Leber hereditary optic neuropathy: respiratory chain dysfunction and degeneration of the optic nerve

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Abstract

Leber hereditary optic neuropathy (LHON) is an inherited form of bilateral optic atrophy in which the primary etiological event is a mutation in the mitochondrial genome. The optic neuropathy involves a loss of central vision due to degeneration of the retinal ganglion cells and optic nerve axons that subserve central vision. The primary mitochondrial mutation is necessary, but not sufficient, for manifestation of the optic neuropathy and secondary genetic and/or epigenetic risk factors are also involved, although they are poorly defined at the present time. There is broad agreement that mutations at nucleotides 3460, 11778 and 14484 are primary LHON mutations, but there may also be other rare primary mutations. It appears that the three primary LHON mutations are associated with respiratory chain dysfunction, but the derangement may be relatively subtle. There is also debate on whether there are mitochondrial mutations that have a secondary etiological or pathogenic role in LHON. The specific pattern of neurodegeneration in LHON may arise from a ‘chokepoint’ in the optic nerve in the region of the nerve head and lamina cribosa and which may be more severe in those LHON family members who become visually affected. It is hypothesized that the respiratory chain dysfunction leads to axoplasmic stasis and swelling, thereby blocking ganglion cell function and causing loss of vision. In some LHON patients, this loss of function is reversible in a substantial number of ganglion cells, but in others, a cell death pathway (probably apoptotic) is activated with subsequent extensive degeneration of the retinal ganglion cell layer and optic nerve. © 1998 Elsevier Science Ltd. All rights reserved.

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1. Introduction

In 1871, Theodor Leber [1] described an inherited form of bilateral optic atrophy that has subsequently been designated Leber hereditary optic neuropathy or LHON (reviewed in [2–6]. It was first observed by Leber [1] and subsequently confirmed in numerous studies, that the risk of vision loss in LHON families is inherited exclusively from the mother. This pattern of maternal inheritance signifies that the primary etiological event in LHON is a mutation within the mitochondrial genome (mtDNA), a unique feature among the optic nerve degenerative disorders.

LHON involves a degeneration of the retinal ganglion cell layer and the accompanying axons of the optic nerve and it is one of a group of optic neuropathies. Optic nerve disease represents a major public health issue. For example, the Baltimore eye survey found that 5.0% of their study population suffered from some form of optic nerve disease, 3.6% of whom had probable or definite glaucoma and 1.4% of whom were affected with a nonglaucomatous optic neuropathy [7]. Quigley [8] has estimated that 66 million people worldwide are affected with glaucoma. Although LHON is a relatively rare eye disease and its etiology is complex, it may provide a model system for the experimental analysis of optic nerve disease. The primary mtDNA mutation is necessary, but not sufficient, for the manifestation of the optic neuropathy and secondary etiologic factors are involved (Fig. 1). This review will discuss the possible pathways that link the primary LHON mutations to the ultimate end-stage, optic nerve degeneration. Further understanding of these pathways...
in LHON should eventually define those structural or functional sites that are the common steps in degeneration of the optic nerve degeneration in a number of disorders and which can be targeted in therapeutic strategies.

2. Primary LHON mutations

Wallace et al. [9] showed that a mutation at mtDNA nucleotide 11778 was a primary etiological factor in establishing the risk of the optic neuropathy in LHON. The 11778 primary LHON mutation changes a highly conserved arginine residue to histidine at amino acid position 340 (designated ND4/R340H) of the ND4 subunit of complex I (NADH-ubiquinone oxidoreductase). There is now broad agreement that sequence changes at nucleotides 3460 (ND1/A52T) and 14484 (ND6/M64V) are also primary LHON mutations and that these three mutations account for the vast majority of LHON cases (reviewed in [10–14]). Mackey et al. [15] analyzed 159 LHON families (totalling over 12000 members, more than 1400 of whom have been affected) from Northern Europe, the United Kingdom and Australia. It was found that 153 families (96%) carried either the 3460 (21 families), the 11778 (109 families), or the 14484 (23 families) primary LHON mutations.

