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Neuro-ophthalmic manifestations of mitochondrial disorders and their management

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Abstract:

The visual system has high metabolic requirements and is therefore particularly vulnerable to mitochondrial dysfunction. The most commonly affected tissues include the extraocular muscles, photoreceptors, retinal pigment epithelium, optic nerve and visual cortex. Hence, the most common manifestations of mitochondrial disorders are progressive external ophthalmoplegia, macular pattern dystrophy, pigmentary retinopathy, optic neuropathy and retrochiasmal visual field loss. With the exception of Leber hereditary optic neuropathy and stroke-like episodes seen in mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, the majority of neuro-ophthalmic manifestations have an insidious onset. As such, some patients may not recognize subtle progressive visual symptoms. When mitochondrial disorders are highly suspected, meticulous examination performed by an ophthalmologist with targeted ancillary testing can help confirm the diagnosis. Similarly, neuro-ophthalmic symptoms and signs may be the first indication of mitochondrial disease and should prompt systemic investigations for potentially life-threatening associations, such as cardiac conduction defects. Finally, the ophthalmologist can offer symptomatic treatments for some of the most disabling manifestations of these disorders.

Keywords:

Dominant optic atrophy, Leber hereditary optic neuropathy, macular pattern dystrophy, mitochondrial disease, pigmentary retinopathy, progressive external ophthalmoplegia

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Introduction

Mitochondria are the powerhouses of mammalian cells. They play a critical role in energy production among other fundamental cellular functions. When mitochondria fail, so does the production of adenosine triphosphate (ATP) due to defective oxidative phosphorylation and dangerous free radical formation ensues. The end result is a wide phenotypic spectrum of complex multisystem disorders. Organ systems with high metabolic activity are preferentially affected; hence, it is not surprising that a malfunctioning visual system features prominently.

Mitochondrial function is maintained by proteins encoded in both the nuclear and mitochondrial genomes. That is, disease can result from abnormalities in both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA); hence, transmission can occur through maternal lines or by Mendelian inheritance, respectively. The prevalence of adults with pathogenic mutations of either mtDNA or nDNA is estimated at 1:4300.[1] By virtue of heteroplasmy in mtDNA and incomplete penetrance in nDNA, not all individuals who harbor the mutations exhibit clinical manifestations. The prevalence of adults that are clinically affected by mitochondrial disease is estimated at 1:10,000 due to mtDNA variants and 1:35,000 due to nDNA variants.[1] The most commonly identified mtDNA mutations within a British

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population are m.3243A>G and primary Leber hereditary optic neuropathy (LHON) mutations. The most common nDNA mutations are in the spastic paraplegia 7 (SPG7) and progressive external ophthalmoplegia 1 (PEO1) genes, all of which are highly associated with neuro-ophthalmic manifestations.[1] Retrospective studies found ophthalmic phenotypes in 35%–81% of patients with confirmed mitochondrial disease.[2,3]

It is imperative that physicians, especially ophthalmologists, recognize common neuro-ophthalmic signs of mitochondrial disease. This may aid in the diagnosis of multisystem disorders and prompt screening for associated life-threatening manifestations. Diagnostic techniques have become less invasive and improvements in next-generation sequencing have led to more reliable and cost-effective examination of nDNA and mtDNA.[4,5] Whereas a variety of tissue samples such as urine, buccal swabs and hair samples were previously used to compensate for heteroplasmy in different organs, peripheral blood sampling has now become the norm.[6,7] Nevertheless, the genetics of mitochondrial disorders remains complex, therefore evaluation of a patient with a possible mitochondrial disorder is best performed in collaboration with a genetic counselor and a medical geneticist.[8]

Currently, there are no highly effective treatments for mitochondrial disorders and management largely involves supportive and symptomatic therapies. Nonetheless, ophthalmologists will be responsible for optimizing the patient's ocular health and visual potential, thus improving their quality of life. Accurate diagnosis of mitochondrial disorders also leads to ongoing ramifications for patients and their families. Family members may elect to undergo genetic screening and young couples now have the option of *in vitro* fertilization techniques that can prevent transmission of mutant mtDNA to their progeny.[9]

Herein, we will discuss the most common neuro-ophthalmic manifestations of mitochondrial disease and summarize their management principles. These include chronic progressive ophthalmoplegia (PEO), macular pattern dystrophy (MPD), pigmentary retinopathy, optic neuropathy and retrochiasmal visual loss.[10]

Progressive external ophthalmoplegia

PEO is a descriptive term for the combination of bilateral, symmetric blepharoptosis and diffuse ophthalmoparesis that gradually worsens over months to years. Chronic PEO (CPEO) is a label better reserved for the mitochondrial condition that exhibits PEO as its dominant feature.[11]

Ptosis alone or in combination with external ophthalmoplegia is one of the most common manifestations of mitochondrial myopathies. It is present in more than half of the affected patients[12,13] and is most commonly seen in patients with Kearns–Sayre syndrome (KSS) and CPEO. The former is diagnosed in patients younger than 20 years, whereas the latter can be diagnosed at any age. Both conditions share many clinical features, but systemic mitochondrial dysfunction is more frequent and more severe in patients with KSS.[11] Detection of PEO should prompt an ophthalmologist to consider investigating for systemic associations of KSS, particularly for cardiac conduction defects.

Other mitochondrial conditions that can have features of PEO include:

- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
- Maternally inherited diabetes and deafness (MIDD)
- Autosomal dominant optic atrophy (DOA) "plus" syndrome
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (SANDO)
- Maternally inherited Leigh syndrome (MILS)
- Pearson syndrome
- SPG7 mutations
- POLG mutations and Alpers syndrome.[2,3,11,12,14-17]

The common systemic associations of some of these disorders will be discussed throughout this review article.

