The Eye on Mitochondrial Disorders

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Abstract

Ophthalmologic manifestations of mitochondrial disorders are frequently neglected or overlooked because they are often not regarded as part of the phenotype. This review aims at summarizing and discussing the etiology, pathogenesis, diagnosis, and treatment of ophthalmologic manifestations of mitochondrial disorders. Review of publications about ophthalmologic involvement in mitochondrial disorders by search of Medline applying appropriate search terms. The eye is frequently affected by syndromic as well as nonsyndromic mitochondrial disorders. Primary and secondary ophthalmologic manifestations can be differentiated. The most frequent ophthalmologic manifestations of mitochondrial disorders include ptosis, progressive external ophthalmoplegia, optic atrophy, retinopathy, and cataract. More rarely occurring are nystagmus and abnormalities of the cornea, ciliary body, intraocular pressure, the choroidea, or the brain secondarily affecting the eyes. It is important to recognize and diagnose ophthalmologic manifestations of mitochondrial disorders as early as possible because most are accessible to symptomatic treatment with partial or complete short-term or long-term beneficial effect. Ophthalmologic manifestations of mitochondrial disorders need to be appropriately diagnosed to initiate the most effective management and guarantee optimal outcome

Introduction

Mitochondrial disorders manifest phenotypically as mitochondrial multiorgan disorder syndrome in the vast majority of the cases.[1] The degree of mitochondrial multiorgan disorder syndrome can be assessed by determining the mitochondrial multiorgan disorder syndrome score, which is calculated by summing the number of affected organs (range: 1-13), the number of abnormalities within an organ (range: 1-94), and the probability that an abnormality is due to a mitochondrial defect (range: 1-3). A score >10 suggests a mitochondrial disorder. The organs most frequently affected in mitochondrial multiorgan disorder syndrome are the skeletal muscle, central nervous system, peripheral nervous system, endocrine system, heart, ears, and the eyes. More rarely, intestines, liver, pancreas, kidneys, bone marrow, cartilage, or bones are affected. Ophthalmologic manifestations of mitochondrial disorders are frequently neglected or overlooked because they can be mild and are frequently not regarded as part of the phenotype but can be the dominant phenotypic feature of a mitochondrial disorder. This review aims at summarizing and discussing etiology, pathogenesis, diagnosis, and treatment of ophthalmologic manifestations of mitochondrial disorders.

Methods

Data for this review were identified by searches of MEDLINE, Current Contents, and references from relevant articles using the search terms ophthalmologic, eye, cornea, lens, ciliary body, retina, choroidal, uvea, optic nerve, ophthalmoparesis, ophthalmoplegia, ptosis, strabismus, and nystagmus in combination with mitochondrial, mtDNA, oxidative phosphorylation, respiratory chain, electron chain, oxidative stress, and mitochondrion. Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were considered. Abstracts

and reports from meetings were not included. Only articles published in English between 1966 and 2015 were considered. Appropriate papers were studied and discussed for their suitability to be incorporated in this review.

Classification of Ophthalmologic Mitochondrial Disorder Manifestations

Ophthalmologic mitochondrial disorder manifestations may be classified according to various different criteria. They may be categorized as isolated or nonisolated, occurring in association with other organ manifestations. Ophthalmologic manifestations may be the dominant feature of the phenotype or a nondominant feature. Mitochondrial disorders with ophthalmologic manifestations may be either due to mitochondrial DNA or nuclear DNA mutations. Ophthalmologic manifestations may be specific for a syndromic mitochondrial disorder (eg, Leber hereditary optic neuropathy) or nonspecific (eg, cataract). They may manifest as the presenting symptom or sign or may follow after occurrence of other manifestations. Ophthalmologic manifestations may be also classified according to the involved ophthalmologic structure as primary, affecting only the bulb (eg, cornea, iris, lens, ciliary body, retina, choroidea, uvea, optic nerve, ocular pressure), or as secondary, affecting structures outside the bulb, such as the extraocular eye muscles, the lid muscles, the vestibular organ, or the brain (Table 1).

Primary Ophthalmologic Mitochondrial Disorder Manifestations

Primary ophthalmologic mitochondrial disorder manifestations may involve the cornea, iris, lens, ciliary body, retina, choroidea, uvea, or the optic nerve.

Cornea

During recent years, some evidence has been provided that the cornea can be involved in mitochondrial disorders. Systematic studies on this matter, however, have not been conducted. Corneal abnormalities associated with mitochondrial dysfunction include astigmatism, corneal dystrophy, corneal clouding, or corneal endothelial dysfunction.[4,5] Endothelial dysfunction of the cornea has been described in Pearson syndrome (Table 1).[5] Astigmatism (keratoconus [thinning of corneal struma]) has been reported in nonsyndromic mitochondrial disorders (Table 1).[6] In a study of 20 patients, keratoconus was attributed to increased oxidative stress resulting from mitochondrial respiratory chain complex-I sequence variations.[70] In a patient with Kearns-Sayre syndrome, progressive external ophthalmoplegia secondarily led to recurrent conjunctivitis and keratitis.[3] Despite almost complete ptosis, spontaneous corneal ulceration occurred.[3] In patients carrying the 3895-bp mitochondrial DNA deletion, the highest mutation load was found in the cornea and retina.[71] Corneal clouding due to structural changes in the endothelium or Descemet membrane has been occasionally reported in Kearns-Sayre syndrome.[2] In a child with Leigh syndrome due to the mutation m.8993T>G, numerous distended mitochondria were found in the corneal epithelium.[7] Nonspecific corneal alterations were also observed in a patient with mitochondrial neurogastrointestinal encephalomyopathy.[8] In a study of 14 patients with pontocerebellar hypoplasia, of which 13 carried a CASK mutation, 2 presented with megalocornea.[9] Though corneal surgery could be an option for astigmatism, it has not been reported in a mitochondrial disorder patient.