Beyond the broad agreement about these three primary mutations, however, there is considerable debate over the mutational spectrum of LHON. There are reports of rare primary LHON mutations [16,17]. For example, we have recently analyzed a Turkish LHON family in which there is a primary LHON mutation in the ND6 gene at nucleotide 14482 which affects the same amino acid residue as the 14484 primary mutation [18]. It has also been proposed that there are mtDNA mutations that have an intermediate or secondary etiological role. For example, a primary role has been proposed for a mutation at nucleotide 15257 that alters an amino acid residue (D150N) in the protonmotive cytochrome b subunit of complex III [13,14]. However, other investigators have concluded that this sequence change is probably a benign polymorphism [15,19]. In summary, there may be a relatively large number of mtDNA mutations that have some role in LHON and Brown and Wallace [10] list a total of 16 LHON mutations (their Table 1). Despite this controversy, the main point is that more than 95% of all LHON patients carry one of three mtDNA mutation that alters a complex I subunit.

Vision loss in LHON is usually permanent, but some patients show objective improvement, sometimes to a dramatic degree. Recovery is rare in affected individuals who carry the 11778 primary mutation; for example, Johns [13] cites a frequency of 4% (see [20] for a well-documented case). In marked contrast, approximately one-half of all 14484 LHON patients show recovery; the frequency of improvement is particularly high in those who lose vision before the age of 30 years.

<table>
<thead>
<tr>
<th>Country</th>
<th>3460 (%)</th>
<th>11778 (%)</th>
<th>14484 (%)</th>
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<tbody>
<tr>
<td>Australia / NZ</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13</td>
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<tr>
<td>United Kingdom</td>
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<td>18</td>
<td>ND</td>
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<td>Netherlands</td>
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<td>Denmark</td>
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<td>Finland</td>
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ND, no data.

<sup>a</sup> Penetrance was calculated only if the total number of matrilineal progeny was >100.

<sup>b</sup> Penetrance was calculated by summing the number of affected males and females and then expressing this number as a percentage of the total matrilineal progeny.
3. The optic neuropathy in LHON

The initial symptom in LHON typically is a blurring or clouding of vision that progresses, usually without pain, over a period of weeks or months to its nadir. Both eyes are often affected simultaneously and with very rare exceptions, vision loss is bilateral. The initial field defect is an enlargement of the blindspot that progresses to an absolute central or cecocentral scotoma. Loss of visual acuity is typically severe and complete blindness can occur; dyschromatopsia is invariably present. The mean age of onset is in the mid-20’s for both sexes, although the range is remarkably broad, ranging from children under the age of 10 years to adults in their 70’s. An early change in the acute phase is a pseudodema of the nerve fiber layer and hyperemia of the optic disk; the disk subsequently ‘flattens’ and becomes pale during the atrophic phase. The peripapillary nerve fiber layer disappears, initially in the papillomacular bundle. A common feature of LHON is a peripapillary microangiopathy, first described by Leber [1], which involves tortuous vessels in the central retina and telangiectatic capillaries (reviewed in [22,4,5]). The microangiopathy is present both in presymptomatic individuals and in affected individuals during the acute phase, but it resolves during the atrophic phase.

Electrophysiological studies of LHON patients have been reviewed by Sherman and Kleiner [3]. During the early acute phase, the visual evoked potentials (VEPs) become desynchronized, the amplitudes are decreased and the latencies are prolonged. At the atrophic stage, the VEPs are almost always extinguished, which indicates the loss of retinal ganglion cell function. In contrast, flash electroretinograms (ERG) and electrooculograms (EOG) are normal, or nearly so, indicating functional integrity of the photoreceptors, bipolar cell layer and retinal pigment epithelium. A peculiar feature of LHON is the frequent preservation of pupillary responses [3,23,5]. The photic blink reflex is also preserved in LHON patients, but not in non-LHON patients with bilateral optic atrophy [24]. The nerve fibers that control the pupillary response and the photic blink response are thought to terminate in pregeniculate structures and the preferential sparing of these pathways in LHON indicates that the optic nerve axons which terminate in the lateral geniculate nuclei are affected in LHON [3,24].

