eyes being eighteen years after the initial attack. When the disease is asymmetric, an afferent pupillary defect is present. Color vision is severely affected and color testing shows deficits in red-green discrimination. Contrast sensitivity is also reduced, the pattern or multifocal visual evoked potentials (VEPs) is clearly impaired, and the electroretinogram may be subnormal [34]. Perimetry may reveal central or cecocentral scotomas, and subclinical visual disorders in the fellow seemingly unaffected eye. Initially

Figure 1. Fundus images of a 16-year-old male patient during the acute phase of LHON. There is bilateral disk hyperemia, peripapillary retinal nerve fiber layer edema, increased vascular tortuosity and retinal telangiectasia (From Tsironi E, Editor. Basic Principles of Ophthalmology, Konstadaras Publications, Athens, 2018).

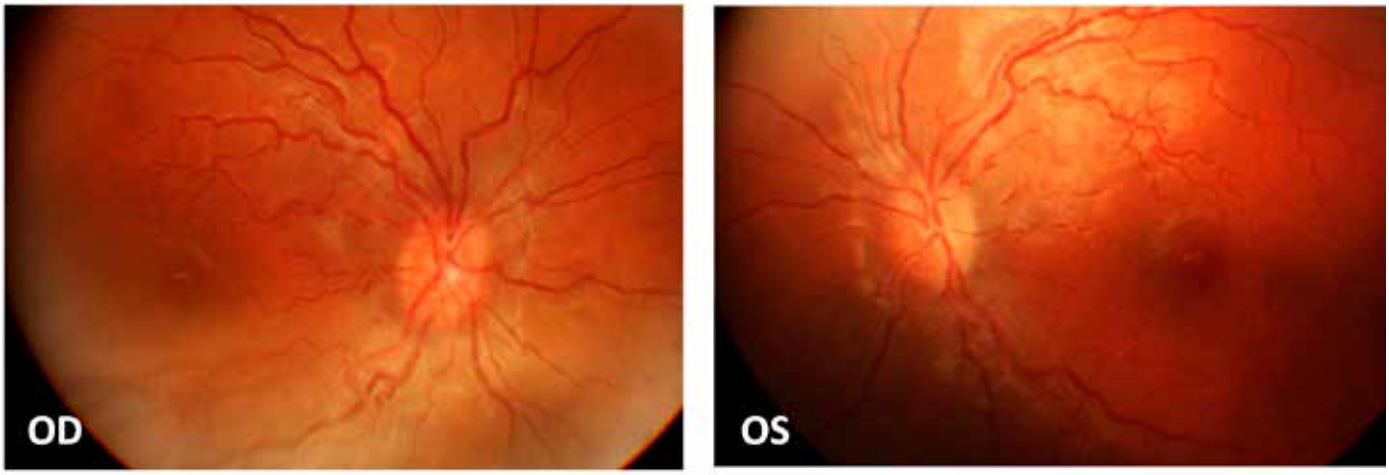
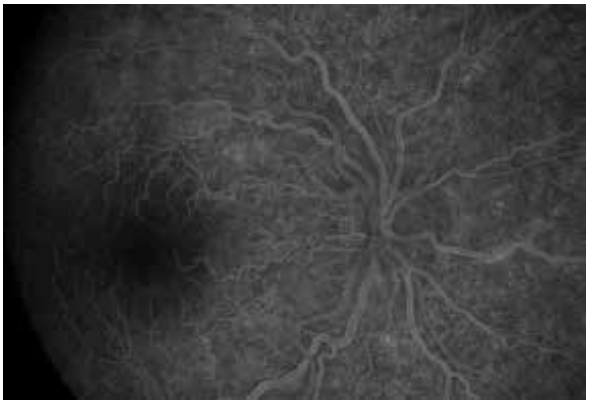


Figure 2. Fluorescein angiography of the right eye of the 16-year-old male patient with LHON. There is no dye leakage from the disk in the peripapillary region, distinguishing LHON from true optic disk edema (From Tsironi E, Editor. Basic Principles of Ophthalmology, Konstadaras Publications, Athens, 2018)



the scotomas may be relative, but with time they become absolute and extend at least 25-30 degrees across the central visual field [35].