Ptosis, orbicularis oculi weakness and exposure keratopathy

In the vast majority of CPEO patients, blepharoptosis typically precedes external ophthalmoplegia by months to years,[12] but rare reports of PEO without ptosis also exist.[18] Due to levator palpebrae superioris (LPS) weakness, ptosis can be observed and quantified as reduced upper lid excursion that is typically <7 mm.[19,20] As ptosis progresses, patients compensate by adopting a chin-up anomalous head posture and frontalis overaction. Weakness of LPS may also be accompanied by weakness of orbicularis oculi such that patients also develop lagophthalmos or involutional ectropion. Furthermore, Bell's phenomenon or the palpebral-oculogyric reflex may be impaired due to weakness of the superior rectus (SR) that forms part of the LPS-SR complex. In combination with reduced spontaneous ocular movements, the corollary is an increased risk of exposure keratopathy.

Management principles of ptosis and exposure keratopathy

Intervention becomes necessary when the patient is no longer able to clear their visual axis with a combination

of chin-up head posture and frontalis overaction; or when their social functioning is impaired.[21] Due to the inherent risk of causing or worsening exposure keratopathy, reversible or temporizing measures are often favored. These include the use of scleral contact lenses, tape, or ptosis crutches to buttress the upper lid.[22,23] Although ptosis props are not well tolerated by patients with mild PEO, they lend themselves well to patients with severely impaired orbicularis oculi function in advanced disease.[21]

Patients with mitochondrial myopathies must be thoroughly counseled regarding the substantial risks associated with ptosis surgery if it is even offered. Immediately postoperatively, intensive lubrication is critical and frequent monitoring for corneal sequelae is necessary. Progressive worsening of orbicularis oculi function and lid closure imparts a long-term risk of exposure keratopathy, along with development of corneal ulcers.[21,24,25] This may necessitate reversal of the upper lid procedure, or tightening of the lower lid to protect the cornea [Figure 1]. Alternatively, ptosis may recur due to progressive weakening of the LPS and frontalis muscles.[21]

Decision-making in ptosis surgery is determined by the affected muscle groups. Levator advancement is preferred in patients with preserved LPS function, but this is rare in mitochondrial myopathies. Hence, frontalis suspension is the more commonly performed procedure in patients with LPS weakness and preserved frontalis function.[21] While several case series report the use of fascia lata for frontalis suspension,[21,24] there is a theoretical benefit of using silicone slings, as this material facilitates postoperative adjustment or reversal.[19,20] In all cases, the extent of upper lid elevation should be titrated cautiously.[24] Surgery is not advisable in patients with severe orbicularis oculi weakness.

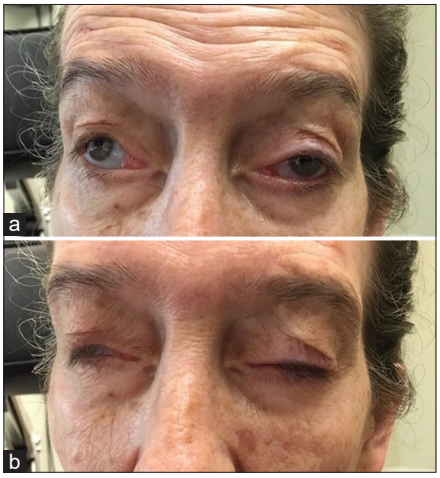

Figure 1: (a) A 44-year-old female with chronic progressive external ophthalmoplegia who has undergone bilateral frontalis suspensions for blepharoptosis with two subsequent tightenings. She requests a third tightening of her slings as progressive levator palpebrae superioris and frontalis weakness has caused recurrent ptosis that occludes her visual axes. (b) Postoperative lagophthalmos due to concurrent orbicularis oculi weakness results in exposure keratopathy, necessitating loosening of her frontalis silicone slings.

Management of exposure keratopathy follows the usual principles, but more aggressive administration may be required. Nonsurgical management includes liberal use of synthetic eye drops, gels and ointments. Preservative-free preparations are preferable especially if frequent instillation is required. Autologous serum eye drops contain epithelio-trophic factors and can be considered in patients with severe dry eyes, particularly if non-healing epithelial defects are present. Punctal plugs and cautery can be utilized to reduce tear outflow, while the use of tape and moisture chambers overnight can prevent nocturnal desiccation of the ocular surface. In severe cases, a temporary tarsorrhaphy may be necessary until there is adequate healing of the corneal ulcer.

External ophthalmoplegia

Gradual paralysis of extraocular muscles may not be recognized by patients with mitochondrial myopathy, due to symmetric muscle involvement combined with facultative suppression of one eye over a long duration. In the early stages of PEO, saccades may be slow and incomplete.[11] Convergence insufficiency with diplopia for near activities is a common early finding. This gradually progresses to omnidirectional ophthalmoplegia that cannot be overcome with a doll's head maneuver.

