Genetics and treatment of Leber's hereditary optic neuropathy (LHON)

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INTRODUCTION

German ophthalmologist, Theodore Leber (1840-1917), described Leber's hereditary optic neuropathy (LHON) for the first time (Puomila et al., 2007). LHON is one of the most common inherited optic neuropathies, with an approximate disease prevalence of 1 in 30,000 (Man et al., 2003). LHON is mostly detected between 15 and 35 years of age, but the range of onset can vary between childhood and over 60 years (Nikoskelanien et al., 1996; Howell, 1997). The age of onset is slightly higher in females (19-55 years, average being 31.3 years) than males (15-53 years, average being 24.3) (Leber, 1871; Howell, 1997). LHON affects mostly males, 80% of patients being male (Spruijt et al., 2007). There may be differences in male to female ratio between mutations: 3:1 for m.3460G>A, 6:1 for m.11778G>A and 8:1 for m.14484T>C. The cause of this predominance is still undetermined.

Almost one in three cases have no definite family history (Man et al., 2003). Patients present with painless visual loss and both eyes become affected either simultaneously (25% of patients) or sequentially (75% of patients). The time difference between the effect of two eyes is about 8 weeks (Huoponen, 2001). Unilateral cases of LHON can rarely be seen (Newman et al., 1991). 5–6 weeks after the onset, visual acuity may severely be reduced to 6/60 or less. Fundus examination reveals a characteristic appearance and discloses changes that consist of a circumpapillary telangiectatic microangiopathy, edema of the retinal nerve fiber layer, tortuosity of the vessels and disc swelling (Harding et al., 1995). But, up to 20–25% of cases may have a normal fundus appearance in the acute stage. The characteristic field defect in LHON is a central scotoma. Visual field examination reveals central or centrocecal defect. In the chronic stage, the loss of retinal ganglion cells results in optic atrophy (Newman et al., 1991; Harding et al., 1995).

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Rarely, visual recovery is seen even several years later (Stone et al., 1992). The chances of visual recovery depends on the type of the mutation, being least with the m.11778G>A mutation that causes the most severe visual loss, and highest with the m.14484T>C mutation; the m.3460G>A mutation discloses an intermediate prognosis. Central visual field defect and dyschromatopsia can also be permanent (Newman et al., 1991; Mackey and Howell, 1992; Nikoskelainen et al., 1994; McFarland et al., 2007; Ortiz et al., 1992). The majority of patients with LHON are legally blind (Ortiz et al., 1992). Neurological examination sometimes reveals LHON plus syndrome which consists of postural tremor, cerebellar ataxia and loss of deep tendon reflexes (Flanagan and Johns, 1993; Funakawa et al., 1995; Newman, 1993; Nikoskelainen et al., 1995). LHON plus has been detected both in the presence (Van Senus, 1963; Gropman et al., 2004) and absence of mtDNA mutations (Abu-Amero et al., 2005).

OPTIC NERVE AND MITOCHONDRIA

The concentrations of mitochondria at the optic disc are high, showing the increased dependence of the optic nerve on the mitochondria. Studies have shown that mitochondria were high in the prelaminar and intralaminar regions (extending into the lamina cribrosa), but low in the retrolaminar region, revealing that they were mainly in the unmyelinated part of the optic nerve (Melov et al., 1997). Some studies point to a defect in the function of the respiratory chain which can create either a defect in ATP synthesis or an increase of oxidative stress (Brune, 2003). According to histopathological studies, there is selective loss in the retinal ganglion cells and the temporocentral portion of the optic nerve is more affected (Howell, 1997). According to histological evidence, there is impaired axonal transport due to mitochondrial dysfunction (Howell, 1998). Most likely, oxidative stress affects the oligodendrocytes of the optic nerves and mitochondria in optic nerve cells which become unable to produce energy resulting in cell death. The process of programmed cell death (PCD) is named as apoptosis (Barron et al., 2004). Some biochemical changes cause the loss of cell membrane, cell shrinkage, chromatin condensation and chromosomal DNA fragmentation. Mitochondria contain pro-apoptotic elements like Smac/DIABLO, apoptosis-inducing factor and cytochrome C. These elements are released through pores in the mitochondrial membrane by apoptotic signals like free radical damage, growth factor deprivation and cell stress. Moreover, nitric oxide can also induce apoptosis by changing the membrane potential of mitochondria (Wang et al., 2008). The evidence suggests that pathology of LHON is related to apoptosis. The change in the optic nerve happens by swelling of mitochondria and cytochrome C (Danielson et al., 2002). It was also suggested that ubiquinone and complex I cause the opening of the mitochondrial pores. These results show that apoptosis plays a major role in LHON (Carelli et al., 2002; Ghelli et al., 2003).

