Leber Hereditary Optic Neuropathy – Therapeutic Challenges and Early Promise

Leber hereditary optic neuropathy (LHON) is the most common primary mitochondrial DNA (mtDNA) disorder in the United Kingdom, with a minimum prevalence of 1 in 31,000. Three mtDNA point mutations account for ~90% of all LHON cases and m.11778G>A is the most frequently identified (~70%) pathogenic variant worldwide (Table 1). It is an important cause of severe visual loss among young adults with a peak age of onset in the second and third decades of life. Management is mostly supportive but recent developments in LHON research are pointing the way towards more effective treatments for this blinding mitochondrial disorder.

Clinical features of LHON
LHON classically presents with acute or subacute painless loss of central vision. The initial visual loss is severe with most patients achieving best corrected visual acuities of 6/60 or worse. There is an associated dense central scotoma and a marked reduction in colour perception. Despite this global reduction in optic nerve function, the pupillary light reflexes are relatively preserved, and this distinctive feature has been ascribed to a special class of melanopsin-containing retinal ganglion cells (ROGs), which are less vulnerable to the downstream consequences of the mtDNA LHON mutations. Bilateral optic nerve involvement occurs in ~25% of LHON cases. If sequential, the second eye is invariably affected within one year of disease onset, unilateral optic neuropathy being exceptionally rare in LHON.

In the acute phase, optic disc hyperaemia, peripapillary telangectatic vessels, vascular tortuosity, and retinal nerve fibre layer oedema can be observed, the latter being due to RGC axonal axialis (Figure 1). In the pre-molecular era, these fundal abnormalities were particularly informative, allowing a presumptive diagnosis of LHON to be made, especially when supported by a maternal family history of early-onset visual loss. In 20-40% of acute cases, the optic discs look entirely normal and these patients are often incorrectly labelled as having functional visual loss. Pallor of the neuroretinal rim develops within six weeks of disease onset and it is initially more apparent temporally due to the accelerated loss of RGCs of the nasal retina, a feature that is most evident in younger patients.

Table 1: Mitochondrial DNA variants associated with LHON

<table>
<thead>
<tr>
<th>Mitochondrial Gene</th>
<th>Nucleotide Change</th>
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<tbody>
<tr>
<td>MTND1</td>
<td>m.3460G&gt;A</td>
</tr>
<tr>
<td>MTND4</td>
<td>m.11778G&gt;A</td>
</tr>
<tr>
<td>MTND6</td>
<td>m.14486T&gt;C</td>
</tr>
<tr>
<td>MTND1</td>
<td>m.3376G&gt;A, m.3653G&gt;A, m.3697G&gt;A, m.3700G&gt;A, m.3733G&gt;A, m.4025C&gt;T, m.4160T&gt;C, m.4171C&gt;A</td>
</tr>
<tr>
<td>MTND2</td>
<td>m.4640C&gt;A, m.5244G&gt;A</td>
</tr>
<tr>
<td>MTND3</td>
<td>m.10237T&gt;C</td>
</tr>
<tr>
<td>MTND4</td>
<td>m.11696G&gt;A, m.11253T&gt;C</td>
</tr>
<tr>
<td>MTND4L</td>
<td>m.10663T&gt;C*</td>
</tr>
<tr>
<td>MTND5</td>
<td>m.1281T&gt;C, m.1284G&gt;C, m.1363T&gt;G, m.1373G&gt;A</td>
</tr>
<tr>
<td>MTND6</td>
<td>m.14325T&gt;C, m.14586C&gt;T, m.14459G&gt;A*, m.14729G&gt;A, m.14832C&gt;A*, m.14495A&gt;G*, m.14498C&gt;T, m.14568G&gt;C*, m.14596A&gt;T</td>
</tr>
<tr>
<td>MTATP6</td>
<td>m.910T&gt;C</td>
</tr>
<tr>
<td>MTCO3</td>
<td>m.9804G&gt;A</td>
</tr>
<tr>
<td>MTCYB</td>
<td>m.1483G&gt;A</td>
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</table>

* These mtDNA variants are definitely pathogenic. They have been identified in a ≥2 independent LHON pedigrees, showing segregation with affected disease status. The remaining putative LHON mutations have been found in singleton cases or in a single family, and additional evidence is required before pathogenicity can be irrefutably ascribed. 

