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Leber's hereditary optic neuropathy – current status of idebenone and gene replacement therapies

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Abstract: Leber's hereditary optic neuropathy (LHON) is the most common mitochondrial disease, and was the first to be linked to mitochondrial DNA (mtDNA) variations. Recently, autosomal recessive forms of LHON were described in addition to the classical mtDNA-associated forms. Clinically, LHON manifests with subacute and painless loss of central visual acuity, in most cases starting unilaterally, and involving the second eye a few weeks later. Almost all LHON cases are caused by pathogenic variants in genes that code for proteins relevant for function of Complex I of the respiratory chain. The Complex I dysfunction in LHON leads to decreased ATP synthesis and to increased production of reactive oxygen species which ultimately initiates dysfunction and apoptosis of retinal ganglion cells and their axons, the optic nerve. Idebenone, a synthetic CoQ derivative, is a potent intramitochondrial antioxidant and can shuttle electrons directly to complex III of the respiratory chain, thereby bypassing complex I deficiency. On the basis of several clinical trials, it has been approved as a treatment for LHON in 2015 (in the EU). In addition, direct intravitreal gene replacement therapy is being investigated, with several late-stage clinical trials already completed. In the future, gene editing of mtDNA variants may also become a therapeutic option.

Keywords: LHON, mtDNA, Complex I, idebenone, gene therapy

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Phenotype and genetics

LHON is the most common mitochondrial disease, affecting about 1 in 31 000 [1] to 1 in 50 000 people [2]. The phenotype of the disorder was first described by Albrecht von Graefe in 1858 and then in more detail by Theodor Leber in 1871 [3]. LHON was also the first disorder ever linked to mitochondrial DNA (mtDNA) variations, in 1988 [4]. The disease primarily affects retinal ganglion cells and their axons (i.e the optic nerve), resulting in significant vision loss and consecutive optic nerve atrophy [5, 6]. Environmental factors, in particular smoking, are important risk factors and can trigger the onset of visual deterioration [7]. This painless loss of vision typically starts in one eye and progresses to the other within weeks to months [8], often leading to legal blindness [9]. Depending on age and genotype, there may be some degree of recovery in a subset of patients but the majority experiences a permanent and severe impact on central visual acuity and quality of life [9].

Most cases of LHON (approximately 90 %) are caused by single missense variants in the mtDNA, in particular m.11778G>A in the mt-*ND4* gene, m.3460G>A in the mt-*ND1* gene and m.14484T>C in the mt-*ND6* gene) (Table 1). Most patients are homoplasmic, i. e. they carry 100 % of the variant in each cell of the body [10]. The mtDNA and accordingly mtDNA-associated LHON is exclusively transmitted through the maternal lineage. Of note, the penetrance of these mtDNA variants is rather low, i.e only a certain proportion of mutation carriers manifests the disease. For the three classic variants combined, the penetrance has recently been calculated to be 17.5 % in males and 5.4 % in females [11], leading to a male-to-female ratio of around 3:1 in affected patients. The penetrance values per mutation and sex are provided in Table 1.

In addition to this mtDNA-associated form of LHON (mtLHON), nuclear gene defects have recently been identified as causes of an autosomal recessive form of LHON (arLHON) [12]. By far the most frequent of these nuclear gene defects is biallelic variants in *DNAJC30*, a single exon gene on chromosome 7 [13, 14]. Despite the different mode of inheritance, *DNAJC30*-associated LHON is clinically near-indistinguishable from mtLHON, and even recapitulates fea-

Table 1: Molecular causes of LHON

Molecular cause	Pathomechanism	Relative proportion or number of cases	Penetrance (m/f)
mtDNA			
m.11778G>A variant in *ND4* gene	ND4 is a subunit of Complex I	69 % [16]	16.2 %/4.3 % [11]
m.14484T>C variant in *ND6* gene	ND6 is a subunit of Complex I	17 % [16]	18.4 %/3.4 % [11]
m.3460G>A variant in *ND1* gene	ND1 is a subunit of Complex I	13 % [16]	18.0 %/5.7 % [11]
nuclear			
DNAJC30 variants	DNAJC30 is involved in maintenance and repair of Complex I [13]	> 90 patients described so far [13, 14, 17, 18]	96.8 %/42.9 % [13]
NDUFS2 variants [15]	NDUFS2 is a subunit of C1	Only one family described so far	n/a

Abbreviations: m, male; f, female; mtDNA, mitochondrial DNA; ND, NADH dehydrogenase subunit

tures such as reduced penetrance and male predominance [13]. Another cause of arLHON, so far described in only one family, is biallelic variants in the *NDUFS2* gene [15]. Of note, all of the above LHON gene defects affect Complex I of the respiratory chain. The mtDNA *ND4*, *ND6* and *ND1* genes as well as the nuclear *NDUFS2* gene code for structural subunits of Complex I while the *DNAJC30* gene codes for a chaperone protein involved in maintenance and repair of Complex I (Table 1) [13, 15].