MITOCHONDRIAL DNA MUTATIONS AND GENETIC TESTING IN LHON

Leber reported young men in four families who had visual loss with a maternal inheritance pattern in 1871 (Leber, 1871; Kerrison and Newman, 1997). Wallace found the mutation at nucleotide position 11778 in patients with LHON in 1988. This was reported as a G to A mutation. Then, short time later, a G to A point mutation at nucleotide position 3460 and a T to C mutation at nucleotide 14484 were reported (Huoponen et al., 1991; Howell et al., 1991; Erickson, 1972; Wallace et al., 1988; Newman et al., 1991).

The modern era of genetic investigations in LHON started with these preliminary findings (Mackey and Howell, 1992; Johns et al., 1992). The three mutations described above are called ‘primary’ mutations. And they are responsible for about 95% of the mutations in LHON (Mackey et al., 1996; Brown et al., 1997; Wallace et al., 1999; Nakamura, 1993; Kim et al., 2003). The 11778 mutation is responsible for 50–70% cases, the 14484 mutation for 10–15% cases and the 3460 mutation for 8–25% cases (Newman, 1993). Some polymorphic mtDNA variants have also been detected and they are thought to affect the clinical expression of the primary mutations (Carelli et al., 2004; Valentino et al., 2004; Zhadanov et al., 2005). There are also ‘secondary’ mutations and these cannot cause LHON in isolation, but the presence of them plus one of the primary mutations seems to lead to LHON. An example is the 11778 primary mutation in addition to secondary mutations 4216,13708 and 15257 causing LHON (Brown et al., 2002; Chinnery et al., 1999).

If genetic testing for a patient with LHON is necessary, then the presence of the three primary mutations should be checked. In case the test is positive, then the result is reported. If the three primary mutations cannot be found, then the secondary mutations are tested (Hofhaus et al., 1996; Battisti et al., 2004; Zanna et al., 2003). Some of the secondary mutations are m.4216T>C, m.13708G>A and m.15257G>A. Secondary mutations should be interpreted cautiously because they may also be found in the normal general population (Howell et al., 1995; Hudson et al., 2007). In case secondary mutations are not found, then very rare mutations listed in Mitomap can be tested too (Table 1). The majority of mtDNA mutations are homoplasmic in LHON and because of that, heteroplasmy level is not important (Abu-Amero and Bosley, 2006, 2007; Abu-Amero et al., 2007, 2006;
Table 1. The Mitomap.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Nt ∆</th>
<th>AA ∆</th>
<th>AA Cons</th>
<th>Patient percent</th>
<th>Control percent</th>
<th>Het. b</th>
<th>Penetrance c % relatives</th>
<th>Penetrance c % males</th>
<th>Percentage recovery d</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTND4*LHON11778A</td>
<td>G-A</td>
<td>R340H</td>
<td>H</td>
<td>69</td>
<td>0</td>
<td>+/-</td>
<td>33-60</td>
<td>82</td>
<td>4</td>
</tr>
<tr>
<td>MTND1*LHON3460A</td>
<td>G-A</td>
<td>A52T</td>
<td>M</td>
<td>13</td>
<td>0</td>
<td>+/-</td>
<td>14-75</td>
<td>40-80</td>
<td>22</td>
</tr>
<tr>
<td>MTND6*LHON14484C</td>
<td>T-C</td>
<td>M64V</td>
<td>L</td>
<td>14</td>
<td>0</td>
<td>+/-</td>
<td>27-80</td>
<td>68</td>
<td>37-65</td>
</tr>
<tr>
<td>MTND1*LHON3635A</td>
<td>G-A</td>
<td>S110N</td>
<td>H</td>
<td>Rare</td>
<td>0</td>
<td>+/-</td>
<td>29 (range 11-64)</td>
<td>54 (range 25-100)</td>
<td>Low</td>
</tr>
<tr>
<td>MTND1*LHON3700A</td>
<td>G-A</td>
<td>A112T</td>
<td>H</td>
<td>Rare</td>
<td>0</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>UN</td>
</tr>
<tr>
<td>MTND1*LHON3733A</td>
<td>G-A</td>
<td>E143K</td>
<td>H</td>
<td>Rare</td>
<td>0</td>
<td>+/-</td>
<td>24-30</td>
<td>36-44</td>
<td>Yes</td>
</tr>
<tr>
<td>MTND1*LHON4171A</td>
<td>C-A</td>
<td>L289M</td>
<td>H</td>
<td>Rare</td>
<td>0</td>
<td>+/-</td>
<td>46</td>
<td>47</td>
<td>Yes</td>
</tr>
<tr>
<td>MTND4L*LHON10663C</td>
<td>T-C</td>
<td>V65A</td>
<td>L</td>
<td>Rare</td>
<td>0</td>
<td>-</td>
<td>56</td>
<td>60</td>
<td>UN</td>
</tr>
<tr>
<td>MTND6*LHDYT14459A</td>
<td>G-A</td>
<td>A72V</td>
<td>M</td>
<td>Rare</td>
<td>0</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td>MTND6*LHON14482A</td>
<td>C-A</td>
<td>M64I</td>
<td>L</td>
<td>Rare</td>
<td>0</td>
<td>+/-</td>
<td>NA</td>
<td>89</td>
<td>Yes</td>
</tr>
<tr>
<td>MTND6*LHON14482G</td>
<td>C-G</td>
<td>M64I</td>
<td>L</td>
<td>Rare</td>
<td>0</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>UN</td>
</tr>
<tr>
<td>MTND6*LHON14495G</td>
<td>A-G</td>
<td>L60S</td>
<td>H</td>
<td>Rare</td>
<td>0</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td>MTND6*LHON14502C</td>
<td>T-C</td>
<td>I58V</td>
<td>H</td>
<td>Rare</td>
<td>0</td>
<td>-</td>
<td>14502:10%</td>
<td>14502:11%</td>
<td>UN</td>
</tr>
<tr>
<td>MTND6*LHON14568T</td>
<td>C-T</td>
<td>G36S</td>
<td>M</td>
<td>Rare</td>
<td>0</td>
<td>-</td>
<td>14502+11778:37%</td>
<td>14502+11778:47%</td>
<td>UN</td>
</tr>
</tbody>
</table>