Richardson *et al*.[26] characterized ophthalmoparesis in 25 patients with CPEO. The vast majority of patients (92%) exhibited an exo-deviation with a vertical component in 26%. No subjects had an esodeviation and an alternative diagnosis should be sought in such patients. SR and medial rectus muscles were the most commonly affected; inferior rectus and superior oblique muscles were the least commonly affected. Symmetric involvement was observed in 68% of patients. Only half of the patients with manifest deviations experienced diplopia, indicating that suppression in adulthood is still possible when ocular deviation occurs so gradually.[26]

PEO is primarily a myopathic process. Mitochondria comprise approximately 60% of cell volume in extraocular muscles, reflective of this tissue's high ATP requirements. This is thought to explain the increased sensitivity to dysfunctional mitochondria in extraocular muscles as compared with skeletal muscles.[26,27] Despite such marked limitation in eye movements, magnetic resonance imaging (MRI) studies report a heterogeneity of findings. Some case series detected significant reduction in cross-sectional volumes of extraocular

muscles,[28,29] while others do not.[30] Some studies noted abnormal extraocular muscle "spongiform" T1 signal[30] and abnormal T2 signal that may correlate with loss of function,[28] whereas other studies did not observe any specific signal abnormalities.[31]

The symmetry of motility deficits has prompted some to consider a supranuclear contribution to PEO. This is supported by small studies that have detected reduced voluntary movement but full movement with vestibulo-ocular reflex,[32] in combination with brainstem abnormalities found on autopsy,[33] metabolic profiling[34] and neuro-imaging.[35] Other case series have not found any evidence supporting a supranuclear component of mitochondrial ophthalmoparesis.[29,31]

Management principles of external ophthalmoplegia

Conservative management of diplopia is in keeping with general management principles of strabismus. Prisms can be utilized for small angle deviations. For those with convergence insufficiency, base-in prisms may offer some relief for near work. For large deviations, image degradation and chromatic aberration preclude the use of prisms; hence, monocular occlusion may be preferable.

Occasionally, strabismus surgery is necessary in PEO patients who complain of intractable diplopia, have a cosmetically objectionable deviation, or have an uncomfortable anomalous head posture.[36,37] Special considerations need to be made. Case series have documented hypotonic and flaccid extraocular muscles that are difficult to recess; or fibrotic muscles that are difficult to dissect. Extra care should be taken to avoid avulsing such thin and friable muscles.[37-39] Rectus resections are far more effective than recessions[38] and are therefore the operation of choice if there is reasonable medial rectus function.[37] If there is complete loss of medial rectus function, or if lateral rectus restriction is detected on forced duction testing, then lateral rectus recessions should be incorporated.[27,37]

In the largest interventional case series examining strabismus in CPEO patients, those who underwent sub-maximal horizontal muscle surgery were undercorrected.[39] Hence, experienced strabismus surgeons recommend maximizing rectus surgery or at least exceeding the millimeters prescribed in standard strabismus tables to achieve the desired result.[38,39] Long-term stability is rarely achieved and patients should be warned that their misalignment will progress slowly such that recurrent diplopia is highly likely.[37,39] Intramuscular botulinum toxin is an acceptable alternative or adjunct to strabismus surgery in patients with smaller deviations or residual deviation despite maximal surgery.[39]

Cataracts

Abnormalities of the crystalline lens are not a prominent feature of mitochondrial disorders. They are a common finding in patients with OPA3 mutations,[40-42] which are relatively rare. Several case reports have described cataracts in patients with MELAS, LHON, MERRF, Pearson syndrome, MILS, MIDD, CPEO and non-syndromic mitochondrial disorders.[43-46] With such few documented cases, however, it remains difficult to determine if cataracts were incidental or a result of the underlying mitochondrial dysfunction.

Macular pattern dystrophy

MPD is highly specific and virtually pathognomonic among patients with MIDD due to the m.3243A>G mutation,[16,47] one of the most prevalent mtDNA mutations.[1] The majority of the affected patients are asymptomatic with normal visual acuity;[47] hence, the condition may go unrecognized unless fundoscopy is specifically requested in patients with a suspected mitochondrial disorder. Rarely, patients will complain of a subtle decline in central vision, paracentral scotoma, or photophobia, and the presence of such visual symptoms is typically associated with advanced retinal pigment epithelium (RPE) changes.[48-52]

The most common MPD phenotype is discontinuous circumferential perifoveal atrophy with corresponding hypo-autofluorescence.[49] A unique feature is that of surrounding occult RPE disruption that is only seen on autofluorescence as a diffuse, speckled pattern that extends beyond the obvious macular abnormalities seen on fundoscopy [Figure 2].[49] Over the years, the patchy macular atrophy can coalesce into a continuous ring with central foveal sparing.[49] A less common

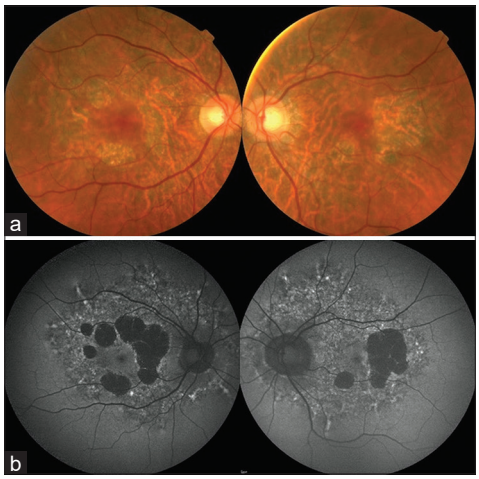

Figure 2: (a) A 55-year-old female with the m.3243A>G mutation and maternally inherited diabetes and deafness. Color fundus photographs show discontinuous circumferential perifoveal atrophy that is typical of macular pattern dystrophy. (b) Large patches of hypo-autofluorescence correspond to the perifoveal areas of macular atrophy. There is diffuse, speckled autofluorescence that extends beyond the temporal arcades that was not apparent on color fundus photographs.

phenotype of MPD looks very similar to pattern dystrophy, with granularity of RPE, pale deposits and pigment clumping at the level of RPE, without significant atrophy in the perifoveal area. Again, there is typically speckled autofluorescence that is not readily seen on fundoscopy.[49]