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Extra-ocular features such as cardiac conduction defects, peripheral neuropathy, dystonia, and myopathy are thought to be more common among LHON carriers compared with the general population.\(^3\) There is also a well-established association between the three primary LHON mutations and a demyelinating illness, which interestingly is clinically and radiologically indistinguishable from multiple sclerosis (Harding’s disease).\(^6\) Other rarer pathogenic mtDNA variants have been linked with more atypical ‘LHON plus’ syndromes where the optic neuropathy is complicated by prominent spastic dystonia, ataxia, juvenile-onset encephalopathy, and psychiatric disturbances.\(^3\)

**Visual prognosis**

The visual prognosis in LHON is poor and most patients remain legally blind. The likelihood of visual recovery is greatest with the m.3460G>A mutation, least with the m.14484T>C mutation, and intermediate with the m.11778G>A mutation.\(^4\) Although delayed visual recovery has been reported, maximal improvement in visual function usually occurs within the first year, if it occurs at all. The appearance of small islands of vision within the patient’s visual field (fenestrations) can greatly help scanning vision, especially if the central scotoma becomes concurrently less dense.

**Genetic counselling**

The mitochondrial genome is maternally inherited and thousands of mtDNA molecules are present in metabolically-active cells. As a result of this high-copy number genome, two possible situations can arise, known as homoplasy and heteroplasy. Among LHON families, 85-90% of carriers are homoplasmic for the mtDNA mutation, i.e. 100% mutant, whereas the remainder are heteroplasmic harbouring a mixture of both wildtype and mutant mtDNA species.\(^4\) The risk of disease conversion is low if the mutational load is below the threshold level of 60%.\(^7\) Male LHON carriers can be reassured that their children will not inherit their mitochondrial genetic defect. On the other hand, female LHON carriers will transmit the mutation to all their offspring. For the minority of mothers with heteroplasmic LHON mutations, it is difficult to accurately predict the mutational level that will be transmitted since rapid generational shifts in mitochondrial allele frequencies can occur due to the ‘mitochondrial bottleneck’ operating in the female germline.\(^4\) Based on published figures, some indication of recurrence risks can be provided to maternal relatives of a LHON proband (Table 2).

Although it is not possible to predict whether or when a LHON carrier will be affected, epidemiological studies have identified major risk factors for visual loss, namely age, sex, and environmental exposure.\(^3\) Over 90% of LHON carriers who will experience visual failure will do so before the age of 50 years. In addition, LHON is characterised by a marked sex bias, male carriers having a ~50% lifetime risk of developing the optic neuropathy compared with only ~10% for female carriers.\(^4\) Unaffected LHON carriers should be strongly advised not to smoke and to minimise their alcohol intake, not only as a general health measure, but because smoking, and to a lesser extent excessive alcohol intake, have been associated with increased risks of disease conversion.\(^4\) In one large study comparing 106 affected and 206 unaffected carriers from 125 LHON families, light and heavy smokers were twice and three times more likely to lose vision compared to non-smokers, respectively.\(^4\)

**Treatment strategies**

Mitochondria provide the bulk of the cell’s adenine triphosphate (ATP) requirements through the tightly-regulated control of electron flux along the mitochondrial respiratory chain. All three primary LHON mutations; m.3460G>A, m.11778G>A, and m.14484T>C disrupt key polypeptide subunits of complex I, resulting in a significant bioenergetic deficit and raised levels of reactive oxygen species (ROS).\(^13\) An intriguing aspect of the pathophysiology of LHON still remains: why are RGCs selectively vulnerable to disturbed mitochondrial function? Several hypotheses have been proposed based on the distinct anatomical, physiological, and cytoskeletal arrangements present within the optic nerve.\(^2\) Notwithstanding these unresolved issues, the final pathological outcome in LHON is apoptotic RGC loss and the aims of treatment for this disorder are threefold: (i) to prevent initial visual loss among LHON carriers, (ii) to protect the unaffected fellow eye in patients with unilateral optic neuropathy, and (iii) to preserve visual function in already compromised optic nerves.