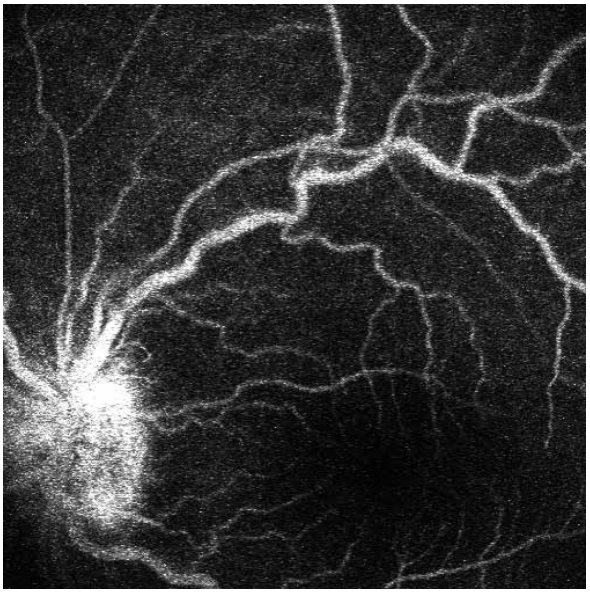
In the acute phase of LHON, funduscopy may reveal a pathognomonic triad of funduscopic abnormalities: circumpapillary telangiectatic microangiopathy with hyperemia and vessel tortuosity, elevation of the optic nerve head, and a thickened peripapillary nerve fiber layer (pseudoedema) (Figure 1). In LHON, there is no dye leakage on fluorescein angiogram, as opposed to true optic disk swelling. In about 20% of affected individuals, the optic disks appear normal in the acute phase, which can delay the diagnosis. With disease progression, the telangiectatic microangiopathy and pseudoedema of the disk resolve. Subsequently, there is rapid RGC axonal loss and optic atrophy with termporal pallor of the optic disk (36). The retinal nerve fiber layer dropout is first observed in the papillomacular bundle and months later, the whole nerve fiber layer becomes atrophic[37], The severe loss of the cells originating the papillomacular bundle is reflected on the thinning of the macular RGC layer on optical coherence tomography (OCT), which is completed after 4-6 months [32] Regarding retinal nerve fiber layer (RNFL) thickness, there is swelling in the first 6 months on OCT, followed by gradual quadrant specific thinning [32]. During the subacute stage visual acuity decreases and then usually stabilizes at approximately 6 months after onset of symptoms, while visual field defects and OCT abnormalities stabilize between 6 months to one year after symptom onset [38].

Vision loss is usually permanent, but partial spontaneous recovery of visual acuity can be observed. Slowly progressive variants of the disease course have been also described [39, 40]. Ocular symptoms and signs of LHON are outlined in Table 3.

6. Diagnostic Procedures

In suspected LHON, patients should undergo visual acuity testing, color vision assessment, dilated funduscopy, visual field examination, and OCT. As described above, fluorescein angiography is performed to distinguish true optic disk edema from pseudoedema. In LHON individuals, there is no dye leakage, although the optic disk may appear swollen (Figure 2, Figure 3). OCT is used for assessment of optic disk elevation in the early stages and for optic atrophy in the late stages of LHON. Specifically, the loss of macular RGCs is observed before the clinical disease onset and in about 4 months, maximal loss

Figure 3. Fluorescein angiography of the left eye of a 12-year-old male patient with panuveitis shows leakage of the disk in the peripapillary region ("hot disk") and enlargement and tortuosity of the retinal vessels (image courtesy of Dr. Kotoula)



has occurred [41]. In OCT, the RNFL appears thicker in the early stages of LHON and thinner in atrophic LHON, while in patients with visual recovery the RNFL seems to be preserved. The temporal fibers (papillomacular bundle) are the first and most severely affected, while the nasal fibers are partially preserved until the late stages of LHON [42]. A recent study of unaffected mutation carriers who converted to affected status found an early RNFL increase before conversion, suggesting that structural changes occur before clinically detectable vision loss [25]. Multifocal VEPs in LHON show impaired neural conduction along the visual pathway, with primary impairment of axons representing the central retina when compared to axons from the mid-peripheral retina [43]. OCT angiography in LHON individuals may demonstrate vascular dilation and tortuosity, in correlation with funduscopy findings [44].

Neuroimaging is essential to exclude intracranial disorders, compressive optic neuropathies, and demyelinating diseases. It should be performed in the presence of additional neurological symptoms, extracranial disease, or strictly unilateral findings with negative family history. MRI is often normal, but may demonstrate optic nerve enhancement, white matter lesions, or chiasmal enlargement and enhancement [45-48]. In the chronic phase, decrease of grey matter volume in the primary visual cortex and reduction of white matter volume in the optic chiasm, optic tract and optic radiations have been also documented [45, 46].