Iris

Involvement of the iris in mitochondrial disorders has been only rarely documented and was particularly described in mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome.[10] In a patient carrying the m.3243A>G mutation in the tRNA(Lys) gene, patchy atrophy of the iris stroma was described.[10] In patients with Leber hereditary optic neuropathy, not only visual function but also pupil responses were reduced although pupil afferent fibers were spared.[11] Additionally, pupillary dysfunction has been reported in a 62-year-old male carrying a large single mitochondrial DNA deletion.[12] Treatment options for these abnormalities are not available.

Lens

The most frequent of the lenticular abnormalities in mitochondrial disorders is cataract. Usually, cataract in mitochondrial disorders is of the posterior subcapsular type.[10] Cataract can be a phenotypic feature of MELAS syndrome[10,13] but has been also reported as initial manifestation in a patient with nonsyndromic mitochondrial disorder due to a mitochondrial DNA deletion.[14] In rare cases, cataract is a feature of Leber hereditary optic neuropathy,[15] myoclonus epilepsy with ragged red fibers (MERRF) syndrome, Pearson syndrome, Leigh syndrome, maternally inherited deafness and diabetes, progressive external ophthalmoplegia, or nonsyndromic mitochondrial disorders (Table 2).[16] Cataract is a typical feature of autosomal dominant optic atrophy resulting from OPA3 mutations.[17] Rarely, Wolfram syndrome manifests with cataract.[18] In all types of mitochondrial disorder, cataract is accessible to surgery. Refraction errors are most frequent in patients with MELAS syndrome or Kearns-Sayre syndrome.[19]

Ciliary Body

The ciliary body has been only rarely reported to be involved in mitochondrial disorders. In a patient dying at age 15 months from Leigh syndrome due to the mutation m.8993T>G in the ATPase6 gene, histopathologic postmortem examination revealed thinning of nerve fibers and ganglion cell layers in the nasal aspect of the macula, mild atrophy of the temporal aspect of the optic nerve head, and numerous distended mitochondria in all cell types, particularly in the retina, nonpigmented ciliary epithelium, and the corneal epithelium.[7] Additionally, the ciliary epithelium was affected in a patient with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency.[20]

Retina

Retinal manifestations of mitochondrial disorders include various retinal dystrophies, of which the best known are pigmentary retinopathy and macular degeneration (Table 1).

Retinitis pigmentosa

Retinitis pigmentosa is a core feature of Kearns-Sayre syndrome and neuropathy ataxia retinitis pigmentosa syndrome.[13] Typical for Kearns-Sayre syndrome is the “salt and pepper” retinitis with regions of increased and decreased pigmentation, particularly in the equatorial fundus.[2] Pigmentary retinopathy is only a rare feature of progressive external ophthalmoplegia and may be milder than in Kearns-Sayre syndrome (Table 1).[13,21] Only some patients with MELAS or MERRF syndrome present with mild pigmentary retinopathy of the posterior pole.[13] Mild pigmentary defects were also found in 2 of 20 patients with Leber hereditary optic neuropathy

due to the m.11778G>A mutation (Table 1).[13] Small pigmentary retinal defects were described in a 4-year-old female with COX deficiency.[22] Furthermore, retinitis pigmentosa has been described in patients with Leigh syndrome due to the mutation m.8993T>G.23 In a study of 44 Chinese patients with Leigh syndrome, pigmentary retinopathy was even found in 22%.24 In a study of 14 patients with pontocerebellar hypoplasia, 4 presented with retinopathy without reporting details.[9] Additionally, retinopathy can be found in mitochondrial neurogastrointestinal encephalomyopathy and nonsyndromic mitochondrial disorders (Table 2). Retinal dystrophy may occasionally manifest with photophobia. In a study of 46 mitochondrial disorder patients, 4 suffered from photophobia. Two patients had Leigh syndrome, of which 1 had rod-cone dystrophy on electroretinography, 1 had Kearns-Sayre syndrome with a normal electroretinography, and 1 had MERRF syndrome with an isoelectric electroretinography.[19]

Macular degeneration

Macular dystrophy has been described in patients carrying the m.3243A>G mutation in the tRNA(Lys) gene.[25] In a single case with Pearson syndrome, parafoveal intraretinal crystals were seen.[26] Bilateral macular dystrophy with circumferentially distributed perifoveal atrophy has been recognized in maternally inherited deafness and diabetes and MELAS syndrome (Figure 1).[27] A rod-cone dystrophy has been recorded on electroretinography in a patient with Kearns-Sayre syndrome.19 Macular dystrophy was a common feature in a study of 54 patients with maternally inherited deafness and diabetes, occurring in 86% of them.[28] Macular dystrophy in these patients manifests as either pigmentary lesions or atrophy of either the choroid or retinal pigmentary epithelium (Table 1).[28] In a study of 35 British subjects with

mitochondrial disorder, 85.7% had macular changes.[29] Electroretinographies were reduced in 4 of 9 patients, and b-wave responses impaired in 2.[29] Pigmentary maculopathy was the cause of poor vision in a 12-year-old boy with Wolfram syndrome.[30]