As MPD is highly specific to patients with MIDD, it is important to distinguish it from other maculopathies. Age-related macular degeneration, Stargardt macular dystrophy, multifocal pattern dystrophy and central areolar dystrophy may all exhibit similar perifoveal areas of atrophy with corresponding hypo-autofluorescence. However, diffuse speckled autofluorescence in the surrounding posterior pole that is not apparent on fundoscopy, is not a typical feature of these other diagnoses.[49,53]

The majority (86%) of patients with MIDD exhibit signs of MPD.[47] The mean age at detection is 46.5 years (range, 27–71 years).[6,47] While some have found that the severity of MPD correlates with the extent of mutant heteroplasmy and clinical severity of systemic disease,[17] other studies have not found this association.[52] Diabetic retinopathy is consistently less prevalent in patients with MIDD when compared with those with type 2 diabetes mellitus of similar duration.[6,17,47,54]

Management principles of macular pattern dystrophy

As MPD is one of the most specific features of MIDD,[16] its detection should prompt multidisciplinary investigation for the m.3243A>G point mutation in addition to other features of MIDD, namely insulin deficiency, sensorineural hearing loss (SNHL), proximal myopathy, cardiomyopathy, renal disease and growth hormone deficiency.[7,47] The same point mutation underlies MELAS, hence this diagnosis also needs to be considered when MPD is identified.[7,53]

There is no definitive treatment for MPD. Coenzyme Q10 has been found to improve insulin secretion and prevent progressive hearing loss in patients with MIDD, but has no effect on retinopathy.[55] Fortunately, the majority of patients are asymptomatic and have a good visual prognosis.

Pigmentary retinopathy

Approximately one third of patients with mitochondrial disease exhibit pigmentary retinopathy.[2,56] Unlike MPD, pigmentary retinopathy is nonspecific and is seen in a wide range of mitochondrial diseases. It is a core feature of neuropathy, ataxia, retinitis pigmentosa (NARP) syndrome and KSS. Pigmentary retinopathy is less prevalent and milder in CPEO compared with KSS[57] and can also be seen in patients with MELAS, MERRF, LHON, MILS, MNGIE and non-syndromic mitochondrial disorders.[2,44,46,58,59] A thorough retinal examination should be performed in patients with PEO, limb weakness or progressive central nervous system (CNS) disease, as the presence of retinopathy might help identify an underlying mitochondrial disorder.

The most common phenotype is a "salt-and-pepper" fundus appearance with characteristic mottled RPE hypopigmentation and hyperpigmentation, representative of disseminated photoreceptor and RPE dysfunction [Figure 3].[10,44,60,61] This phenotype imparts good visual prognosis, with 50% of the affected patients reporting only mild vision loss.[10] In fact, mild pigmentary retinopathy is often difficult to detect without meticulous funduscopy, such that ancillary tests such as autofluorescence, fluorescein angiography and visual electrophysiology are frequently necessary.[44]

When pigmentary retinopathy is not obvious on clinical examination, scotopic electroretinography (ERG) is a useful adjunct. B-wave sensitivities are significantly depressed in patients with mitochondrial disease, whether or not fundus abnormalities are present.[62] This contrasts with ERG responses seen in other retinal degenerative disorders, in which early loss of b-wave amplitude is more common than loss of b-wave sensitivity.[62]

Some patients progress to develop retinal vessel attenuation with bone spicules, along with atrophy of the retina, RPE and choriocapillaris, and optic atrophy.[56] In KSS, retinal changes are very gradual and usually do not progress to severe vision loss or electroretinographic features typical of classic retinitis pigmentosa.[44] Also distinct from classic retinitis pigmentosa, advanced mitochondrial associated pigmentary retinopathy may result in gross clumping of pigment at the maculae with associated central visual loss.[10,56]

Optic neuropathies

The optic nerve, a white matter tract of the CNS, is a highly metabolic tissue with high energy

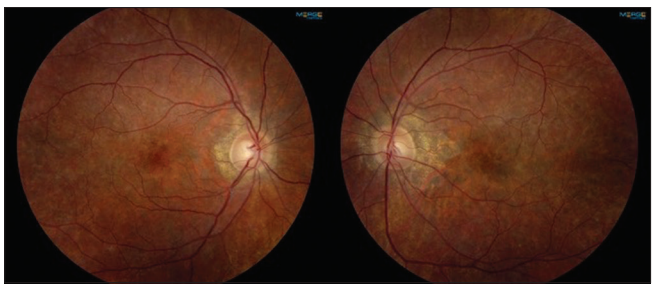

Figure 3: A 28-year-old female with Kearns–Sayre syndrome who is visually asymptomatic, exhibits mottled retinal hypopigmentation and hyperpigmentation, also known as "salt-and-pepper" retinopathy.

requirements. This energy is provided by the mitochondria via ATP production mediated by oxidative phosphorylation. Mitochondrial dysfunction results in the generation of excessive reactive oxygen species that perpetuates retinal ganglion cell apoptosis. There is an abrupt decrease in mitochondrial numbers within the optic nerve just distal to the lamina cribrosa, making the proximal papillomacular bundle especially vulnerable to injury.[63]

Optic neuropathy can exist as the sole manifestation of mitochondrial dysfunction, as in LHON and autosomal DOA; or be part of a syndrome with multisystem involvement [Table 1]. The entity of mitochondrial optic neuropathy has expanded to include genetic and neurodegenerative disorders in which mitochondrial dysfunction is the final common pathway leading to optic neuropathies.[10]

Isolated optic neuropathies

Leber hereditary optic neuropathy

LHON is the most common primary mitochondrial disorder causing optic neuropathy with an estimated prevalence of 1:30,000–50,000 in Northern Europeans populations and an estimated incidence of 1:1,000,000 in the Japanese population.[64,65] Three point mutations within the mitochondrial genome, m.3460G>A (MTND1), m.11778G>A (MTND4) and m.14484T>C (MTND6), account for 90% of all LHON cases, although prevalence varies with geographic location.[66] For example, in Japan and China, the majority of cases (90%) harbor the 11778 mutation.[67,68]