Gene testing may identify one of the three most Lfrequent LHON mutations, which are present in 90% of affected individuals. Targeted mtDNA testing for these three primary mutations is commercially available. A diagnostic algorithm of LHON is presented in Figure 4.

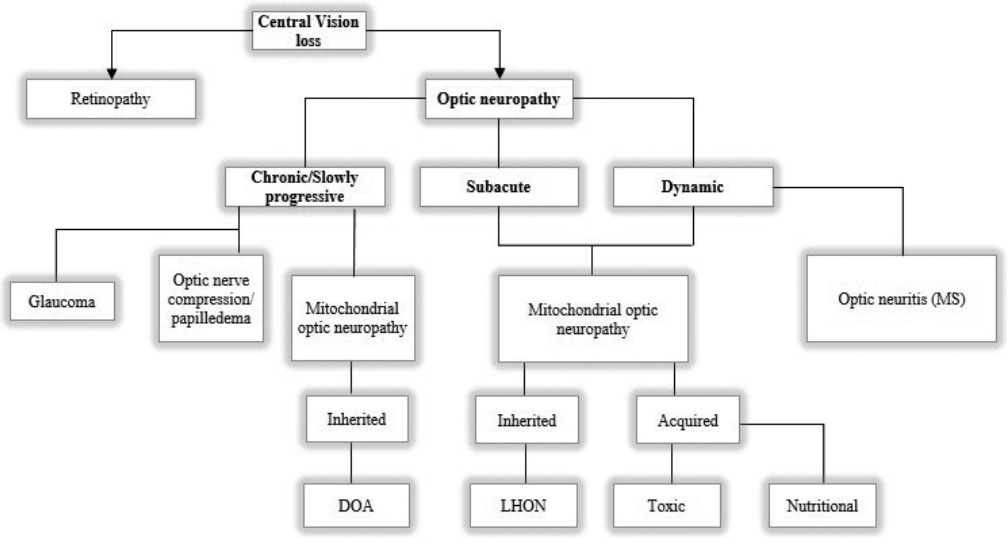
7. Differential Diagnosis

LHON should be included in the differential diagnosis of bilateral optic neuropathy. Unilateral involvement is exceptionally rare in LHON. Demyelinating optic neuritis, compressive optic neuropathy, toxic optic neuropathy, autosomal dominant optic atrophy, other inherited optic atrophies, normal tension glaucoma and bilateral anterior ischemic optic neuropathy should be excluded. In clinical practice, presentation and evolution of the disease should be taken under consideration and additional examinations such as autoantibody testing, screening for vasculitis, evaluation of oligoclonal bands in the cerebrospinal fluid and neuroimaging might be necessary. In the acute phase of LHON, the differential diagnosis includes a wide variety of non-genetic causes. However, in the

Table 3. Ocular symptoms and signs of LHON

Ocular symptoms and signs of LHON
Bilateral, painless subacute visual loss • Visual acuity < 20/200 • Visual fields: enlarging dense central or centrocecal skotomas
Triad of fundoscopic abnormalities: • circumpapillary telangiectatic microangiopathy with hyperemia and vessel tortuosity • elevation of the optic nerve head • thickened peripapillary nerve fiber layer (pseudoedema)
Note: Approximately 20% of affected individuals show no fundal abnormalities in the acute stage. • Thinning of RNFL - macular RGC layer • Optic disc atrophy

Figure 4. Diagnostic algorithm of LHON - Adapted from [32, 49, 50]



Diagnostic algorithm of LHON - Adapted from [32, 49, 50]

DOA = dominant optic atrophy; LHON = Leber's hereditary optic neuropathy; MS = multiple sclerosis.

chronic phase, the diagnosis of LHON is more challenging as optic atrophy is a multivariate condition. In these cases, neuroimaging and molecular genetic testing are necessary to establish the diagnosis [17].

8. Management

In 2017 a consensus on the clinical characteristics and treatment of LHON has demonstrated, that during the dynamic phase, 6-12 months after onset, there are progressive RNFL changes, while there is stability regarding the RGC loss in the macula [32, 51]. Hence the consensus group concluded that the chances for visual recovery are probably better during the subacute phase in comparison with the dynamic phase [32].