Pathomechanisms

Complex I is the entry point of electron flow through the mitochondrial respiratory chain and interacts with coenzyme Q to facilitate proton translocation across the inner mitochondrial membrane. Both electron flow and build-up of an electrochemical gradient are ultimately needed to drive mitochondrial energy production in the form of ATP [19].

Complex I deficiency, as caused by the gene defects described above, lead to decreased ATP synthesis and, even more importantly, to increased production of reactive oxygen species (ROS) [5]. Subsequently, ROS and complex I deficiency lead to opening of the mitochondrial permeability transition pore (MPTP) initiating dysfunction and ultimately apoptosis of cells [20, 21].

Why is LHON so tissue-specific and affects (in most cases) only the retinal ganglion cells (RGCs) and their axons, the optic nerve? The photoreceptors convert incoming visual signals into a receptor potential, which is transmitted via the bipolar cells and then processed in the RGCs. The axons of the RGCs (optic nerve) transmit the signal to the brain as action potentials [6]. These axons are partially unmyelinated (until they enter the optic nerve) to maintain the nerve fiber layer's permeability to light which requires energy-intense continuous instead of energy-saving saltatory conduction, rendering them particularly vulnerable to compromised mitochondrial ATP supply [5, 6]. It is unclear, however, why the RGCs and the optic nerve can remain unaffected in other mitochondrial disorders and even in other forms of Complex I defect.

Idebenone therapy

Idebenone is a synthetic CoQ derivative with a shorter side chain. It can act as an electron carrier in the respiratory chain to contribute to ATP production and also functions as a potent intramitochondrial antioxidant. Of note, it can shuttle electrons directly to complex III of the respiratory chain, thereby bypassing complex I deficiency which renders it a very attractive treatment option for Complex I defect disorders such as LHON [22].

Following positive anecdotal reports, a randomized study with 900 mg/d idebenone vs. placebo over 24 weeks in 85 patients with LHON showed no significance for the primary endpoint, but consistent trends or significances in secondary endpoints and various subgroups favored efficacy [23]. In a retrospective analysis, 45.5 % of 44 treated LHON patients experienced at least partial vision recovery, compared to only 32.2 % of 59 untreated patients [24]. An Expanded Access Program with open-label treatment of 111 LHON patients with 900 mg/d idebenone showed improved chances of stabilization in those patients with well-pre-

Table 2: Studies of Idebenone in LHON

Study	No. of patients	Study design and dosage	Inclusion criteria/Study cohort	Results
Klopstock et al., 2011: *RHODOS study* [23]	85	Prospective, randomized, double-blind, placebo-controlled study; 900mg/day	m.11778G>A-, m.3460G>A- or m.14484T>C-variant; Age between 14 and 64; vision loss due to LHON within 5 years before inclusion	No significant difference after 24 weeks, subgroup analysis showed benefit for m.11778G>A and m.3460G>A
Carelli al., 2011 [24]	103	Retrospective study of treated and untreated patients, varying dosages	Follow-up ≥ 5 years; in treated patients start of idebenone within first year after disease onset	Showed benefit for m.11778G>A-patients; time from disease onset to the start of treatment has been shown to be important
Catarino et al., 2020: Expanded Access Program [25]	111	Retrospective study of treated patients, 900mg/day	m.11778G>A-, m.3460G>A- or m.14484T>C-variant; idebenone therapy started within first year after onset	46 % (40/87) of patients showed clinically relevant recovery
van Everdingen et al., 2022 [29]	72	Retrospective study, 900mg/day	Complex I-affecting variants	56 % (40/72) of patients showed clinically relevant recovery
Yu-Wai-Man et al., 2024: *LEROS study* [26]	199 + 372 (natural history cohort)	Open-label, interventional study, 900mg/day	Patients up to 5 years after onset, treatment period of 2 years	More patients had clinically relevant recovery after 12 and 24 months in comparison to natural history cohort: 47.9 % vs. 33.3 % when treatment was started in subacute/dynamic phase; 31.9 % vs. 16.1 % when treatment was started in chronic phase (24 months data)

served vision (in 50 % of patients) or clinically relevant recovery in those with significantly reduced vision. The latter was observed in 46.0 % of treated patients (versus 31.1 % in a historical control group), with an average improvement of more than 7 lines on the eye chart [25]. The totality of study results led to the European approval of idebenone in 2015. A post-approval study confirmed the efficacy of idebenone when initiated in the subacute/dynamic phase (up to 1 year after onset) as well as in the chronic phase (1–5 years after onset) but also showed that the treatment effect varies depending on disease phase and causative mtDNA mutation [26]. In addition, patients with *DNAJC30*-associated arLHON benefit markedly from idebenone as well [13, 18]. Since idebenone needs to be reduced intracellularly by an enzyme called NAD(P)H oxidoreductase 1 (NQO1) to exert its beneficial effects [22, 27], response to idebenone therapy is also dependent on NQO1 activity, particularly in patients with the m.3460G>A variant [28]. (Table 2)

Gene replacement therapy

In addition to the established idebenone therapy, novel gene therapy approaches are being explored. These approaches primarily involve the permanent provision of a functional gene copy to compensate for the defective native gene. Currently, three similar gene therapy vectors based on recombinant adeno-associated viruses (rAAV) are undergoing clinical trials, with studies being conducted in the USA, Europe, and China.