Age of onset is typically between 15 and 35 years, but LHON has been reported in patients spanning the range of 2–87 years.[69,70] There is a male preponderance, with reported gender ratios as high as 9:1.[66]

Several "risk factors" have been studied to determine their effect on disease expression including tobacco smoking, alcohol,[71] nutritional deficiencies, systemic illnesses, medications and toxins. Apart from tobacco smoking, none have been found to play a definitive role in disease onset. An increased lifetime penetrance among male smokers has also been noted.[72]

Patients present with subacute, unilateral, painless, central vision loss, with visual acuities typically deteriorating to 6/60 or worse.[10,70] Three clinical stages described in an international consensus statement have been defined according to the timing of visual loss, namely subacute (<6 months), dynamic (6–12 months) and chronic (>12 months).[73] Fellow eye involvement is seen within a year in at least 97% of patients.[66,74]

Table 1: Salient clinical features of isolated optic neuropathies and diseases associated with optic neuropathies

Disease entity	Clinical manifestations
Isolated optic neuropathies	
LHON	Severe subacute bilateral, often sequential, painless, central vision loss. Second eye involvement in >97% of cases by 1 year
DOA (Kjers disease)	Slowly progressive, insidious, symmetric painless bilateral visual loss with central or cecocentral scotomas, usually detected in the first two decades of life or incidentally found
Optic neuropathies with multisystem involvement	
DOA plus	Optic neuropathy with one or more of: SNHL, ophthalmoplegia, myopathy, peripheral neuropathy and ataxia
LHON plus (dystonia)	Dystonia, bulbar dysfunction, pyramidal tract involvement and cognitive impairment
Wolfram syndrome	Optic neuropathy with childhood-onset diabetes mellitus, SNHL, diabetes insipidus, cataracts, nystagmus, glaucoma and pigmentary maculopathy. May have neurologic and urologic signs and symptoms. May be pauci-symptomatic with just optic neuropathy or optic neuropathy and hearing loss
MELAS	Hemianopia, seizures, stroke-like episodes, lactic acidosis, optic neuropathy, salt-and-pepper retinopathy, progressive ophthalmoplegia and macular pattern dystrophy
MERRF	Generalized seizures, myoclonus, ataxia, myopathy, peripheral neuropathy, cognitive impairment, and rarely optic neuropathy
MNGIE	Gastrointestinal dysmotility, peripheral neuropathy, progressive leukoencephalopathy, ophthalmoparesis, ptosis, pigmentary retinopathy and optic atrophy
MILS	Severe subacute necrotizing encephalomyelopathy with early death. Dystonia, optic atrophy, pigmentary retinopathy, ataxia, nystagmus, seizures and central respiratory hypoventilation
FRDA	Progressive ataxia, dysarthria, loss of deep tendon reflexes, loss of joint position and vibration sense, pes cavus, cardiomyopathy and scoliosis. Mild optic neuropathy
CMT/HMSN VI	Axonal peripheral neuropathy with optic atrophy
Complicated HSP (SPG7)	Progressive spastic paraparesis, optic atrophy

LHON=Leber hereditary optic neuropathy, DOA=Dominant optic atrophy, MELAS=Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes, MERRF=Myoclonic epilepsy with ragged red fibers, MNGIE=Mitochondrial neurogastrointestinal encephalopathy, MILS=Maternally inherited Leigh syndrome, FRDA=Friedreich's ataxia, HSP=Hereditary spastic paraparesis, SPG7=Spastic paraplegia 7, CMT=Charcot-Marie-Tooth, SNHL=Sensorineural hearing loss, HMSN=Hereditary motor and sensory neuropathy

In 25%–50% of cases, there is simultaneous bilateral involvement at the first presentation.[64,75]

Color vision is affected early and even in asymptomatic carriers, both tritan and deutan color vision defects have been reported.[76] Typical visual field defects are central or cecocentral scotomata. Occasionally, subclinical progressive field loss can occur in the contralateral "asymptomatic" eye with preserved visual acuities.[77,78] Fundus examination in the subacute phase may show pseudo-disc edema [Figure 4] with apparent swelling of the peripapillary retinal nerve fiber layer (RNFL), circumpapillary telangiectatic microangiopathy and vascular tortuosity, but no late leakage on fluorescein angiography.[79,80] Nonetheless, there is considerable heterogeneity in the appearance of the fundus, with normal optic disc appearance in up to 50% of patients.[10,66] In those with bilateral involvement, a relative afferent pupillary defect may be difficult to detect. When combined with subtle or absent disc abnormalities, this can lead to an initial misdiagnosis of non-organic vision loss.

As the disease progresses, there is rapid axonal loss with temporal pallor of the optic nerve within 6 weeks followed by diffuse pallor and sometimes cupping. Optical coherence tomography (OCT) in the subacute phase shows thickening of the RNFL due to the presence of pseudo-disc edema.[81] In chronic LHON, OCT shows profound RNFL and retinal ganglion cell complex (GCC) loss.[81,82] OCT and pattern electroretinography have detected abnormalities in ganglion cell structure and function even in asymptomatic carriers, but the presence of these findings is not predictive of who will lose vision.[83] MRI of the brain may show chiasmal T2 hyperintensity and enlargement, most often without enhancement.[84] Radiologic involvement of the prechiasmal optic nerves and rarely the optic tracts has also been reported. This should be differentiated from inflammatory optic nerve and chiasmal disorders in which the enhancement is usually robust.

