MITO 101 - Ophthalmology

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Key Points

- Ocular complications are common in mitochondrial disorders and depend on the underlying mutation.
- Patients can have optic nerve disease and atrophy, which can be the only manifestation such as in LHON.
- Eye muscle problems can cause ocular misalignment and drooping of the lids as in chronic progressive external ophthalmoplegia.
- Retinal disease causes rod and/or cone photoreceptor cell dysfunction with color vision abnormalities or a degeneration that looks like retinitis pigmentosa.
- Patients with mitochondrial diseases should undergo periodic eye examination that may include specific testing of optic nerve or retinal function.

Retinal Disease

- The retina is made of several types of neurons, including rods and cones (photoreceptors), ganglion cells, and other types of cells. The photoreceptors depend on a healthy retinal pigment epithelium (RPE) for their appropriate functioning. The RPE is one of the most metabolically active layers of cells in the body and is very rich in mitochondria: hence any significant mitochondrial dysfunction has the potential to lead to photoreceptor dysfunction and retinal degeneration. Furthermore, ganglion cell disease will lead to optic atrophy.
- Cone dysfunction has been observed in a number of mitochondrial cytopathies, although the literature on the subject is scant. Cone dysfunction leads to color vision deficits, central vision loss with decreased visual acuity, and visible macular changes in some patients. Cone dysfunction can be detected using electroretinography.
- Rod dysfunction causes loss of peripheral vision and night blindness. There are several clinical syndromes that result from specific mitochondrial DNA mutations that feature retinal degeneration as a major clinical component (Table).

Optic Nerve Disease

- The optic nerve is made of axons that originate from retinal ganglion cells. These cells constitute the innermost layer of the retina and for unclear reasons may be selectively involved in certain mitochondrial cytopathies in which retinal photoreceptors are spared. In these situations, the electroretinogram is normal while the visual evoked potentials are reduced.
- One disorder in which the optic nerve is selectively affected with no other systemic or neurological abnormalities in most patients is Leber hereditary optic neuropathy (LHON) (Table). Mitochondrial dysfunction is also responsible for an autosomal dominant form of optic neuropathy (DOA) called Kjer optic atrophy.
- Optic atrophy has been observed in a variety of mitochondrial cytopathies in which one or more of the protein complexes involved in oxidative phosphorylation are dysfunctional.

Eye Muscle Weakness

- Extraocular muscles (of which there are six) and the levator palpebrae muscle are very susceptible to mitochondrial dysfunction. Hence the occurrence of so-called chronic progressive external ophthalmoplegia (CPEO) as an isolated problem or in the context of Kearns Sayre syndrome (see table). Patients with CPEO start by having ptosis (droopy lids), followed by progressive inability to move their eyes in all directions of gaze. Some patients have double vision and have to adopt various head positions to align their deviated eyes and achieve single binocular vision.
In addition to ophthalmoplegia, Kearns Sayre syndrome is characterized by pigmentary degeneration of the retina and cardiomyopathy. Lesser features include: pharyngeal and facial weakness, skeletal muscle weakness, deafness, small stature and markedly raised cerebrospinal fluid protein.

Treatment of Ocular Complications of Mitochondrial Cytopathies
- There are no specific therapies for the ocular complications of the various mitochondrial diseases.
- Vitamin and other supplements that improve mitochondrial function have anecdotal positive effects on retinal function.
- Spontaneous recovery of vision occurs in patients with LHON and is mutation-dependent, being least common with the 11778 mutation. Drugs interacting with mitochondrial function, alcohol consumption and smoking should be avoided.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene Defect</th>
<th>Clinical Findings</th>
<th>Ocular Findings</th>
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<tbody>
<tr>
<td>Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP)</td>
<td>ATPase6 gene at position 8993</td>
<td>Migraine headaches, seizures, proximal neurogenic muscle weakness, sensory</td>
<td>Mild salt and pepper pigmentary changes to full-blown retinitis pigmentosa-like picture</td>
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<td>Mitochondrial Myopathy, Lactic Acidosis and Stroke-Like Episodes (MELAS)</td>
<td>tRNA(leu)(UUR), gene at position 3243</td>
<td>Vomiting, headache, seizures and recurrent stroke-like episodes that may result</td>
<td>Pigmentary retinopathy similar to retinitis pigmentosa</td>
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<tr>
<td>Leber hereditary optic neuropathy (LHON)</td>
<td>mtDNA point mutation at position 11778 (65% of cases); 1448 (25%); 3460 (10%); other minor mutations</td>
<td>Rare MS-like signs and symptoms, Rare dystonia</td>
<td>Subacute visual loss, affecting both eyes simultaneously or sequentially.</td>
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<td>Hyperemia of optic nerve head followed by atrophy.</td>
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<td>Central vision is lost almost completely, while peripheral field is spared to</td>
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<td>varying degrees</td>
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<td>Kearns-Sayre Syndrome (KSS)/ Chronic progressive external ophthalmoplegia (CPEO)</td>
<td>5kb or other deletions in the mtDNA of muscle mitochondria</td>
<td>Ophthalmoplegia, pigmentary degeneration of the retina and cardiomyopathy. Lesser features include: pharyngeal and facial weakness, skeletal muscle weakness, deafness, small stature and electroencephalographic changes and markedly raised cerebrospinal fluid protein. Electrocardiographic abnormalities include complete heart block</td>
<td>Ophthalmoplegia, pigmentary degeneration of the retina</td>
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References