Other retinal abnormalities

Retinal abnormalities other than pigmentary retinopathy or macular degeneration include retinal dystrophy, retinal hypertrophy, and pigmentary maculopathy. Retinal dystrophies can be most easily assessed by electroretinography and can be found in patients with Kearns-Sayre syndrome, Leigh syndrome, MELAS syndrome, MERRF syndrome, and Leber hereditary optic neuropathy.[19] In patients with autosomal recessive spastic ataxia with leukoencephalopathy and autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSAL/ARSACS), retinal hypertrophy has been described.[31] In a family with Mohr-Tranebjaerg syndrome, 6 affected males had blindness resulting from nonspecified retinal degeneration.[32] Treatment options for retinopathy in general are limited.

Choroidea, Uvea

Choroidea and uvea are only rarely affected in mitochondrial disorders. The most frequent manifestation of mitochondrial disorders in the choroidea is choroidal atrophy.[10] Choroidal atrophy has been particularly described in MELAS syndrome.10 Atrophy of choroid pigmentary epithelium also occurs in maternally inherited deafness and diabetes.[28] Central choroidal dystrophy as confirmed by electroretinography was reported in 1 patient with Mohr-Tranebjaerg syndrome.32

Additionally, chorioretinal dystrophy was reported in a single patient carrying a large mitochondrial DNA deletion.[33]

Optic Nerve

The main mitochondrial disorder manifestation of the optic nerve is optic atrophy. Optic atrophy is a common mitochondrial disorder manifestation but frequently missed or misinterpreted. This is due to the difficulty diagnosing optic atrophy. Optic atrophy can be most accurately assessed by funduscopy if the distal portion of the optic nerve is affected or by magnetic resonance imaging (MRI) of the orbita if the more proximal parts of the nerve are affected. An indication of optic nerve atrophy is a reduced amplitude of visually evoked potentials.[73]

Among syndromic mitochondrial disorders, optic atrophy has been particularly described in Leber hereditary optic neuropathy and autosomal dominant optic atrophy, conditions in which optic atrophy is the dominant phenotypic feature.[34] Both conditions and their ophthalmologic abnormalities are thus described in more detail in the section “Mitochondrial Disorders Primarily Manifesting in the Eye.” More rarely, optic atrophy has been reported in MELAS syndrome, Kearns-Sayre syndrome, Pearson syndrome, pontocerebellar hypoplasia, Mohr-Tranebjaerg syndrome, Alpers-Huttenlocher disease, or Wolfram syndrome.[2,9,19,34] Partial or total optic atrophy also has been reported in patients with MERRF syndrome.[13,19,35] Optic atrophy is a typical phenotypic feature of hereditary motor and sensory neuropathy type VI (HMSN-IV) due to MFN1 mutations.[34] Additionally, C12orf65 (COXPD7) mutations manifest phenotypically with optic atrophy and a Leigh-like phenotype.[36] Only in a single family was optic atrophy associated with neuropathy ataxia retinitis pigmentosa syndrome due to the m.8993T>G mutation in the ATPase6 gene.[37] In a

study of 44 Chinese patients with Leigh syndrome, optic atrophy was described in 22.5%.[24] Only in a single patient with mitochondrial neurogastrointestinal encephalomyopathy, optic disc alterations were observed.[8] Optic atrophy can also be a feature of infantile-onset spinocerebellar ataxia[38] or mitochondrial depletion syndrome.[39] Nonsyndromic mitochondrial disorders with optic atrophy were due to an ACI1 mutation,[40] due to an ND5 mutation together with cataract and retinopathy,[41] or due to an unknown genetic cause.[42] Optic atrophy is not accessible to treatment.

Intraocular Pressure

Increased intraocular pressure (glaucoma) is a rare phenotypic feature of mitochondrial disorders. Two main types of glaucoma can be differentiated, open-angle glaucoma and closure-angle glaucoma. Additionally, normotensive and hypertensive glaucoma is differentiated. Rarely, open-angle glaucoma can be found in patients with Leber hereditary optic neuropathy[43] or autosomal dominant optic atrophy (Table 1). Funduscopic findings may show a mixture of abnormalities typical for glaucomatic retinopathy and a Leber hereditary optic neuropathy fundus. Glaucomatous changes of the optic disc were found by visual field examination and optical coherence tomography in a single patient with mitochondrial neurogastrointestinal encephalomyopathy.[8] In a study of 14 patients with pontocerebellar hypoplasia, 1 presented with glaucoma.[9] Normal tension glaucoma is associated with polymorphisms in the OPA1 gene.[44] Glaucoma was also reported in a family with Wolfram syndrome.[45] There are indications that ND5 mutations are associated with the development of open-angle glaucoma.[46] Glaucoma in mitochondrial disorders may be accessible to treatment with drugs or surgery.

Secondary Ophthalmologic Mitochondrial Disorder Manifestations

Secondary ophthalmologic mitochondrial disorder manifestations are due to affectation of the extraocular muscles, the eyelids, the vestibulum, or the brain.

Bulb Motility

The most frequent abnormalities affecting bulb motility include nystagmus and strabismus. They may occur independent of each other or together. They may occur with or without other ocular or extraocular mitochondrial disorder manifestations.