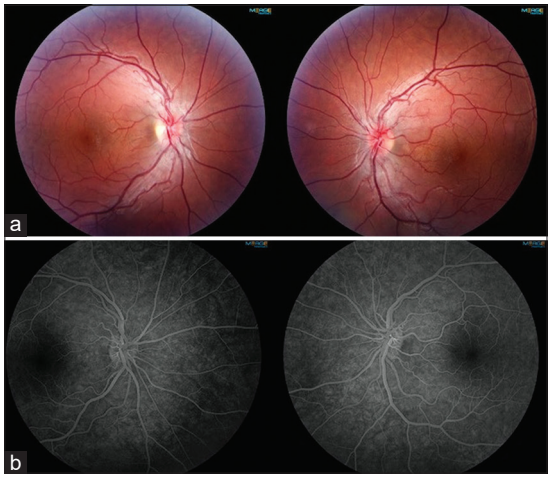

Figure 4: (a) A 23-year-old male with Leber hereditary optic neuropathy in the subacute stage. There is mild pallor of the right optic disc and hyperemia of the left optic disc. (b) Fluorescein angiography does not show any late leakage, confirming that there is no true optic disc swelling.

Spontaneous visual recovery, variously defined, has been reported in only 14% of patients with the 11778 mutation,[70] and recovery in those with the 3460 mutation is thought to be similar. Those with the 14484 mutation have a much higher chance of recovery at 71%.[82,85] In a small minority of patients with LHON, cardiac conduction defects have been reported and therefore a baseline electrocardiogram (ECG) should be obtained.

Dominant optic atrophy

The worldwide prevalence of autosomal DOA rivals that of LHON at 1:50,000 with no gender bias.[86] In contrast with LHON, the causative mutation occurs in nDNA, hence is acquired through Mendelian inheritance.[87] OPA1 is the most commonly affected nuclear gene, which encodes a protein within the inner mitochondria that is essential for fusion and maintenance of the mitochondrial cristae network.[88]

DOA typically begins during the first two decades of life.[89] The onset of vision loss is insidious, slowly progressive and symmetric;[87,89] hence, diagnosis may occur incidentally at a routine ophthalmic examination or only when disease is advanced and symptomatic. Phenotypic heterogeneity exists with visual acuities ranging from 6/6 to light perception, with more than 80% of patients retaining vision of 6/60 or better.[87,90,91]

Typically, optic discs in DOA exhibit temporal pallor, temporal excavation or shallow shelving of the disc and an absence of fine superficial capillaries [Figure 5]. This excavated appearance may give the false impression of "glaucomatous cupping."[91] A critical differentiating feature is that of neuroretinal rim pallor that is characteristic of DOA, as opposed to a preserved pink neuroretinal rim seen even in advanced glaucoma. Central, cecocentral, or paracentral scotomas are noted

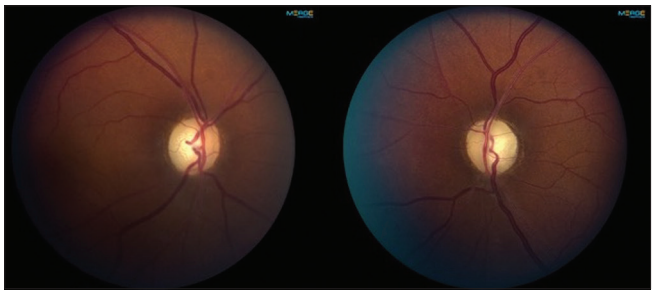

Figure 5: A 71-year-old male with OPA1 gene mutation and progressive bilateral visual loss since childhood. His visual acuities are now 6/40 OU. He has bilateral temporal optic disc pallor that is typical of dominant optic atrophy.

on visual field testing.[87,91] OCT demonstrates temporal RNFL thinning (unlike glaucoma) and central GCC loss corresponding to the injured papillomacular bundle. Diffuse RNFL and GCC loss manifests as the disease progresses.[87]

Vision loss in DOA is very gradually progressive and spontaneous recovery does not occur. Currently, there is no effective therapy. Nonetheless, DOA patients have a much better visual prognosis compared with LHON and maintain useful vision for most of their lives such that they are able to function independently and oftentimes retain their driving capacity.[66,82,88,92]

Optic neuropathies with multisystem involvement

Dominant optic atrophy plus

The OPA1 gene mutation is a nonsense or frameshift mutation that accounts for the majority of DOA cases. Occasionally, missense mutations in the same gene result in aberrant replication and multiple large-scale deletions of mtDNA, leading to a wider phenotype that is broadly categorized as DOA plus.[93] In addition to optic atrophy, patients may suffer from SNHL (autosomal DOA and deafness), ophthalmoplegia, myopathy, peripheral neuropathy, ataxia[93] and cataracts.[94]

Leber hereditary optic neuropathy plus

Rarely, patients with LHON may also develop dystonia and other neurological features including bulbar dysfunction, corticospinal abnormality and early-onset dementia.[95,96] Such presentations are categorized under the entity "LHON plus." Bilateral basal ganglia abnormalities including striatal necrosis can be seen on neuroimaging.[95] Most of these patients have a different underlying mtDNA mutation, although occasionally one of the three primary LHON mutations is found.

Wolfram syndrome

This is a rare genetic neurodegenerative disorder with classical features of childhood-onset diabetes mellitus, optic atrophy, SNHL, diabetes insipidus and other neurologic and urologic signs and symptoms.[97] Two causative nDNA genes (WFS1 and WFS2) have been identified.[98] Transmission is usually by autosomal recessive inheritance but autosomal dominant mutations have also been described.

