

Mitochondrial optic neuropathies

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A model for a unifying theory

Many optic neuropathies produce a similar clinical presentation. Investigations show that these optic neuropathies involve inherited or acquired impairments of mitochondrial function. Further reflection on these diseases and the selected sites of injury may provide a useful model of the pathophysiological mechanisms involved.

Recent studies have made clear the molecular basis of an intriguing optic neuropathy: Leber's hereditary optic neuropathy (LHON). This well characterised sub-acute affection of the optic nerves, typically inherited through the maternal line, is due to mitochondrial dysfunction, usually demonstrated to be a consequence of one of three pathogenic point mutations in the mitochondrial DNA (mtDNA).^{1,2,3} All three of these pathogenic mutations affect complex I in the respiratory chain and the biochemical defect they induce is still under investigation. Both an impairment of energy production and/or a chronic increase of reactive oxygen species (ROS) are the potential consequences of the underlying LHON pathogenic mutations leading to optic nerve degeneration.^{4,5}

The disease has many oddities. These include the disproportionate number of men who are affected and the amazing fact that a person will see well for two decades and then suddenly go blind, at about the same time, in both eyes.⁶

The LHON clinical presentation is stereotypic. A previously unaffected person, often a man in his 20s, will present with an acute onset of visual loss in one eye. Within a few days the patient notes a loss of colour vision, a significant loss of visual acuity, and a central visual field defect. Within weeks, the second eye almost always becomes involved in a remarkably similar way.^{6,7}

With this clinical picture in mind, it was quite surprising when we saw tens of thousands of patients with bilateral symmetric visual loss and a similar presentation as part of the epidemic of blindness in Cuba in 1993.^{8,9,10} It would have been preposterous, however, to have expected a mitochondrial mutation to have suddenly affected such an enormous population. Our thinking, therefore, was that whereas LHON represents a genetically determined mitochondrial dysfunction, the Cuban epidemic was possibly affecting mitochondria on an

acquired basis.^{7,8} Indeed, further studies showed that the Cuban patients were in fact affected by a combination of environmental factors leading to impaired oxidative phosphorylation. Prominent among these were formate accumulation secondary to folic acid vitamin deficiency and chronic methanol consumption,^{7,8} other vitamin deficiencies, and exposure to cyanide.¹¹ This leads us to consider the question as to whether other optic neuropathies might also be based on compromises of mitochondrial function.

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Indeed, several optic neuropathies share six prominent clinical features found in both LHON and in the Cuban epidemic:

- Fairly symmetric visual losses
 - Loss of visual acuity and high spatial frequency contrast sensitivity
 - Early and profound loss of colour vision
 - Centrocecal visual field defects (with good preservation of the peripheral field)
 - Temporal pallor of the optic discs (delayed)
 - Preferential loss of the papillomacular bundle of the retinal nerve fibre layer.
- Six classes of optic neuropathies, at minimum, share this remarkable clinical picture:
- Leber's hereditary optic neuropathy (LHON)
 - Cuban epidemic of optic neuropathy (CEON)
 - Tobacco alcohol amblyopia (TAA).
 - Nutritional deficiencies especially the vitamin deficiencies of B-12 and folic acid

- Ethambutol and certain other anti-infectives
- Methanol, cyanide, and other toxins that specifically block oxidative phosphorylation.

There may be some slight variations between these many optic neuropathies, especially in regard to the speed of onset or the extent or severity of visual loss. Some of the optic neuropathies may present early and incompletely. For example, in TAA the central scotomas may be small and only relative whereas in most cases of LHON the scotomas are large and almost absolute. However, all six of these types of optic neuropathies have remarkably similar clinical presentations. The symmetry of involvement and the centrocecal field defects are particularly striking. Cone dystrophies may also occur progressively and symmetrically. However, in cone dystrophies less temporal pallor or atrophy is seen and along with ERG changes, this permits clear distinction.

Before considering the question of how impairment of mitochondrial function leads to an optic neuropathy a more general question must be addressed: In so far as mitochondria are ubiquitous and their functions systemic, why is the pathophysiology of mitochondrial impairment not more widespread? In particular why should mitochondrial dysfunction be largely limited to the nervous system? It turns out that in several of the syndromes described above, there also is found a peripheral neuropathy.^{11,8} Involvement of the peripheral nervous system would suggest that the longest fibres of the nervous system are also selectively vulnerable. Why?

In the CNS, mitochondrial impairments of this type (LHON, TAA, CEON) lead largely to injury to the optic nerve and, to a lesser extent, to the acoustic nerve.^{7,8} Why? Within the optic nerve, there is selective mitochondrial related damage to the centrally located papillomacular bundle of the nerve fibre layer.^{1,7} We need to focus on why this broad collection of mitochondrial optic neuropathies all show preferential involvement of the smallest optic nerve fibres and do so at the specific point where the axons exit the eye.