Several studies have addressed the neuropathology of LHON (reviewed in [6]). Those studies were usually performed on patients who lost vision many years prior to death and it may be risky to extrapolate to the neuropathological status at the time of the acute phase. These limitations notwithstanding, LHON is consistently associated with a degeneration of the ganglion cell layer and optic nerve without signs of a marked inflammatory process.

LHON family members can display additional abnormalities including peripheral neuropathy, tremor, CNS signs and heart conduction defects [25,4,26]. There also appears to be an increased incidence of an MS-like demyelinating disorder in LHON families, (e.g. [27,28]). In addition to ‘classical’ LHON families, in which the optic neuropathy is the dominant pathology, there is a second group of families in which severe neurological abnormalities predominate. For example, Wallace and co-workers have analyzed ‘LHON plus dystonia’ families who carry a pathogenic mutation at nucleotide 14459 (ND6/A72V; [29,30]). The proximity of this mutation to the primary LHON mutation at nucleotide 14484 is striking. De Vries et al. [31] have recently shown that a large Dutch family, in which the LHON-like optic neuropathy is associated with maternally transmitted hereditary spastic dystonia, carries both a heteroplasmic mutation at nucleotide 11696 (ND4/V312I) and a homoplasmic mutation at nucleotide 14596 (ND6/M26I); either or both of these mutations may be the primary pathogenic event. Wallace [32] described a LHON family in which the optic neuropathy was associated with an array of neurological abnormalities including ataxia, dystonia and a juvenile onset encephalopathy. The analysis of the mtDNA from this family suggests that the neurological abnormalities are caused by a mutation at nucleotide 4160 which affects the ND1 subunit while the optic neuropathy is caused by the 14484 primary LHON mutation [11].

4. LHON and incomplete penetrance

The optic neuropathy in LHON families shows incomplete penetrance. Historically, ≈50% of the males and 10% of the females in large European LHON families lost vision, (e.g. [22,4]). This incomplete penetrance indicates that, in addition to the primary mtDNA mutation, secondary genetic and/or epigenetic factors are necessary (Fig. 1). In ≈15% of LHON patients, the primary mutation is heteroplasmic: one mtDNA subpopulation carries the wildtype allele and another carries the mutant allele, (e.g. [33,34]). Loss of vision is rare unless the proportion of the primary mutation is >75%. Heteroplasmy of the primary mutation, however, cannot provide a general explanation for
the incomplete penetrance because most LHON families are homoplasmic for the primary mutation. The marked disparity in penetrance between males and females initially suggested an X-linked susceptibility locus [35]. More recent studies have failed to locate such a locus, (e.g. [36,37]) and male predominance may be due to gender-based physiological and/or anatomical differences. Heavy alcohol and/or tobacco use increases the risk of the optic neuropathy in LHON family members [13,4,26], but other environmental or physiological results have also been associated with the onset of the acute stage. One of the difficulties in ‘pinning down’ the secondary risk factors in LHON is that it is not clear if they act immediately prior to the onset of the acute phase.