Nystagmus

Nystagmus or roving eye movements can be due to central nervous system or vestibular involvement in mitochondrial disorders and are the most common ophthalmologic manifestations as a presenting symptom in pediatric mitochondrial disorder patients.[47] Nystagmus has been reported in patients with Leigh syndrome, Alpers-Huttenlocher disease, and Pearson syndrome (Tables 1 and 2).[47] Gaze-evoked nystagmus has been described in a single patient with “LHON plus” who not only carried the m.11778G>A primary Leber hereditary optic neuropathy mutation but also the m.3394T>C mutation.[48] Recording of eye movements in MELAS patients may show saccadic dysmetria, prolonged saccadic reaction time, impaired suppression of reflex eye movements, prolonged reaction during antisaccades, downbeat nystagmus, square wave jerks, or impaired pursuit.[49] Epilepsy in MELAS patients may manifest as epileptic nystagmus, impaired smooth pursuit, or temporary eye deviation.[74] Moreover, nystagmus has been reported in a patient carrying a point mutation in the DGUOK gene who additionally presented with retinal blindness.[50]

Nystagmus in addition to retinitis pigmentosa was also reported in a patient with nonsyndromic mitochondrial disorder due to the m.15995G>A mutation in the tRNA(Pro) gene manifesting as ataxia, deafness, and leukoencephalopathy.[51] In a study of 7 Czech autosomal dominant optic atrophy patients, nystagmus was part of the phenotype.[52] Nystagmus is also a common feature of ARSAL/ARSACS.[53] In a study of 44 Chinese patients with Leigh syndrome, nystagmus was found in 14%.24 Nystagmus can be also a feature of Wolfram syndrome,[54] recessive ataxia (dystonia and mild cerebellar ataxia) syndrome, or mitochondrial depletion syndrome.[55] Roving eye movements and nystagmus may additionally occur in nonsyndromic mitochondrial disorders.[42] Resolution of nystagmus is possible for those cerebral or vestibular forms that respond to treatment.

Strabismus

In a study of 44 Chinese patients with Leigh syndrome, strabismus was the most frequent ophthalmologic abnormality and present in 41% of patients.[24] Among those with strabismus, 13 had exotropia and 5 esotropia.[24] Strabismus was also reported in some patients with X-linked sideroblastic anemia with ataxia.[56] Divergent strabismus has been reported as the presenting manifestation in 25% of juvenile mitochondrial disorders.[47] In a study of 14 patients with pontocerebellar hypoplasia, of which 13 carried a CASK mutation, 2 presented with strabismus.[9] Strabismus has been reported also in other patients with pontocerebellar hypoplasia, without knowing the underlying mutation.[57,58] In a child with a large mitochondrial DNA deletion, the initial presentation at birth was cataract and strabismus.[14] He later developed Leigh-like pathologies and strokelike episodes.[14] Additionally, strabismus has been reported in

patients with nonsyndromic mitochondrial disorders (Tables 1 and 2).[47] In some cases, surgery may have a beneficial effect on strabism.

Mitochondrial Disorder Manifestations of the Extraocular Muscles

Affectation of the extraocular muscles in mitochondrial disorders results in progressive external ophthalmoplegia. Progressive external ophthalmoplegia is a frequent ophthalmologic manifestation of mitochondrial disorders. It may be complete, resulting in walled-in bulbs, or incomplete. It may affect all directions of bulb movements or only some of them. It may affect one eye or both eyes. Progressive external ophthalmoplegia is most frequently associated with single or multiple mitochondrial DNA deletions. Single mitochondrial DNA deletions may cause progressive external ophthalmoplegia, Kearns-Sayre syndrome, or Pearson syndrome.[27] Multiple mitochondrial DNA deletions going along with progressive external ophthalmoplegia may be due to mutations in nuclear genes such as PEO1, POLG1, SLC25A4, RRM2B, POLG2, or OPA1.[27] Additionally, progressive external ophthalmoplegia may be due to mitochondrial DNA point mutations, particularly in transfer RNA (eg, tRNA(Lys)) genes.[27] Transfer RNA mutations manifesting with progressive external ophthalmoplegia frequently occur sporadically akin to mitochondrial DNA deletions and can be detected only in muscle.[75] Progressive external ophthalmoplegia may be the sole manifestation of the m.3243A>G mutation, which commonly manifests as MELAS syndrome.[59] Upward gaze was reduced in 2 patients with mitochondrial disorder.[60] Progressive external ophthalmoplegia was a phenotypic feature in a patient with mitochondrial neurogastrointestinal encephalomyopathy,[8] Wolfram syndrome,[54] Leigh syndrome, autosomal dominant optic atrophy, and mitochondrial recessive ataxia syndrome.[61] Progressive external

ophthalmoplegia has been also described in MERRF syndrome.[62] Infantile-onset spinocerebellar ataxia is a Finnish disease, and some of the 24 cases reported so far developed ophthalmoplegia.[63] A hallmark of the sensory ataxic neuropathy with dysarthria and ophthalmoparesis syndrome is ophthalmoparesis.64 Sensory ataxic neuropathy with dysarthria and ophthalmoparesis is due to mutations in either the POLG1 or PEO1 gene resulting in multiple mitochondrial DNA deletions.[64] Additionally, ophthalmoparesis can be found in mitochondrial depletion syndrome[65] or patients with nonsyndromic mitochondrial disorders.[66] Ultrastructural changes on muscle biopsy from extraocular muscles are clearly different in patients with Leber hereditary optic neuropathy and progressive external ophthalmoplegia.[76]