**Neuroprotection**

Various treatment ‘cocktails’ have been used to mitigate the deleterious impact of mitochondrial dysfunction on RGC survival.\(^14\) Co-enzyme Q10 (CoQ\(_{10}\)) is a quinone, a free-radical scavenger and based on limited evidence; it is frequently prescribed to patients with mitochondrial disease. Idebenone is a related compound, a shorter-chain synthetic benzoquinone analogue, which is thought to have a better bioavailability profile compared with CoQ\(_{10}\). Idebenone is able to bypass complex I inhibition and by Shutting electrons directly from the cytosol to complex III, ATP production is optimised with a decrease in toxic ROS levels.\(^15\) This dual mode of action is an attractive therapeutic combination and anecdotally, some patients with LHON have experienced
significant visual recovery following treatment with idebenone. In collaboration with clinical partners in the UK, Germany, and Canada, we therefore conducted a multicentre double-blind randomised controlled trial (RCT) to investigate the safety/tolerability, and efficacy of high-dose idebenone in LHON. RHODOS (Rescue of Hereditary Optic Disease, Outpatient Study) successfully enrolled 85 patients harbouring the three most common mtDNA LHON mutations: m.3460G > A (n=11), m.11778G > A (n=57), and m.14484T > C (n=17). These patients were randomised in a 2:1 ratio to receive either high-dose idebenone (300mg) or placebo over a 24-week treatment period. A major finding of the RHODOS trial is that patients with LHON were more likely to benefit from idebenone if they were treated relatively early in the course of the disease (Figure 2). No adverse drug reactions were reported and idebenone is currently under review by the European Medicines Agency for regulatory approval. Besides idebenone, other neuroprotective agents are also being investigated as potential treatment options in LHON. In an attempt to rescue the disease phenotype, to circumvent these technical difficulties, a possible solution is the so-called allotopic approach where the gene of interest is transfected into the nuclear genome, and the encoded protein is engineered with a specific targeting sequence that facilitates its uptake into the mitochondrial compartment. RGC loss was dramatically reduced, in both in vitro and in vivo experimental LHON models, by transfecting them with an adenovirus vector containing the human SOD2 gene. In these conditions of heightened oxidative stress, the overexpression of the antioxidant enzyme superoxide dismutase is thought to promote RGC survival by exerting an anti-apoptotic influence. Another attractive and more direct approach is to replace the dysfunctional subunit encoded by the mtDNA LHON mutation. Proof of concept has recently been demonstrated in a rat model harbouring a defective ND4 gene with the m.11778A-G mutation. Visual loss was reversed by transfecting RGCs with the wild-type version of the ND4 gene, the level of transept expression being sufficient to rescue RGCs and maintain normal physiological responses.

Looking into the future

RHODOS is the first RCT for a primary mitochondrial disorder and the results obtained with high-dose idebenone are encouraging. A number of novel neuroprotective agents are currently in the pipeline for other mitochondrial cytopathies and these could also prove beneficial for patients with LHON. Gene therapy is a valid complementary approach to pharmacological intervention but long-term safety data is essential before human clinical trials can be advocated. After two decades of sustained research, we are now at the start of an exciting translational phase not only for LHON, but for other mitochondrially-determined optic neuropathies, which as a group represent an important cause of chronic visual morbidity in the population.

REFERENCES