In considering those agents that are best known to cause optic neuropathy, it is remarkable that most are known to interfere with oxidative phosphorylation. For example, arsenic and cloquinol

Abbreviations: LHON, Leber's hereditary optic neuropathy; ROS, reactive oxygen species; CEON, Cuban epidemic of optic neuropathy; TAA, tobacco alcohol amblyopia; mPTP, mitochondrial permeability transition pore

produce an uncoupling effect on oxidative phosphorylation: carbon monoxide, and cyanide inhibit cytochrome c oxidase (complex IV); ethambutol chelates metals such as copper and iron, which are essential for complex IV and I function, respectively; hexochlorophene also is known to block oxidative phosphorylation: methanol leads to formate which precludes electron transport: plasmodium (an anti-malarial agent) also uncouples oxidative phosphorylation.¹²⁻¹⁵ A few other toxins may have nothing to do with oxidative phosphorylation. For example, INH blocks the production of myelin and leads to a local vasculitis.¹⁴ However, the vast majority of toxic optic neuropathies impair mitochondrial function and have a similar clinical presentation, which involves a symmetric, progressive loss of vision associated with dyschromatopsia, centrocecal scotomas, and the loss of high spatial frequency contrast sensitivity.¹⁶

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It remains to be explained by what pathophysiological mechanism mitochondrial dysfunction produces selective losses, especially of the papillomacular bundle of the optic nerve of the CNS. Mitochondria are now understood to be central to very important cellular functions.¹⁷ Through oxidative phosphorylation they provide most of the ATP necessary for energy dependent functions of cells. As a byproduct, the mitochondria are also the main cellular source of ROS. Finally, mitochondria, mainly through the opening of the mitochondrial permeability transition pore (mtPTP) and the consequent release of cell death promoting factors (such as cytochrome C), may switch on apoptosis. Impairments of oxidative phosphorylation and increased production of ROS may both contribute to the opening of the mtPTP activating the apoptotic cascade and inducing cellular death.

It turns out that both hypotheses, that of energy depletion and that of accumulation of ROS predict the particular vulnerability of those retinal ganglion cells that contribute axons to the papillomacular fibre bundle.

Mitochondrial impairment interferes with oxidative phosphorylation and causes a decrease in ATP that in turn compromises axonal transport. Axonal transport is highly energy dependent and ironically mitochondria themselves

rely critically on this transport system.¹⁸ Hence mitochondria, which arise solely in the soma and have a lifespan of only about 7 to 14 days may not make it to the distal terminals if the efficiency of transport is compromised due to energy depletion. This would only aggravate the energy problem in the distal axon terminals. This situation would be particularly problematic in long fibres, such as those of the peripheral nervous system, or in axons of very narrow calibre, those with minimal or no myelin, and those with a rapid rate of firing. These last three features are all found in retinal ganglion cells of the papillomacular bundle whose high and constant firing rate increases energy demands, whose high surface area to volume ratio favours energy consumption over energy production, and whose lack of myelination deprives them of the efficiency of saltatory conduction. This might also explain why the metabolically very active outer retina does not show more dysfunction in LHON. The inner segments of photoreceptors are filled with mitochondria but there are no threshold effects nor a positive feedback system imposed by the logistics of mitochondrial axonal transport.

Furthermore, this concept shows a vicious cycle by which mitochondrial impairment leads to decreased ATP production, which in turn negatively impacts axonal transport, which leads to further mitochondrial and energy depletion distally. This, therefore, explains the “all or nothing phenomena” seen in LHON and expressed in clinically adult patients who almost always go from normal vision to devastating visual loss in only a couple of days.^{7, 19} Finally, the great distance between these mitochondria transported far down an axon and their nucleus, probably precludes any effective signally pathway that could promote nuclear encoded antioxidants to be provided to counteract the ROS.

In short, the small fibres that constitute the papillomacular bundle of the optic nerve are the “canary in the coal mine” for at least certain types of mitochondrial impairment. These are sensory fibres that constantly fire: they are lightly myelinated after the lamina cribosa and completely unmyelinated in the retina, their axons are fairly long, and by being of low calibre these axons have the lowest volume (energy source) to surface area (energy demands) ratio. In LHON, as well as in other acquired forms of mitochondrial impairment, these optic nerve fibres go first and go quickly. Because these fibres subservise the macula, it is no wonder that in these diseases the control visual field is most adversely affected. Of course, there remain several other questions currently unexplained. For example, in LHON why are men more susceptible than woman

(might it be because of the higher basal metabolic rate found in men that increases the energy demand)? Why are some family members in the pedigree fully affected and the others completely spared (might it be epigenetic or nuclear factors which add insult to injury and cross the threshold in an “all or nothing” system)?

Understanding the pathophysiology of congenital or acquired mitochondrial optic neuropathies suggests certain strategies for treating these neuropathies. Are there ways to unblock oxidative phosphorylation or provide alternative pathways? Are there ways to sop up ROS with free radical scavengers? Idebenone, for example, is a quinone analogue recently used in a few cases of LHON that should ameliorate the net ATP synthesis by providing an alternate pathway, as well as scavenging free radicals (it has the advantage of concentrating readily in mitochondria).²⁰ We may be able to modulate apoptosis by absorbing ROS or by stabilising the mitochondrial membrane. Patients who have already lost vision in one eye from LHON might be excellent candidates for pharmacological manipulation of mitochondrial metabolism to protect the second eye.

Studies along this line have already begun to bear fruit. For example, we are beginning to understand and mitigate in cell culture (by adding copper, iron, and zinc), the mitochondrial optic neuropathy produced by ethambutol.⁷ Such approaches might lead to clinical strategies that would be applicable to a wide range of optic neuropathies.

J Neurol Neurosurg Psychiatry
2002;72:424-426

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