Mitochondrial Disorder Manifestations of the Eyelid

One of the most frequent mitochondrial disorder manifestations is ptosis (Figure 2). It may occur unilaterally at onset but usually becomes bilateral during the disease course. Ptosis may be the sole manifestation of a mitochondrial disorder, particularly at onset of the disease, or associated with other manifestations. Ptosis may show dynamic alterations specifically at onset of the disease, giving rise to misinterpretation as myasthenia gravis.[77] Particularly at onset, ptosis may be discrete such that it is missed on clinical exam. Ptosis may be associated with progressive external ophthalmoplegia or other ocular manifestations of a mitochondrial disorder. Ptosis may be a phenotypic manifestation in syndromic as well as nonsyndromic mitochondrial disorders. Among the syndromic mitochondrial disorders, ptosis has been particularly reported in progressive external ophthalmoplegia, MELAS, MERRF, Kearns-Sayre syndrome, sensory ataxic neuropathy with dysarthria and ophthalmoparesis,[67] Pearson syndrome, mitochondrial neurogastrointestinal

encephalomyopathy, and autosomal dominant optic atrophy (Table 2).[19] In a study of 44 Chinese patients with Leigh syndrome, ptosis was present in 16%.[24] Isolated cases with maternally inherited deafness and diabetes,[60] mitochondrial neurogastrointestinal encephalomyopathy,[8] or mitochondrial depletion syndrome68 also presented with ptosis. In a Persian Jew with mitochondrial myopathy, lactic acidosis, and sideroblastic anemia due to a PUS1 mutation, weak lid closure was described.[69] Ptosis is accessible to surgical repair, but has a strong tendency to recur after correction.

Other Manifestations

Madarosis (alopecia of eyelashes) is an extremely rare mitochondrial disorder manifestation and has been reported only in 1 patient so far.[79] Alopecia of the eyebrows occasionally occurs in patients with nonsyndromic mitochondrial disorders (Finsterer J, MD, PhD, KAR, Vienna, Austria) but has not been reported in patients with syndromic mitochondrial disorders. Blepharospasm, a form of focal dystonia, may be also a rare manifestation of nonsyndromic mitochondrial disorders.[80]

Mitochondrial Disorders Primarily Manifesting in the Eye

There are a few syndromic mitochondrial disorders that primarily present with ophthalmologic manifestations. Among these are Leber hereditary optic neuropathy and autosomal dominant optic atrophy. Thus, both are described in more detail below.

Leber Hereditary Optic Neuropathy

Leber hereditary optic neuropathy is a maternally inherited blinding disorder due to mutations in genes encoding for subunits of respiratory-chain complex I. Mutations in 3 genes account for almost 90% of all Leber hereditary optic neuropathy cases.[35] The 3 most prevalent Leber hereditary optic neuropathy mutations (primary Leber hereditary optic neuropathy mutations) include the m.3460A>G mutation in the ND1 gene, the m.11778G>A mutation in the ND4 gene, and the m.14484T>C mutation in the ND6 gene.[35] Clinically, Leber hereditary optic neuropathy is characterized by bilateral, painless, subacute visual failure that develops during young adult life.81 Leber hereditary optic neuropathy is 4 to 5 times more frequent in males compared with females. Affected individuals are usually entirely asymptomatic until they develop visual blurring affecting the central visual field in 1 eye.81 Similar symptoms occur in the other eye an average of 2 to 3 months later. Visual acuity is severely reduced to counting fingers or even worse in the majority of cases, and visual field testing shows an enlarging dense central or ceco-central scotoma.[81] After the acute phase, the optic discs become atrophic. Funduscopic findings typical for Leber hereditary optic neuropathy include microangiopathy, hyperemic discs, retinal telangiectasias (ectatic capillaries), peripapillary microangiopathy, and tortuosity of vessels (twisted vessels) (Figure 3). MRI of the orbita may show atrophy of the nerve with compensatory widening of the space below the optic sheath. Mutations in the mitochondrial ND3, ND4, or ND6 genes may cause Leber hereditary optic neuropathy with dystonia.[82] Currently, there is no effective treatment available.

Autosomal Dominant Optic Atrophy

Autosomal dominant optic atrophy is a blinding disorder, which, unlike Leber hereditary optic neuropathy, does not exhibit a gender bias.[34] It is due to mutations in

the nuclearly encoded OPA1 gene.[34] Autosomal dominant optic atrophy also may be due to OPA3 mutations, which go along with cataract.[17] Autosomal dominant optic atrophy is clinically characterized by progressive, painless, bilaterally symmetric visual loss.[27] The most frequent visual field abnormalities in autosomal dominant optic atrophy are central, ceco-central, or para-central scotomas consistent with early involvement of the papillo-macular bundle.[27] Optic disc atrophy may be subtle, diffuse, or present as temporal “wedge” defect.[83,84] In some families, OPA1 mutations may not only manifest with optic atrophy but also with progressive external ophthalmoplegia, ptosis, and hypoacusis.[85] Because glaucoma neuropathy, autosomal dominant optic atrophy, and Leber hereditary optic neuropathy occasionally present with similar topographic optic disc changes, they cannot be discriminated upon disc assessment alone.[86] Currently, there is no effective treatment available.