The recommended investigations for patients with LHON in both diagnostic and follow up visits, include measurement of the best-corrected visual acuity, static or kinetic perimetry, assessment of color vision, contrast sensitivity, measurement of macular RGC layer and RNFL thickness with OCT, electrophysiology, ECG findings with or without cardiac symptoms, neurological screening for symptoms and signs, genetic consultation and in some cases neuroimaging and/or lumbar puncture. The recommended follow-up visits should be performed in 3-month intervals during the subacute and dynamic phases, then in 6-month intervals during the second year after disease onset, and then in annual intervals.

Regarding preventive measures, individuals with established LHON should avoid smoking and excessive alcohol consumption [52]. Although there is not sufficient evidence about the environmental risk factors, it is necessary to avoid industrial toxins, drug-induced mitochondrial toxicity and other aggravating visual loss factors [53]. Several agents are recommended: Vitamins and cofactors including vitamin B12, CoenzymeQ$_{10}$ (CoQ$_{10}$), riboflavin, creatine, folic acid and L-carnitine, electron acceptors such as vitamin C, free radical scavengers such as vitamin E, alpha lipoic acid, EPI-743 and curcumin, and inhibitors of toxic metabolites, such as dicholoroacetate. However, the efficacy of these interventions is unclear [54].

8.1. *Mitochondrial neuroprotection: idebenone*

The ubiquinone family, including Coenzyme Q$_{10}$, has shown protective effects in other inherited mitochondrial diseases, in which its deficiency causes encephalomyelopathy [55]. However, due to the inability of coenzyme Q$_{10}$ to cross the blood-brain barrier after oral ingestion, a beneficial effect of Coenzyme Q$_{10}$ in LHON has been reported in only a few cases [56].

In order to overcome this limitation, idebenone, a synthetic hydrosoluble analog of coenzyme Q$_{10}$, was introduced [57]. The first LHON patient treated with idebenone was a 10-year-old boy who received 90 mg of idebenone daily. Pre-treatment visual acuity was 6/90 on either eye and reached 6/6 in the right eye after 4 months and in the left eye after 7 months [58]. Further case reports and case series have shown promising results, and idebenone (Raxone®)

was approved for LHON in 2015 by the European Medicines Agency in adults and adolescents at 900 mg/day given as three equally divided doses [32, 59].

Raxone was instituted as treatment of choice in LHON through the RHODOS study (Rescue of Hereditary Optic Disease Outpatient Study) [60]. This study was a prospective, double-blind, randomized placebo-controlled trial which was completed recently. RHODOS randomized 85 patients with genetically confirmed LHON and visual loss <5 years to receive either idebenone 900 mg/day (300 mg three times daily) or placebo. Treatment duration was 24 weeks, the primary endpoint was the best recovery in visual acuity and the secondary endpoint was the change in best visual acuity. During the trial, no safety concerns were raised. The authors found no significant differences in best recovery in visual acuity between idebenone and placebo. However, there was a trend in favor of idebenone regarding change in best visual acuity and after exclusion of patients with the 14488 mutation, who have better chances for spontaneous recovery [60]. After two years, the treatment effect persisted in 60 of 85 patients from the first study [61]. Visual benefit in patients treated with idebenone was likely to be higher when treatment was initiated within the first year of disease onset [10, 62, 63]. The aim of the ongoing "Post-Authorisation Safety Study with Raxone® in LHON Patients" (PAROS) study (NCT02771379) is to assess the long-term safety of idebenone.

Current treatment algorithms recommend initiation of 900 mg/day idebenone as soon as possible in patients with subacute and dynamic disease (less than 1 year from symptom onset). Treatment with idebenone is introduced for at least 1 year aiming to a positive response, or until an improvement plateau is documented. A clinically relevant visual response to idebenone is the improvement of 2 lines of visual acuity and automated perimetry (mean deviation). If a clinically relevant improvement is observed, and a plateau has been reached, the treatment is continued for another year. Idebenone should be discontinued if no visual recovery is documented and is currently not offered in patients during the chronic stage of LHON [60].

8.2. *Medical neuroprotective treatments*

EPI-743 and MTP-131 (elamipretide) are neuroprotective and antioxidant drugs, which represent potential treatment candidates for LHON [62]. Four out of five LHON patients who started EPI-743 within the first 4 months after the onset of visual decline, demonstrated visual improvement [65]. MTP-131 is under investigation in 12 patients with LHON with disease duration between 1-10 years (https://clinicaltrials.gov/ct2/show/NCT02693119).