Johns and Berman [38] observed that sequence changes ND1/Y304H (at nucleotide 4216), ND2/N150D (4917) and ND5/A458T (13708) may act as secondary LHON mutations. There is a strong association of the 11778 and 14484 primary mutations with a European-specific haplotype that is defined by the presence of the 4216 and 3708 secondary LHON mutations [39,14,40]. The mtDNA haplotypes that carry the 4216, 4917, or 13708 secondary mutations form a single monophyletic cluster and each mutation has arisen once within this cluster [41]. Therefore, the 11778 and 14484 primary LHON mutations cannot be increasing the frequency at which the secondary mutations arise or are fixed within the population. Furthermore, the 11778 and 14484 primary mutations have arisen multiple times within this phylogenetic cluster [41] and a marked ‘founder’ effect is therefore an unlikely explanation (see also [42]). These secondary mutations may increase the penetrance of the optic neuropathy [14,42]. Among 11778 Australian LHON families, the penetrance of the optic neuropathy was higher in families whose mitochondrial genomes carry the 4216 and 13708 secondary LHON mutations than in those who do not [43], but other studies have found no pathogenic effect of these secondary mutations [19]. It is also possible that primary LHON mutations arise and/or fixed more frequently in the 4216/13708 mtDNA haplotype.

The hypothesis that penetrance in LHON pedigrees is a function of the mtDNA haplotype may be extremely difficult to test because penetrance is sensitive to a number of poorly defined factors. The results in Table 1 summarize the extensive data of Mackey et al. [15]. For each of the three primary mutations, penetrance varies more than 2-fold among different study populations. Penetration is difficult to measure accurately because of the marked variability in age of onset among individuals and the values in Table 1 were derived by simply dividing the number of affected individuals by the total number of matrilineal progeny. Furthermore, simple classification into ‘affected’ and ‘non-affected’ may be misleading because there are LHON family members who report no vision problems but who have objective signs of optic neuropathy, (e.g. [18]).

5. Mitochondrial respiratory chain dysfunction in LHON

It seems obvious that, because LHON mutations alter complex I subunits, the clinical defects result from respiratory chain dysfunction. However, such a straightforward association has been difficult to prove. Larsson et al. [45] isolated mitochondria from affected and unaffected members of an 11778 LHON family and they found no decrease in complex I specific activity (or in any other respiratory chain complex). On the other hand, flux through the entire chain with NADH-linked substrates was decreased to about one-half of the values found in mitochondria from normal controls. There was no decrease in flux with succinate as substrate, which enters the chain through complex II. The authors suggested that complex I function was impaired in its association with the proximal dehydrogenases. Essentially the same results were obtained by Majander et al. [46] in studies with EB-virus transformed lymphocytes from 11778 LHON patients. Smith et al. [47] detected a small decrease (25%) in platelet mitochondrial complex I specific activity when non-smoking 11778 LHON patients were compared to non-smoking controls; no difference was found when smokers were included in the two groups. Vergani et al. [48] have constructed cybrid lines in which mitochondria from control or 11778 LHON patients were transferred to cells that lack their own mtDNA (designated rho-zero lines). The 11778 primary LHON mutation caused decreased cellular respiration and lower mitochondrial complex I specific activity, although the latter decrease was not statistically significant. Similarly, there was a 40% decrease in mitochondrial respiration with NADH-linked substrates in another set of 11778 cybrid lines, although there was no decrease in complex I specific activity [49].

Degli Esposti et al. [50] also found that complex I activity in platelet mitochondria of 11778 LHON pa-
tients was not decreased, but-more importantly-they observed increased resistance to rotenone, as well as changes in the affinity of the complex for ubiquinone substrate analogs. They suggested that the arginine residue that is altered by the 11778 LHON mutation occurs in a region of the ND4 subunit which is involved in quinone reduction and that the substitution with histidine may result in decreased stability of the semiquinone intermediate during redox catalysis. They further speculated that this catalytic 'short circuit' in their terminology may not decrease complex I turnover, but that it could decrease the oxidation rates of NADH-linked substrates because of lowered ubiquinol production (see also the additional studies in [51]).

The results for the 3460 primary mutation have been more clear-cut. In our initial studies [52], platelet mitochondria were isolated from 3460 LHON family members. When specific activities of the respiratory chain complexes were normalized to the specific activity of mitochondrial citrate synthase, there was ~80% reduction in complex I specific activity, whereas there was no reduction in those of complex II or complex IV (cytochrome oxidase). The complex I dysfunction was equally severe in both affected and unaffected LHON family members and in both males and females [52]. Similar results were obtained by Majander et al. [46], Smith et al. [47] and Carelli et al. [51].