Discussion

This review shows that ophthalmologic involvement in mitochondrial disorders is frequent, variable, and diverse. Among primary ophthalmologic manifestations of mitochondrial disorders, cataract, pigmentary retinopathy, and optic atrophy appear to be the most frequent, and among the secondary manifestations it is progressive external ophthalmoplegia, ptosis, and nystagmus. Rare ophthalmologic manifestations of mitochondrial disorders include glaucoma, choroidal abnormalities, strabismus, macular degeneration, abnormalities of the ciliary body, or corneal lesions. Ocular abnormalities in mitochondrial disorders may occur isolated or may occur in association with other organ manifestations of a mitochondrial disorder. Organs other than the eyes affected in mitochondrial disorders include the muscles,

nerves, central nervous system, endocrine organs, heart, gastrointestinal tract, kidneys, bone marrow, skin, or the bones. Involvement of the central nervous system or the vestibular system may secondarily affect the eyes. Ocular abnormalities may dominate the phenotype, such as in Leber hereditary optic neuropathy, progressive external ophthalmoplegia, or autosomal dominant optic atrophy or may be nondominant. If ophthalmologic manifestations are mild or if other more dominant features prevail, ophthalmologic abnormalities may be missed. Ocular abnormalities may be accessible to therapy or may be inaccessible to treatment. Ophthalmologic involvement in mitochondrial disorders needs to be appreciated because there is appropriate cure available in some cases, which strongly determines the outcome. Blepharospasm responds favorably to botulinum toxin, surgery can be beneficial for ptosis, ophthalmoparesis, strabismus, glaucoma, or cataract, and drugs may be effective for glaucoma, or central nervous system or vestibular causes of nystagmus. Inaccessible to treatment are retinitis pigmentosa, optic atrophy, or abnormalities of the ciliary body or the choroidea. Recognizing ophthalmologic abnormalities in mitochondrial disorders is also important to differentiate them from causes other than mitochondrial disorder.

Ophthalmologists should not only look into but also around the eyes of a mitochondrial disorder patient. Each physician involved in the management of mitochondrial disorder patients must have a close look into the eyes of their patients. Ophthalmologic complaints must be taken seriously and must be followed up and assessed until an appropriate diagnosis has been established. Ophthalmologic manifestations of mitochondrial disorders may go undiagnosed if the abnormality is subclinical or mild. Ophthalmologic symptoms that patients with mitochondrial disorders may report include visual impairment, blurring, clouding, photophobia,

double vision, visual field defects, tear-dropping, dry eyes, lid drop, loss of eyelashes or eyebrows, ocular pain at rest or at bulb movement, vertigo, or headache. Ocular symptoms can be easily retrieved, and an orientating ophthalmologic investigation can be carried out by each physician. Simple tests for visual acuity, double vision, field defects, nystagmus, pupillary reactions, or voluntary or pursuit eye movements can be carried out. More sophisticated investigations should be reserved for the ophthalmologist.

In conclusion, this review about ophthalmologic manifestations in mitochondrial disorders shows that the eye is frequently affected in syndromic as well as nonsyndromic mitochondrial disorders. Primary and secondary ophthalmologic manifestations can be differentiated. The most frequent ophthalmologic manifestations of mitochondrial disorders include ptosis, progressive external ophthalmoplegia, optic atrophy, retinopathy, cataract, and nystagmus. It is important to recognize and diagnose ophthalmologic manifestations of mitochondrial disorders because they may lead to the diagnosis of the mitochondrial disorder, and some of them are accessible to symptomatic treatment with partial or complete short-term or long-term beneficial effect. If the neurologist is alert to ophthalmologic symptoms and signs, he will not miss the gate to mitochondrial disease via the eyes.

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Table 1. Primary and Secondary Ophthalmologic Manifestations of mitochondrial disorders.

Primary abnormalities	Specific manifestation	Occurring in	Reference
Conjunctiva	Conjunctivitis	KSS	3
Cornea	Endothelial dysfunction	PS, KSS	2, 4, 5
	Astigmatism (keratoconus)	NS	6
	Keratitis, ulcer	KSS	3
	Nonspecific alterations	MNGIE, LS	7, 8
	Megalocornea	PCH	9
Iris	Atrophy	MELAS	10
	Pupillary dysfunction	LHON, NS	11, 12
Lens	Cataract	MELAS, WS, ADOA, LHON, NS, MERRF, MDD, PEO	10, 13-18
	Refraction error	MELAS, KSS	19
Ciliary body	Epithelial dysfunction	LS	7, 20
Retina	Pigmentary retinopathy	KSS, MELAS, PCH, LS, MNGIE	2, 9, 12, 13, 21-24
	Macular degeneration	MELAS, PS, MDD, KSS, NS, WS	25-30
	Retinal dystrophy	KSS, LS, MELAS, MERRF, LHON	19
	Retinal hypertrophy	ARSAL	31
	Nonspecific retinal degeneration	MTS	32
Choroidea	Atrophy	MELAS, MDD, MTS, NS	10, 28, 32, 33
Optic nerve	Optic atrophy	LHON, ADOA, MELAS, PCH, NS, AHD, WS, MERRF, HMSN-IV, NS, NARP, LS, MNGIE, IOSCA, MDS, MTS	2, 8, 9, 13, 19, 24, 34-42
Intraocular pressure	Glaucoma	LHON, ADOA, MNGIE, WS, NS, PCH	8, 9, 43-46
Secondary abnormalities			
Bulb motility	Nystagmus	LS, AHD, LHON, MELAS, ADOA	24, 42, 47-55
PS, NS			
Strabism		LS, XLASA, PCH, NS	9, 14, 24, 47, 56-58
Roving eye movements		NS	42
Extraocular muscles	PEO	PEO, KSS, PS, NS, SANDO, MDS, MELAS, MNGIE, WS, LS, ADOA, MIRAS	8, 27, 54, 59-66
	Ptosis	PEO, MELAS, MERRF, KSS, PS, SANDO, MNGIE, ADOA, LS, MDD, MDS, MLASA	8, 19, 24, 63, 67-69