H, High amino acid conservation; M, moderate; L, low; NA, not applicable; Ter, termination codon.
Het., Heteroplasmy; +, detected; -, not detected.
NA, not applicable; UN, unknown; penetrance values are rough estimates.
Low, anecdotal low degree of vision recovery; Yes, anecdotal moderate to high degree of vision recovery; UN, unknown; NA, not applicable.

Fraser and Ross-Cisneros, 2008; La Morgia et al., 2010. In families with the disease, almost 90% of the carriers are homoplasmic for the mutation and the remainder may be heteroplasmic. In case the mutational load is below 60% which is the threshold for the onset of the disease, the risk is low (Man et al., 2003; Yu-Wai-Man et al., 2009; Fraser et al., 2010; Harding et al., 1992). Male carriers can be told that their offspring will not inherit the genetic defect, but the female carriers will transmit the mutation (Cree et al., 2009). It is very difficult to predict whether a carrier will lose vision, but some other factors like sex, age and environment will play a role, too. Male carriers have a higher risk for developing the disease and other factors like smoking or heavy alcohol consumption increase the risk (Harding et al., 1992; Chinnery et al., 2001; Cree et al., 2009; Kirkman et al., 2009; Yu-Wai-Man et al., 2011).

TREATMENT

Coenzyme Q10 is an analogue of quinone and frequently prescribed in mitochondrial disease. The evidence for its treatment effect is limited. Idebenone is a similar compound with better bioavailability (Yu-Wai-Man et al., 2011; Haefeli et al., 2011; Klopstock et al., 2011). It has a dual mode of action; it can bypass complex I inhibition and optimise ATP production (Haefeli et al., 2011; Klopstock et al., 2011). There are studies showing that significant visual recovery can be achieved with Idebenone treatment (Cree et al., 2009). High dose Idebenone treatment was also tested by RHODOS (Rescue of Hereditary Optic Disease Outpatient Study). Eighty-five patients were involved in the placebo controlled, double-blind study. The patients were randomised to receive either high-dose idebenone (900 mg) or placebo during a 24 week study. No adverse drug reactions were detected. Patients, especially the ones treated early after onset, enjoyed better vision than placebo (Giordano et al., 2011).