Cyclosporine A inhibits mitochondrial permeability transition, thus blocking apoptosis. Oral cyclosporine A has been investigated in five patients with subacute, unilateral LHON, but visual acuity in the first affected eye worsened, and second-eye involvement was not prevented [64].

Finally, brimonidine is an α-2 agonist, which reduces apoptosis and has a neuroprotective action on optic nerve injury. Brimonidine was used in nine patients with subacute LHON although it did not prevent involvement of the fellow eye [67].

8.3. *Oestrogens*

The fact that male sex is predominant in LHON could raise suspicions about a protective role of female sex hormones. Recent investigations indicate that estrogens reduce reactive oxygen species levels and simultaneously increase the efficiency of antioxidant enzyme superoxide dismutase. Consequently, mitochondrial oxidative phosphorylation becomes more effective [68, 69]. It remains to be seen if such intervention can be of use in LHON.

8.4. *Gene therapy*

Gene therapy is a novel therapeutic strategy in LHON, which involves intravitreal injection of a modified adeno-associated virus (AAV) vector and insertion of an unmutated MT-ND4 gene into the mitochondria of RGCs. The first effort was accomplished in 2002 by Guy et al. They transfected a synthetic ND4 subunit mutation, using an Adeno Associated Viral Vector [68]. The authors reported success in the restoration of complex I-dependent respiration, because three times as much ATP was produced by the transfected cells when compared to the mock-transfected cybrids. Further animal models using intravitreal AAV gene delivery of human ND4 have proven the safety of the injection technique and confirmed that the AAV expressed its genetic content inside the mitochondria [71-74].

The first phase 1 clinical trial in five legally blind patients with G11778A LHON showed no serious safety problems, with two of five showing significant improvement in visual acuity [75, 76]. In 2017, the RESCUE and REVERSE clinical trials (phase III), reported on patients who received a unilateral injection with GS010. GS010 is a recombinant, AAV, which contains a cDNA encoding the mitochondrial ND4 protein (rAAV2/2-ND4). This study reported a three-line increase in visual acuity (15 letters) and also showed that viral vector DNA was transferred via the optic pathways from the injected to the fellow eye [53, 77].

RESTORE is the longitudinal follow-up study of individuals who received treatment in the RESCUE and REVERSE studies. RESTORE showed that the

treatment effect of rAAV2/2-ND4 on visual acuity and vision-related quality of life reported 2 years post therapy in RESCUE and REVERSE was maintained at 3 years in the RESTORE [78].

8.5. *Mitochondrial replacement therapy*

MtDNA is transmitted maternally and so *in vitro* fertilization techniques could contribute in avoiding developing mtDNA pathogenic variants. Mitochondrial replacement with pronuclear transfer for clinical use was approved by the Human Fertilization and Embryology Authority in the United Kingdom since 2015 [79, 80]. Due to ethical and legal considerations, mitochondrial replacement therapy still remains controversial [80]. Eleven clinical trials on treatment agents in LHON have been already completed and 5 of then are active now (Table 4).

9. Genetic counseling

LHON is a maternally-inherited disease. Mothers of affected individuals have the mtDNA mutations, except for the rare occurrence of *de novo* mtDNA mutations. A female carrier of LHON-related mtDNA mutation passes the mutation to all of her children, while a male carrier of LHON-related mtDNA mutation cannot pass the mtDNA mutation to any of his children. However, genetic counseling is challenging because of the reduced penetrance characterizing the LHON-causing mtDNA pathogenic variants [81].

Similarly, prenatal investigations for heteroplasmic female LHON carriers is not very helpful, and the prenatal presence of mtDNA pathogenic variant for LHON cannot predict occurrence of disease, age of onset, or vision loss. The reason is that the mutant load in amniocytes and chorionic villi may not reflect the mutant load in other fetal cell populations, especially those programmed to mature into the RGCs [81].

10. Prognosis

The prognosis of LHON is related to the specific mutation [82, 83]. Individuals with the T14484C mutation have the higher chances of spontaneous visual recovery, which usually occurs 1-2 years after disease onset. The recovery in visual acuity is usually partial, but a few patients regain near-normal visual acuity in at least one eye, even years after the initial visual decline [82-84]. Visual field recovery is usually incomplete.