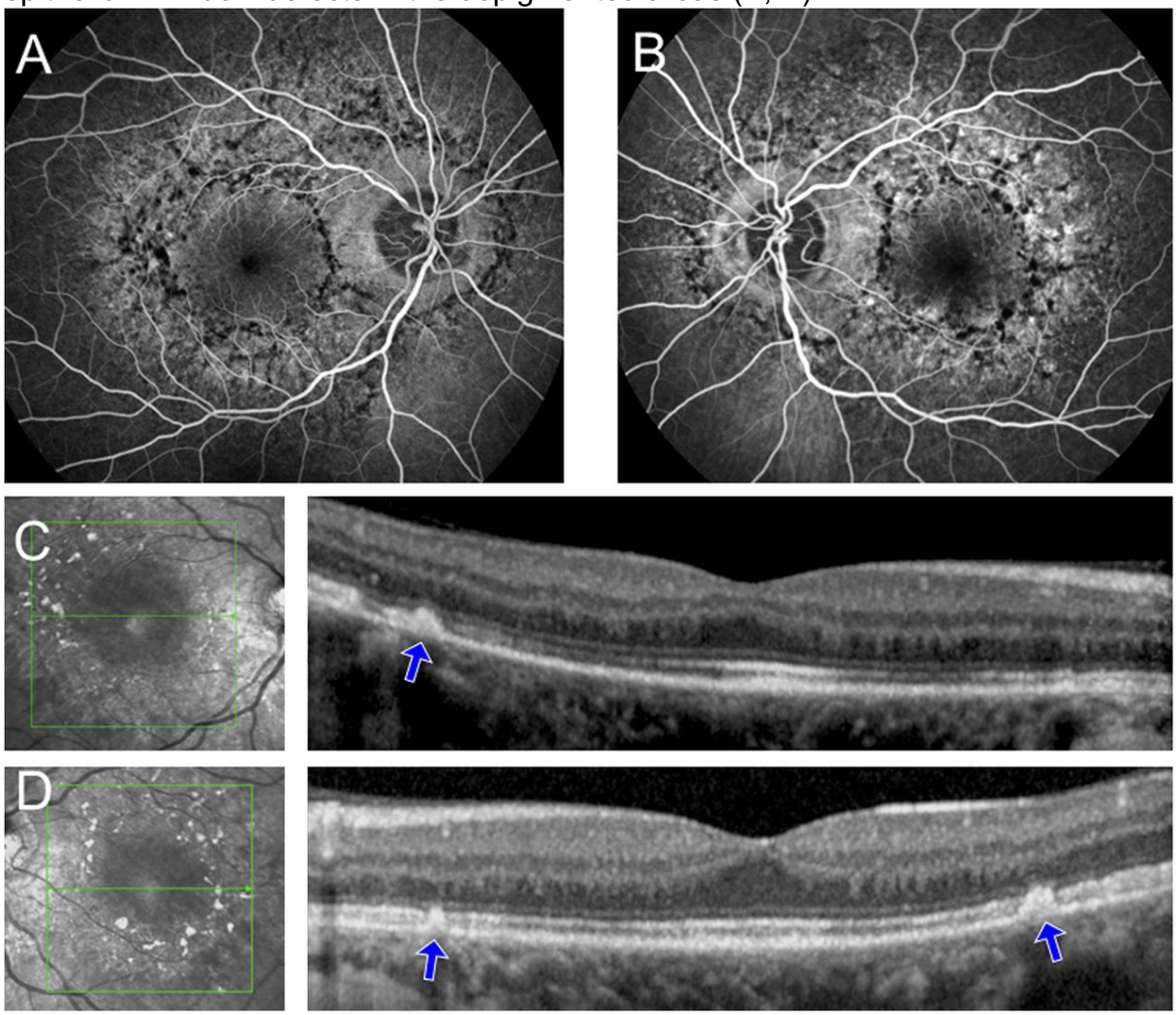
Abbreviations: ADOA, autosomal dominant optic atrophy; AHD, Alpers-Huttenlocher disease; HMSN-IV, hereditary motor and sensory neuropathy type IV; IOSCA, infantile-onset spinocerebellar ataxia; KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; LS, Leigh syndrome; MD, mitochondrial disorder; MDD, maternally inherited deafness and diabetes; MDS, mitochondrial depletion syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MERRF, myoclonus epilepsy with ragged red fibers; MIRAS, mitochondrial recessive ataxia syndrome; MLASA, mitochondrial myopathy, lactic acidosis, and sideroblastic anemia; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; NARP, neuropathy ataxia retinitis pigmentosa; NS, nonsyndromic; PCH, pontocerebellar hypoplasia; PEO, progressive external ophthalmoplegia; PS: Pearson syndrome; SANDO, sensory ataxic neuropathy with dysarthria and ophthalmoparesis; WS, Wolfram syndrome; XLASA, X-linked sideroblastic anemia with ataxia.