The reported effects of the 14484 primary LHON mutation upon respiratory chain function have been contradictory. Parker et al. [53] measured an ~80% reduction in complex I specific activity in platelet mitochondria from QLD1 LHON patients. The interpretation of these results, however, is complicated by the simultaneous presence of the 14484 LHON and 4160 mutations (see above). Cock et al. [54] found no respiratory chain dysfunction in fibroblast mitochondria from '14484 only' LHON patients. Other studies, in contrast, indicate a marked complex I defect in 14484 fibroblast mitochondria (Bindoff, personal communication; [55]). Jun et al. [30] have analyzed respiratory chain function in mitochondria from both EBV-transformed lymphoblast lines and transmitochondrial lymphoblast lines from patients with the 14459 'LHON plus dystonia' mutation. Complex I specific activities were reduced by ~50%, but there is no reduction in mitochondrial respiration with either NADH-linked substrates or with succinate (the inverse pattern that is seen for the 11778 primary LHON pattern).

We have measured the release of lactate and pyruvate from intact, dividing fibroblasts in an effort to avoid the problems that are associated with isolation of mitochondria and the assay of respiratory chain function. The lactate:pyruvate ratio is a sensitive indicator of the NADH/NAD balance and it will be, in large part, 'set' by flux through the mitochondrial respiratory chain. When the respiratory chain is blocked, the NADH generated by the citric acid cycle and glycolysis accumulates and the lactate:pyruvate ratio increases. Our preliminary results indicate that all three primary LHON mutations are associated with mitochondrial respiratory chain dysfunction, although the defect associated with the 11778 mutation appears to be less severe (Howell et al., manuscript in preparation). It is possible that mitochondrial function in the ganglion cell layer may be necessary to maintain the proper NAD/NADH redox balance, rather than for ATP biosynthesis per se, because complex I is the site of NADH reoxidation. Taken together, the biochemical studies are paradoxical because the 11778 primary mutation is the most severe in terms of the optic neuropathy, but apparently the least severe in terms of the severity of the respiratory chain defect. One must be cautious in the interpretation of these biochemical studies, not least because they utilized cell types that are not those pathologically affected.

The causal relationship between mitochondrial mutations and a focal degeneration of the ganglion cell layer and optic nerve suggests that LHON involves neurodegeneration of those cells (viz., retinal ganglion cells) that have the highest demand for mitochondrially-produced energy, (e.g. [56,57]). In fact, however, it has been recognized for 40 years that the photoreceptor layer of the retina is the richest in the enzymes of oxidative metabolism [58]. Furthermore, Ames et al. [59] showed that phototransduction in the rabbit retina was dependent upon energy generated by the mitochondrial respiratory chain, whereas neurotransmission through the inner retina was fueled predominantly by glycolysis (also, see [60]). It appears more likely, therefore, that the retinal ganglion cell layer and optic nerve are selectively affected in LHON, not because they have the highest overall oxidative demand, but because they are the most susceptible to disruption of complex I at a specific point in the vision pathway, metabolic and/or anatomical (see below). There is a 'forgotten' set of studies that support this distinction.

In the 1950's and 1960's, the antibiotic chloramphenicol was used to treat children with cystic fibrosis [61], but this treatment caused an optic atrophy [62–64]. In a presentation that was remarkably similar to LHON, there was a sudden onset, bilateral loss of central vision with the formation of central scotomata; papilloedema and subsequent pallor of the disk were also documented. There was also an engorgement and tortuosity of the retinal veins with occasional retinal hemorrhage. Neuropathological studies revealed degeneration in the ganglion cell layer, degeneration and demyelination of the optic nerve (particularly in the papillomacular bundle) and gliosis of the nerve fiber layer [64]. The use of chloramphenicol in cystic fibrosis patients was undertaken before it was recognized that this antibiotic is a specific inhibitor of mitochondrial
Fig. 2. A proposed biochemical scheme for the optic neuropathy in LHON. The figure shows one possible pathway of the early steps that link the primary LHON mutations and the degeneration of the optic nerve (see text for detailed discussion). There appear to be several different apoptotic pathways and the one shown here is based upon studies in neuronal systems. In addition, the different steps shown may occur simultaneously.