Idebenone has currently been under review by
Table 2. Other candidate Leber’ s hereditary optic neuropathy mutations found as single family or singleton cases.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Nt Δ</th>
<th>AA Δ</th>
<th>AA Cons H</th>
<th># Patients</th>
<th># Controls</th>
<th>Het. a</th>
<th>Recovery b</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTND1*LHON4025T</td>
<td>C-T</td>
<td>T240M</td>
<td>M</td>
<td>1 family; 3 cases</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTND2*LHONS5244A</td>
<td>G-A</td>
<td>G259S</td>
<td>H</td>
<td>1 case</td>
<td>0</td>
<td>+</td>
<td>UN</td>
</tr>
<tr>
<td>MTND2*LHON4640A</td>
<td>C-A</td>
<td>I57M</td>
<td>L</td>
<td>1 family; 4 cases</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTND3*LHON10237C</td>
<td>T-C</td>
<td>I60T</td>
<td>H</td>
<td>1 family; 2 cases</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTND4*LHON11253C</td>
<td>T-C</td>
<td>I165T</td>
<td>H</td>
<td>1 case</td>
<td>0</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>MTND4*LYT11696G/</td>
<td>A-G</td>
<td>V312I</td>
<td>L</td>
<td>1 family; 11 cases</td>
<td>0</td>
<td>+</td>
<td>UN</td>
</tr>
<tr>
<td>MTND6*LYT14596A</td>
<td>G-A</td>
<td>I26M</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MTND5*LHON12811C</td>
<td>T-C</td>
<td>Y159H</td>
<td>M</td>
<td>1 family; 2 cases</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTND5*LHON12848T</td>
<td>C-T</td>
<td>A171V</td>
<td>H</td>
<td>1 case</td>
<td>0</td>
<td>+</td>
<td>UN</td>
</tr>
<tr>
<td>MTND5*LHON13051A</td>
<td>G-A</td>
<td>G239S</td>
<td>H</td>
<td>1 family; 3 cases</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTND5*LHON13637G</td>
<td>A-G</td>
<td>Q434R</td>
<td>L</td>
<td>1 family; 3 cases</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTND5*LHON13730A</td>
<td>G-A</td>
<td>G465E</td>
<td>M</td>
<td>1 case</td>
<td>0</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>MTND6*LHON14279A</td>
<td>G-A</td>
<td>S132L</td>
<td>M</td>
<td>1 family; 2 cases</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTND6*LHON14325C</td>
<td>T-C</td>
<td>N117D</td>
<td>L</td>
<td>1 case</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTND6*LHON14498T</td>
<td>C-T</td>
<td>Y59C</td>
<td>M</td>
<td>1 case</td>
<td>0</td>
<td>+/-</td>
<td>UN</td>
</tr>
<tr>
<td>MTATP6*LHON9101C</td>
<td>T-C</td>
<td>I192T</td>
<td>L</td>
<td>1 case</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTCO3*LHON9804A</td>
<td>G-A</td>
<td>A200T</td>
<td>H</td>
<td>Multiple unrelated singleton cases</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
<tr>
<td>MTCYB*LHON14831A</td>
<td>G-A</td>
<td>A29T</td>
<td>M</td>
<td>1 case</td>
<td>0</td>
<td>-</td>
<td>UN</td>
</tr>
</tbody>
</table>

H, High amino acid conservation; M, moderate; L, low; NA, not applicable; Ter, termination codon.
Het., Heteroplasmy; +, detected; -, not detected.
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Low, anecdotal low degree of vision recovery; Yes, anecdotal moderate to high degree of vision recovery; UN, unknown; NA, not applicable.

European–agencies (Qi et al., 2007). Gene therapy: The inner membrane of mitochondria is relatively impermeable and a highly efficient vector (for example, adenovirus) is necessary to transfect a sufficient number of mitochondria per cell. A solution for this problem is to bypass the mitochondrial genome by an allotopic approach. The specific targeting sequence that can facilitate its uptake into the mitochondria. This approach may compensate for the mtDNA mutation and the retinal ganglion cell loss may be dramatically reduced (Cree et al., 2009; Qi et al., 2007). In these situations when the oxidative stress is high, enzyme superoxide dismutase exerts an anti-apoptotic effect. In a study, a defective ND4 gene transfect a sufficient number of mitochondria per cell. A solution for this problem is to bypass the mitochondrial genome by an allotopic approach. The specific targeting sequence that can facilitate its uptake into the mitochondria. This approach may compensate for the mtDNA mutation and the retinal ganglion cell loss may be dramatically reduced (Cree et al., 2009; Qi et al., 2007). In these situations when the oxidative stress is high, enzyme superoxide dismutase exerts an anti-apoptotic effect. In a study, a defective ND4 gene in a rat with the m.11778A>G mutation was transected with the wild type version of the ND4 gene and visual loss was reversed.

DISCUSSION

LHON is considered a model for the other mitochondrial diseases. The collected data for LHON may also be important for other conditions. The nerve cell damage in LHON has been found to be similar to the damage in Parkinson’s disease, Alzheimer’s and glaucoma. These neurodegenerative diseases affect millions in the world. The onset and time span of LHON is more rapid compared with other slowly progressing neurodegenerative diseases. For the time being, it is not known for sure whether the genetic mutations are sufficient alone to explain the visual loss. The effects of environmental factors (for example, smoking and excess alcohol) play an important role, too. The combination of genetics and environmental factors are subjects for ongoing research in neurodegenerative diseases. The results of RHODOS have been encouraging and idebenone is being used for the treatment trials of LHON. Other neuroprotective agents and gene therapy will be the subjects of future studies. The findings from this research will be very important for the treatment trials of other mitochondrial diseases.

REFERENCES