Since direct gene transfer to mitochondria is not yet established in human, the AAV vectors are targeted to the nucleus where the wild-type gene is transcribed into mRNA. The mRNA is then translated at cytosolic ribosomes into protein that, guided by a mitochondrial targeting sequence, can enter mitochondria via their physiological protein import machinery [6].

The most advanced gene therapies target patients carrying the m.11778G>A variant of the mt-*ND4* gene. The rAAV2/2-ND4 vector contains [30] the wild-type *ND4* gene, an upstream mitochondrial targeting sequence required for the transfer of the translated protein across the mitochondrial inner membrane [31], and downstream the 3'-untranslated region (3'-UTR) of the nuclear *COX10* gene which turned out to be advantageous for allotopic expression [30].

Lenadogene nolparvovec, a recombinant adeno-associated virus 2 (rAAV2) vector containing a wildtype version of the *ND4* gene (the whole construct being abbreviated as

Table 3: Gene therapy studies in LHON

Study	Vector	Study type and design	Patients	Outcomes
Feuer et al., 2016 [34]	scAAV2-P1ND4v2	Phase I, open-label	5 patients received unilateral treatment	No serious systemic adverse events
Guy et al., 2017 [35]	scAAV2-P1ND4v2	Phase I, open-label	14 patients received unilateral treatment	Low and medium dosages proved to be safe
Lam et al., 2022 [36]	scAAV2-P1ND4v2	Phase I, open-label	28 patients received unilateral treatment	Favorable safety and tolerability profile
Wan et al., 2016 [37]	rAAV2-ND4	Not applicable	9 patients	Favorable safety profile
Vignal-Clermont et al., 2021: REVEAL study [38]	Lenadogene nolparvovec	Phase I/IIa open-label, 5 yrs follow-up	15 patients received unilateral treatment	Overall well tolerated, most frequent TEAEs were intraocular inflammation and elevation of intraocular pressure, showed improvement in both eyes (LogMAR), with no significant difference after 5 yrs
Yu-Wai-Man et al., 2020: REVERSE study [33]	Lenadogene nolparvovec	Phase III, randomized, double-blind	37 patients with vision loss for 6–12 months had unilateral vector and contralateral sham injection	Showed CRR in vector-treated and sham-treated eyes (LogMAR) after 48 and 96 weeks, but no significant difference between both eyes
Newman et al., 2021: RESCUE study [32]	Lenadogene nolparvovec	Phase III, randomized, double-blind	39 patients with vision loss < 6 months had unilateral vector and contralateral sham injection	Showed improvement in vector-treated and sham-treated eyes (LogMAR) after 96 weeks, but no significant difference between both eyes
Biousse et al., 2021: RESTORE study [39]	Lenadogene nolparvovec	3–5 yrs follow-up after RESCUE and REVERSE studies	61 patients	Progressive and sustained improvement in 3–5 yrs follow-up
Newman et al., 2023: REFLECT study [8]	Lenadogene nolparvovec	Phase III, randomized, double-blind	48 patients had bilateral vector injection; 50 patients had unilateral vector and contralateral sham injection	Better treatment effect in bilateral than in unilateral vector injection after 1.5 yrs

Abbreviations: yrs, years; TEAEs, treatment-emergent adverse events; CRR, clinically relevant response

rAAV2/ND4), was the first compound to be investigated in Phase III clinical trials. In two parallel studies, unilateral injection of the gene therapy vector 0–6 months (RESCUE) [32] or 6–12 months (REVERSE) [33] after onset unexpectedly led to bilateral improvement of visual acuity which was beneficial for the patients but foiled the predefined primary endpoint of both studies. A later study (REFLECT) [8] showed additional benefit of bilateral as compared to unilateral injection of rAAV2/2-ND4.

All gene therapy studies in LHON so far are summarized in Table 3. However, as of July 2024, no gene therapy approach has been approved for LHON by regulatory authorities in the USA or the EU.

Further treatment approaches in development

Gene replacement therapies targeting the m.3460G>A variant have also demonstrated promising results in mouse experiments [40]. Currently, a gene therapy vector targeting the m.3460G>A variant is investigated in a Phase I/II clinical trial (ClinicalTrials.gov ID: NCT05820152).

In the future, gene editing of mtDNA variants may become a viable therapeutic option. While the application of the CRISPR/Cas9 system is limited due to the difficulty of importing guide RNA into mitochondria [41], CRISPR-free mitochondrial base editing is currently under preclinical investigation [42–44], and may have broad implications for the future treatment of mitochondrial disorders.

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