Optic atrophy appears at a mean age of 11 years (range of 6 weeks to 19 years).[99,100] Other neuro-ophthalmic manifestations include cataracts, nystagmus, glaucoma and pigmentary maculopathy. Prognosis is poor when the full syndromic gamut manifests, with death occurring at a median age of 39 years usually due to brainstem atrophy and neurodegeneration that leads to central respiratory failure.[101] Remarkably, mutations in the Wolfram gene can sometimes lead to isolated nonsyndromic optic atrophy, or a limited combination of optic atrophy and hearing loss, inherited in an autosomal recessive or dominant fashion.[102]

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes

Optic atrophy may occur in patients with MELAS. However, the more common neuro-ophthalmic manifestation is a visual field deficit due to a retro-chiasmal lesion and hence will be later discussed under this heading.

Myoclonic epilepsy with ragged red fibers

MERRF is a mitochondrial disorder characterized by generalized seizures, myoclonus and ataxia. Point mutations of the MT-TK gene in mtDNA are the most common cause.[103] Optic atrophy, ptosis and rarely ophthalmoparesis can be seen,[3] in addition to myopathy, peripheral neuropathy, progressive spasticity and gradual intellectual decline.

Mitochondrial neurogastrointestinal encephalopathy

MNGIE is an autosomal recessive disorder, caused by TYMP gene mutations in nDNA, which leads to progressive acquisition of secondary mtDNA mutations and failure of oxidative phosphorylation.[104] Clinical features develop when 80%–90% of total mitochondria are mutated. It usually affects adolescents or young adults and the mean age of mortality is 37.5 years. The phenotype is dominated by gastrointestinal dysmotility, peripheral neuropathy and progressive leukoencephalopathy, although there is considerable heterogeneity.[105] Optic atrophy has been reported although the more common neuro-ophthalmic manifestations include ophthalmoparesis, ptosis and pigmentary retinopathy.[106] As in other mitochondrial disorders, varying degrees of cardiac anomalies, endocrine dysfunction and SNHL can occur. Skeletal muscle biopsy may show ragged red fibers.[107,108]

Maternally inherited Leigh syndrome

MILS results from point mutations in mtDNA and most commonly affects the mitochondrial respiratory chain complex V.[109,110] One of these mutations is also responsible for NARP. Typically, the NARP phenotype occurs with a mutation load of 60%–70% and the MILS phenotype occurs at mutation loads above 90%.[10,109] Onset can begin *in utero* with oligohydramnios and intrauterine growth restriction, but some cases do not become clinically apparent until the second or third decade of life.[111] MILS is characterized by subacute necrotizing encephalomyelopathy associated with dystonia, optic atrophy, pigmentary retinopathy, ataxia, nystagmus, seizures, lactic acidosis, central respiratory

hypoventilation and early death.[112] There is necrotic degeneration of the basal ganglia, diencephalon and the brainstem.

Friedreich's ataxia

Friedreich's ataxia (FRDA) is the most common autosomal recessive hereditary ataxia. The disease is caused by a GAA trinucleotide repeat expansion in the frataxin gene on chromosome 9q13–q21.1. This gene encodes a mitochondrial protein whose main role is iron–sulfur protein homeostasis within the mitochondria. FRDA is a neurodegenerative disorder characterized by progressive limb and gait ataxia, dysarthria, loss of deep tendon reflexes, loss of joint position and vibration sense, pes cavus, cardiomyopathy and scoliosis.[113] Although optic neuropathy is a common feature of FRDA, most patients are visually asymptomatic and severe vision loss rarely occurs.[10]

Hereditary motor sensory neuropathy

Hereditary motor sensory neuropathy (HMSN), also known as Charcot–Marie–Tooth disease, refers to a group of inherited peripheral neuropathies. HMSN Type VI is defined by the combination of axonal peripheral neuropathy and optic atrophy.[114] It is an autosomal dominant condition caused by mutation in the mitofusin-2 gene that encodes a protein critical for mitochondrial fusion.[115] The onset of visual symptoms tends to occur years after peripheral neuropathy is diagnosed and patients develop a subacute to chronic decline in visual acuity that can approach 6/120.[116,117] Color vision is impaired[118] and bilateral central scotomas are seen on visual field testing. A subset of patients with HMSN VI may recover some vision years after the onset of optic neuropathy.[119]

Complicated hereditary spastic paraparesis

Hereditary spastic paraparesis (HSP) is a neurodegenerative disorder characterized by progressive spastic ataxia. When associated with additional neurologic signs and symptoms, it is classified as "complicated HSP." Several genetic subtypes have been described involving all patterns of Mendelian inheritance as well as mitochondrial transmission. HSP with optic atrophy can be seen in nDNA mutations that affect mitochondrial function, in particular SPG7 and MT-ND4.[120]

Optic neuropathies associated with Parkinson's disease, Alzheimer's disease and Huntington's disease

A growing body of literature reports that disturbed mitochondrial dynamics leads to a large and heterogeneous group of disorders including, but not limited to, age-related and autosomal Parkinson's disease,[121] Huntington's disease,[122] Alzheimer's disease (AD)[123] and frontotemporal dementia with amyotrophic lateral sclerosis (FTD-ALS).[124] The protein products of some of the implicated genes potentiate pro-fission activity, indicating a strong consistent link between mitochondrial dysfunction and neurodegeneration. Mouse models of AD provide supporting evidence that defective mitochondrial biogenesis and increased mitochondrial fission are at the core of synaptic neuronal degeneration. Pathogenic mutations in genes encoding mitochondrial intermembrane space have been identified in patients with FTD-ALS.