In general, permanent visual loss is usual and most people with LHON eventually qualify for registration as legally blind. Vision is typically worse than 20/200 OU, but light perception is usually preserved, and complete blindness is rare. In approximately 50% of male carriers and 90% of female carriers, blindness will not ensue during their lifetime. Finally, a younger age at onset and childhood-onset LHON have a more favorable prognosis for visual acuity [28]. A better visual acuity at the nadir and large optic disks have been also associated with higher rates of visual recovery and better visual outcome, due to less crowding of the RGC axons in the optic nerve [85, 86]. On the other hand, the presence of peripapillary telangiectasias and optic disk hyperemia have been considered as poor prognostic factors [86].

11. Conclusions

Although, the clinical and molecular diagnosis of LHON is unambiguous, management of patients with LHON remains largely supportive, including prescription of low vision aids, reconfiguration of the working environment and participation of the patient to the social services. LHON mainly affects the retinal ganglion cell layer with pronounced cell body and axonal degeneration, while sparing the photoreceptor layer. The targeted vulnerability of retinal ganglion cells layer still remains unexplained. In the future, it is hence necessary to understand the complex pathophysiology of LHON, in order to develop new therapeutic strategies. Research should focus on identifying individuals at higher risk for LHON. In the future, therapy in LHON mutation carriers may be also indicated in order to preventing disease onset.

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Table 4. Active studies 2021/LHON

Study title	Goal study	Phase	Recruitment status	Study type	Actual enrollment	Allocation	Masking	Primary purpose	Actual study start Date:	Estimated study completion Date:	Locations
REFLECT Efficacy & Safety Study of Bilateral IVT Injection of GS010 in LHON Subjects Due to the ND4 Mutation for up to 1 Year	Asessment of the safety and efficacy of GS010, a gene therapy, in improving the retina functional & structural outcomes in subjects with LHON due to the G11778A ND4 mitochondrial mutation when vision loss duration is present up to one year.	3	Active, not recruiting	Interventional Genetic: GS010Drug: Placebo	90 participants	randomized	Double (Participant, Investiagtor)	treatment	March 12, 2018	June 30, 2024	USA and UK
A Single Intravitreal Injection of rAAV2-ND4 for the Treatment of Leber's Hereditary Optic Neuropathy	This study is meant to evaluate the safety and efficacy of rAAV2-ND4 treatment for Leber hereditary optic neuropathy with the G11778A mutation in mitochondrial DNA.	3, 2	Active, not recruiting	Interventional Drug: rAAV2-ND4	159 participants	N/A	None (Open Label)	treatment	December 27, 2017	January 15, 2025	China
An Open-label Dose Escalation Study of an Adeno-associated Virus Vector (scAAV2-P1ND4v2) for Gene Therapy of Leber's Hereditary Optic Neuropathy(LHON) Caused by the G11778A Mutation in Mitochondrial DNA	The primary hypothesis being tested is that there will be no toxicity resulting in loss of vision to no light perception in injected eyes.	1	Active, not recruiting	Interventional Drug: injection of scAAV2-P1ND4v2 1.18x10e9 vg (Low), Drug: injection of scAAV2-P1ND4v2 5.81 X10e9 vg (Med)	28 participants	Non-randomized	None (Open Label)	treatment	July 14, 2014	March 2023	USA

Table 4. Continuity

Study title	Goal study	Phase	Recruitment status	Study type	Actual enrollment	Allocation	Masking	Primary purpose	Actual study start Date:	Estimated study completion Date:	Locations
				Drug: injection of scAAV2-P1ND4v2 2.4 X10e10vg (High) Drug: injection of scAAV2-P1ND4v2 1.0 X10e11vg (Higher)							
Efficacy Study of Gene Therapy for The Treatment of Acute LHON Onset Within Three Months	Efficacy Study of Gene Therapy for The Treatment of Acute Leber's Hereditary Optic Neuropathy (LHON) onset within three months		Completed	Interventional Drug: rAAV2-ND4	120 participants	N/A	None (Open Label)	treatment	January 8, 2018	December 30, 2020	China
RESCUE/REVERSE Long Term follow-up	Assessment of long-term safety and efficacy of GS010, gene therapy, and quality of life in subjects with **LHON** due to the G11778A ND4 mitochondrial mutation and who were treated in the Rescue or Reverse studies	3	Active, not recruiting	Interventional Genetic:GS010 Drug: Placebo	61 participants	randomized	None (Open Label)	treatment	January 9, 2018	August 2022	USA, Europe

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