LEARNING OBJECTIVES
1. Describe the clinical characteristics of mitochondrial optic neuropathies (MON)
2. Explain the risk factors of the optic disc size and shape for MON
3. Describe reasons why some glaucomas have mitochondrial impairments as a pathophysiological mechanism

CME QUESTIONS
1. What are the two hereditary MONs?
2. Which hereditary MON may masquerade as glaucoma?
3. What protein helps regulate optic nerve size and is the pathophysiological basis of DOA?

KEYWORDS
1. Mitochondrial Optic Neuropathies
2. Glaucoma
3. Dominant Optic Atrophy

There are several mitochondrial optic neuropathies (MON). There are probably many glaucomas. So perhaps it is not surprising that there exist overlaps in these two conditions. More importantly, however, the pathogenic mechanisms recently elucidated in MON may provide insights and opportunities in the management of at least some glaucomas. Furthermore, there is a growing body of evidence that mitochondrial disease may affect tissues of the eye other than retinal ganglion cells (e.g., trabecular meshwork and the optic nerve) and may even directly alter some of the dynamics that determine intraocular pressure\(^1\). The purpose of this talk and manuscript is to delve into the relationship between mitochondria and glaucoma. In particular, we will address these considerations:
1. There are many similarities between some glaucomas and mitochondrial optic neuropathies (MON).
2. These similarities are greatest for low tension glaucoma that often present with paracentral scotomas that remind us of MON.
3. Dominant Optic Atrophy (DOA) is a hereditary MON with particular connection to glaucoma including the optic disc appearance.
4. Leber’s Hereditary Optic Neuropathy (LHON), another MON, has disc size as a risk factor for visual loss and the severity of this loss (large discs do better).
5. We are exploring the role of OPA-1 on development of the optic nerve as well as the degeneration of DOA.
6. Mitochondrial metabolism and dynamics may play a role in the pathology of glaucoma and provide clues to new therapeutic approaches.

MON represent a group of optic neuropathies that can be genetic, nutritional or toxic in basis\(^2-4\). For example, hereditary mitochondrial optic neuropathy may be in the autosomal form as DOA or maternally inherited through mtDNA mutations as LHON. In the former case, over 212 mutations have been described\(^2\). There are 3 major mtDNA mutations that produce LHON\(^2\). The clinical presentation of MON is characterized by bilateral loss of central vision, dyschromatopsia, central or cecocentral scotomas\(^5,6\). Ophthalmoscopic features during the acute/subacute stage often reveal a hyperemic optic disc and peripapillary retinal nerve fiber layer swelling\(^7\). With time, temporal pallor of the optic disc develops. There is no relative afferent pupillary defect due in part to symmetric optic nerve involvement. The fibers of the papillo-macular bundle (PMB) are most susceptible due to their long unmyelinated segment in the retina and their small caliber. Preferential involvement of the PMB is a feature common to a wide range of acquired and genetic mitochondrial optic neuropathies\(^3,7,8\).

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Nutritional optic neuropathies are often (but not always) mitochondrial as well\(^5\). Deficiencies, especially of B-12 and folic acid can impair mitochondrial metabolic pathways and produce diseases that mimic LHON or DOA. An ever larger body of toxins, especially antibiotics, have been shown to impair mitochondrial function and also mimic or produce a similar clinical profile. Drugs proven to cause MON by blocking oxidative phosphorylation include ethambutol, chloramphenicol, linezolid, erythromycin, streptomycin,
and antiretroviral drugs. Once again, the small fibers of the PMB are the main site of injury.

Leber’s hereditary optic neuropathy is characterized by severe visual loss, which may manifest acutely or subacutely in young adulthood. In 1988, the genetic basis was determined to be due to a mitochondrial DNA (mtDNA) point mutation. This Wallace mutation, at nucleotide 11778/ND4, was discovered first and later 14484/ND6 and 3460/ND1 were established as other common mtDNA mutations. These three mutations affected components of respiratory complex I, and account for about 95% of LHON cases.

The typical story would be that of a young adult male who first notices abrupt and profound loss of vision in one eye, and then, weeks to months later, suffers a similar loss of vision in the other eye. Less commonly, LHON occurs later in life and may occur in women at menopause. There is evidence that estrogen, by controlling mtDNA copy number, is protective, explaining the menopausal association as well as the gender bias for conversion. Environmental factors such as smoke and excessive alcohol, may act as triggers for visual loss in LHON.  

The optic disc can play a role in the pathogenesis of LHON. The optic disc was found to be larger in LHON carriers than in LHON-affected, suggesting that a small optic disc may be a risk factor for LHON carriers to convert to affected. In fact, amongst LHON-affected, larger optic discs were also associated with a better visual outcome and the propensity for some recovery of vision. It is intriguing to consider that mechanical factors, such as those that may play a role in the pathogenesis of glaucoma or anterior ischemic optic neuropathy, may also influence the outcome in LHON.

Dominant optic atrophy is autosomal in genetics and in most cases due to a mutation in the OPA1 gene. It affects both genders equally and usually presents as a slow and insidious progressive visual loss starting in prepubescence. The central scotoma is smaller and grows more slowly than in LHON and the optic disc atrophy usually confined to the temporal side. The temporal disc may also become excavated or cupped in appearance. It is not surprising, then, that the main differential diagnosis in DOA is for low tension glaucoma. Furthermore, the optic disc in DOA is smaller than in controls, suggesting a role for OPA1 in regulating apoptosis and thereby controlling the size and shape of the optic nerve head.

On the flip side, there is substantial evidence that patients with primary open angle glaucoma may have mitochondrial impairment. In particular, Lee and colleagues found that lymphoblasts from glaucoma patients had complex-I impairments leading to decreased ATP production in many ways analogous to that seen in LHON that leads to RGC death. Furthermore, mitochondrial DNA polymorphisms are not uncommon in low tension glaucoma. Hence, it is likely that at least some glaucomas have mtDNA mutations or polymorphisms as a risk factor. Mitochondrial dysfunction probably predisposes RGCs to glaucoma damage. Furthermore, elevations of intraocular pressure may damage mitochondria through oxidative stress.

This overlap in glaucoma and mitochondrial impairment that leads to retinal ganglion cell (RGC) death should not be surprising. We are reminded that RGCs are probably exquisitely sensitive to mitochondrial dysfunction due to their having a very long unmyelinated segment and that the PMB fibers, by virtue of their small caliber, have a particularly poor “mitochondrial stress index” imposed because of the exposed membrane-to-mitochondrial volume ratio. Superimposed, of course, may be stressors at the lamina cribrosa that relate to pressure gradients.

The role of mitochondria in apoptosis makes it a major “final common pathway”. Glaucosa is now sometimes viewed as a neurodegenerative disease of the optic nerve. The accelerated death of RGCs and their axons may be due to primary mitochondrial impairment and the role of mitochondria in apoptosis. Neuro-opthalmologists and glaucoma specialists interested in the optic nerve head, have much to talk about.

CME ANSWERS
1. LHON and DOA
2. DOA
3. OPA-1

REFERENCES