Management principles of mitochondrial optic neuropathies

Currently, there are no approved disease-modifying therapies available for mitochondrial optic neuropathies. However, recent gene therapy trials[70] show promise for an imminent paradigm shift. A single intravitreal injection of GS010 gene therapy was trialed in one eye of LHON-affected patients with the m.11778G>A mutation which resulted in clinically meaningful improvement of bilateral visual acuity from week 48 to week 96.[125] While improvement in the control eye was unexpected, transfer of GS010 into the sham-treated eye was a more plausible explanation than spontaneous recovery.[70,125,126]

Multiple studies show limited efficacy of idebenone for LHON within 5 years of vision loss, although there was some visual benefit in patients who had earlier initiation of treatment.[127,128] In June 2015, the European Medicine Agency approved idebenone for the treatment of visual impairment in patients with LHON at a dose of 900 mg per day in three divided doses. However, some controversy remains regarding the optimal target population and the timing, dose and frequency of administration.

Broader management principles include genetic counseling and discussion of modifiable risk factors such as tobacco smoking and avoidance of mitochondrial toxins. Drugs known to cause mitochondrial impairment include ethambutol, chloramphenicol, linezolid, erythromycin, streptomycin, antiretroviral medications, chlorpromazine, fluphenazine and valproate.[129,130] Low vision services should be introduced early and patients should be counseled about their prognosis, thereby facilitating informed decisions about their vocation. If current clinical trials are available, then patients should also be provided information regarding potential participation.

Retrochiasmal visual loss

Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes

MELAS is the mitochondrial disorder most consistently associated with retrochiasmal visual loss, although

metabolic strokes can occur in a variety of primary mitochondrial disorders. It is a multisystem disorder with onset typically in childhood, although adult presentations have been reported. Eighty percent of patients with MELAS syndrome carry the m.3243A>G mutation. The severity of clinical features depends on the extent of mutant heteroplasmy.

Stroke-like episodes encompass periods of cerebral dysfunction lasting hours, weeks or months, that are accompanied by migraine-like prodromes, acute confusional states and focal seizures. Common precipitating factors include acute illness, surgery and medications, although spontaneous presentations can certainly occur. There is preferential involvement of the parietal and occipital lobes, resulting in homonymous hemianopic visual field deficits [Figure 6]. In the early stages of the disease, stroke-like episodes tend to be reversible; although with increasing frequency, the cumulative effect gradually impairs motor abilities, vision and mentation, resulting in permanent neurologic deficits. Generalized tonic-clonic seizures can be associated with postictal hemiparesis or hemianopia. Migraine with or without visual aura is a common manifestation.[131,132] Other ocular manifestations include PEO, MPD, pigmentary retinopathy and optic atrophy.[44] Systemic manifestations include SNHL, myopathy, diabetes mellitus, left ventricular dysfunction, gastrointestinal dysmotility, ataxia and episodic coma.

Diagnosis of MELAS is based on a combination of clinical findings and molecular genetics. Elevated serum and cerebrospinal fluid lactate and pyruvate concentrations are typically seen; however, levels may also be normal at rest, with elevated markers only noted after exercise.

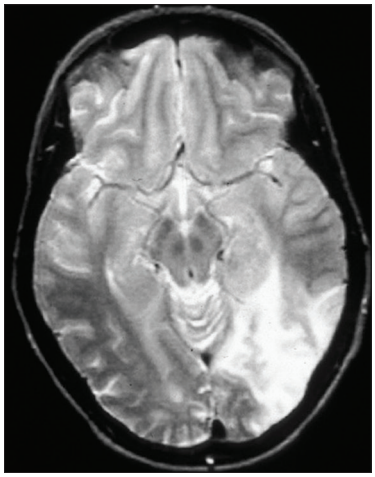

Figure 6: A 31-year-old female with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes developed a left parieto-occipital stroke-like episode with T2 hyperintensity in the left parieto-occipital region not corresponding to a typical large-vessel vascular territory. She had the expected corresponding right homonymous hemianopia.

Management principles for mitochondrial retrochiasmal vision loss

No disease-modifying therapy is currently available for MELAS. Referral to low vision services is recommended where patients can acquire aids and strategies to help compensate for their hemianopia and visual neglect. Common migraine therapies and antiepileptics can be employed, although valproate should be avoided as it is a potential mitochondrial toxin. Patients with deafness can benefit from cochlear implants and stroke rehabilitation provides favorable outcomes in some patients. Surveillance with annual blood sugar levels, ECG and echocardiogram can facilitate the early identification of endocrinopathies and cardiomyopathy.

Conclusions

While some of the neuro-ophthalmic presentations that we have discussed are common, many have unusual features that should make an ophthalmologist stop to consider the underlying diagnosis and prompt systemic investigations and genetic confirmation. For example, the combination of slowly progressive ptosis and divergent strabismus with pigmentary retinopathy should prompt cardiology screening for conduction defects. Abnormal retinal autofluorescence that is out of keeping with fundoscopy findings should instigate further history taking with regard to diabetes and deafness. Non-glaucomatous optic neuropathies, both acute and insidious, should precipitate a broader discussion of systemic and neurologic symptoms, in addition to a thorough family history. Reversible homonymous visual field loss in children and young adults should prompt referral to a neurologist for thorough assessment and treatment of associated seizures and other neurologic deficits.

We live in a time of rapid advancements in detection methods and treatment of inherited conditions. Genetic disorders are on the forefront of medicine and mitochondrial disease is among one of the most prevalent. Ophthalmologists play a vital role in establishing a clinical diagnosis and making timely referrals to other specialists for assessment of systemic sequelae. Although treatment for the affected individual remains largely supportive and symptomatic, this is likely to change over the coming years and is already occurring in the realms of family planning and gene therapy trials.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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