protein synthesis. The characteristics of this optic neuropathy provide the strongest and most direct evidence that the human ganglion cell layer and optic nerve are exquisitely sensitive to the disruption of mitochondrial biogenesis.

6. Models for optic nerve degeneration in LHON

At the present time, much is known about the genetic basis of LHON and progress is being made on the biochemical analysis of the respiratory chain defects. However, relatively little is known about the pathway that connects the respiratory chain dysfunction to loss of vision and neurodegeneration. For the purposes of stimulating further discussion and experimentation, one possible pathway is shown in Fig. 2. There are studies on the microanatomy and histochemistry of the retina and optic nerve, that may explain, at least in part, the selective involvement of the ganglion cell layer and optic nerve in LHON. Burde [65] has developed the ‘disk at risk’ concept in which he identified the anatomical features that are common to several optic neuropathies including LHON: a relatively small optic nerve head, absent or small cup, increased branching of the central retinal vessels within the disk and a crowding or ‘heaping up’ of the nerve fiber layer. He further postulated that the region in and around the lamina cribrosa is particularly vulnerable to ischemia (complex I dysfunction in LHON) because of the limited vascularization. The septae of the lamina cribrosa are more closely packed and thicker walled along the horizontal meridian of the optic nerve [66] and these are the ‘channels’ for the nerve fibers that subserve the central and temporal portion of the visual field, which are the areas most severely affected in LHON (also, see [2]). Significantly, there is an accumulation of mitochondria in the unmyelinated segments of the prelamellar optic nerve axons before they transverse the lamina cribrosa [67,68]. This accumulation of mitochondria indicates impaired or labile axoplasmic transport, a ‘chokepoint’, in this region of the optic nerve. Kageyama and Wong-Riley [67] showed that parafoveal ganglion cells in the monkey retina are less intensely stained for cytochrome oxidase than those in the periphery and that the larger ganglion cells tended to be more intensely stained than those of medium and small size. Their results suggest that parafoveal ganglion cells may be ‘poorer’ in mitochondrial content and thereby more susceptible to disruption of the respiratory chain in the chokepoint.

One can thus envisage that the primary LHON mutation produces a respiratory chain defect that compromises axoplasmic transport and which results in axon swelling and compression of the vessels and nerve fibers, particularly in the lamina cribrosa ‘chokepoint’, but not so severely that there is a frank loss of retinal ganglion cell function (Fig. 1). Further physiological or environmental stress, particularly in those individuals that are anatomically ‘vulnerable’, triggers a more profound slowing of axoplasmic transport to a level that precludes normal functioning of the smaller diameter ganglion cells [65]. According to this hypothetical scheme, the peripapillary microangiopathy in presymptomatic LHON patients may be a secondary consequence of the swelling of the optic nerve axons in the anatomically constricted chokepoint and which resolves during the acute phase because the neurodegeneration relieves the crowding in this region. Riordan-Eva et al. [4] have proposed that the LHON family members who become visually affected may have congenital crowding of the ganglion cell axons at the disk and in the peripapillary region, leading to the preferential degeneration of the smaller diameter M and P ganglion cells.

The respiratory chain dysfunction in LHON may cause ganglion cell and axon swelling through a pathway that activates the mitochondrial permeability transition and activation of the redox-sensitive NMDA (N-methyl-D-aspartate) channel (Fig. 1). Apoptosis is usually triggered by some ‘external’ signal; in nerve cells, for example, by excitotoxic levels of glutamate.
There is accumulating evidence that opening of the mitochondrial transition pore and of the NMDA channel are early steps in apoptotic pathways [69–71]. Skulachev [72] has proposed that the mitochondrial permeability transition is triggered by the build-up of reactive oxygen species, particularly superoxide anion which can result from respiratory chain dysfunction. Exposure of neurons in culture to NMDA caused an increase in mitochondrial ROS production, probably as a consequence of uncoupling of the respiratory chain [73]. It has been shown that rotenone, a Complex I inhibitor, induces apoptosis in some cell lines [74,75]. Complex I is a key site for free radical formation and it is striking that the three most prevalent primary LHON mutations affect Complex I subunits. In LHON, the apoptotic cascade apparently runs ‘in reverse’ because the initial signal is internal (respiratory chain dysfunction), not external.

Although it has not been demonstrated directly, neurodegeneration of the ganglion cell layer and optic nerve in LHON probably occurs through apoptosis, rather than necrosis (Fig. 2). In the first place, the neurodegeneration in LHON has never been associated with the overt signs of inflammation, which accompanies necrosis but is not observed in apoptotic cell death. Secondly, ganglion cell apoptosis has been observed in a wide variety of conditions. (1) During development, the number of retinal ganglion cells is more than twice the number found in the adult retina. The ‘extra’ ganglion cells die through a pathway that has the morphological features of apoptosis and which is prevented by overexpression of the anti-apoptotic bcl-2 protein [76]. (2) Apoptosis in induced by optic nerve axotomy in rodents, but degeneration of the ganglion cell layer is ameliorated by overexpression of bcl-2 [77,78]. (3) Quigley et al. [79] have reported that ganglion cell death in experimental glaucoma occurs by apoptosis. Significantly, there is also considerable evidence that an excitotoxic pathway ‘triggers’ the optic nerve degeneration in glaucoma [80,81]. (4) Levin and Louhab [82] have described a patient with anterior ischemic optic neuropathy in which there were morphological signs of apoptosis in the ganglion cell layer. The apparent involvement of bcl-2 in regulation of apoptosis in the ganglion cell layer is intriguing and it suggests another possible step in LHON neurodegeneration. It has recently been shown that release of mitochondrial cytochrome c is involved at an early step in apoptosis, prior to caspase activation and that bcl-2-which is associated with mitochondria-prevents its release [83,84]. It is attractive to suggest that the respiratory chain dysfunction in LHON can initiate a pathway that involves mitochondrial swelling and release of cytochrome c, which ultimately triggers apoptosis. One must be cautious, however, because there may be multiple apoptotic pathways. Thus, Susin et al. [85] have described a cell system in which bcl-2 blocks apoptosis through inhibition of the release of a 50 K apoptosis-inducing factor (AIF) from mitochondria.

In the case of the 11778 primary mutation, for reasons which are not yet known, the ‘commitment to death’ is made with only rare exception. At the opposite extreme, the commitment to death is much less strong or less frequent for the 14484 primary mutation and a substantial proportion of the retinal ganglion cells can remain inactive but viable for prolonged periods of time. It is important to stress that the neurodegeneration is not an ‘all-or-none’ phenomenon and that it is the extent of ganglion cell death that varies. If this hypothesis is correct, recovery of vision in 14484 LHON patients might occur as the result of a small amount of neurodegeneration, thus reversing the anatomical block to axoplasmic transport in the viable but inactive neurons. This suggested mechanism can also explain the peak incidence of LHON in the mid-20’s: starting in the second decade, there is a slow loss of foveal ganglion cells [86], thus widening the choke-point and commensurately diminishing the subsequent risk of vision loss.

Further investigation will elucidate the intermediate steps between the primary LHON mutations and end-point of retinal ganglion cell and optic nerve neurodegeneration. This additional information will undoubtedly provide many fundamental insights, but more importantly, it will allow the development of therapeutic strategies to prevent or minimize the devastating ophthalmological consequences of these mitochondrial mutations.

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