Table 2. Ocular Manifestations of Syndromic and Non-syndromic mitochondrial disorders.

MD	Cor	IA	CAT	RP	Glau	Chor	DBM	OA	PEO	PT
MELAS	−	+	+	+	−	+	+	+	+	+
MERRF	−	−	+	+	−	−	−	+	+	+
LHON	−	+	+	+	+	−	+	+	−	−
PEO	−	−	+	+	−	−	−	−	+	+
KSS	+	−	−	+	+	−	−	+	+	+
PS	+	−	+	+	−	−	+	+	−	+
NARP	−	−	−	+	−	−	−	+	−	−
LS	+	−	+	+	−	−	+	+	+	+
MDD	−	−	+	+	−	−	−	−	+	+
MNGIE	+	−	−	+	+	−	−	+	+	+
ARCO	−	−	−	−	−	−	−	−	+	−
MLASA	−	−	−	−	−	−	−	−	−	+
XLASA	−	−	−	−	−	−	+	−	−	−
PCH	+	−	−	+	+	−	+	+	−	−
ADOA	−	−	+	−	+	−	+	+	+	+
IOSCA	−	−	−	−	−	−	−	+	+	−
ARSAL	−	−	−	+	−	−	+	−	−	−
SANDO	−	−	−	−	−	−	−	−	+	+
MIRAS	−	−	−	−	−	−	−	−	+	−
MTS/DDS	−	−	−	+	−	+	−	+	−	−
WS	−	−	+	+	+	−	+	+	+	−
DYTCA	−	−	−	−	−	−	+	−	−	−
AHD	−	−	−	−	−	−	−	+	+	−
MDS	−	−	−	−	−	−	+	+	+	+
NS	+	+	+	+	+	+	+	+	+	+

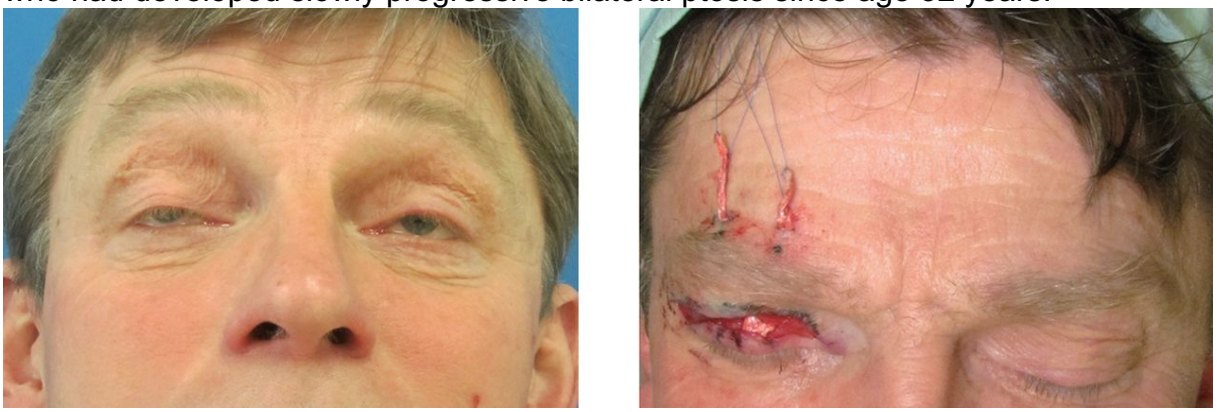
Abbreviations: ADOA, autosomal dominant optic atrophy; AHD, Alpers-Huttenlocher disease; ARCO, autosomal recessive cardiomyopathy and ophthalmoplegia; ARSAL, autosomal recessive spastic ataxia with leukoencephalopathy; CAT, cataract; Chor, chronic chorodieal abnormality; Cor, corneal involvement; DBM, disturbed bulb motility; DYTCA, dystonia and mild cerebellar ataxia; Glau, glaucoma; IA, iris atrophy; IOSCA, infantile-onset spinocerebellar ataxia; KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; LS, Leigh syndrome; MD, mitochondrial disorder; MDD, maternally inherited deafness and diabetes; MDS, mitochondrial depletion syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MIRAS, mitochondrial recessive ataxia syndrome; MLASA, mitochondrial myopathy, lactic acidosis, and sideroblastic anemia; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; MTS, Mohr-Tranebjaerg syndrome; NARP, neuropathy ataxia retinitis pigmentosa; NS: nonsyndromic mitochondrial disorder; OA, optic atrophy; PCH, pontocerebellar hypoplasia; PEO, progressive external ophthalmoplegia; PS, Pearson syndrome; PT, ptosis; RP, retinopathy; SANDO, sensory ataxic neuropathy with dysarthria and ophthalmoparesis; WS, Wolfram syndrome; XLASA, X-linked sideroblastic anemia with ataxia.

Figure 1. Fluorescein angiography showing blocking of background fluorescence in areas of hyperpigmentation and hyperfluorescence due to a retinal pigment epithelium window defects in the depigmented areas (A, B).



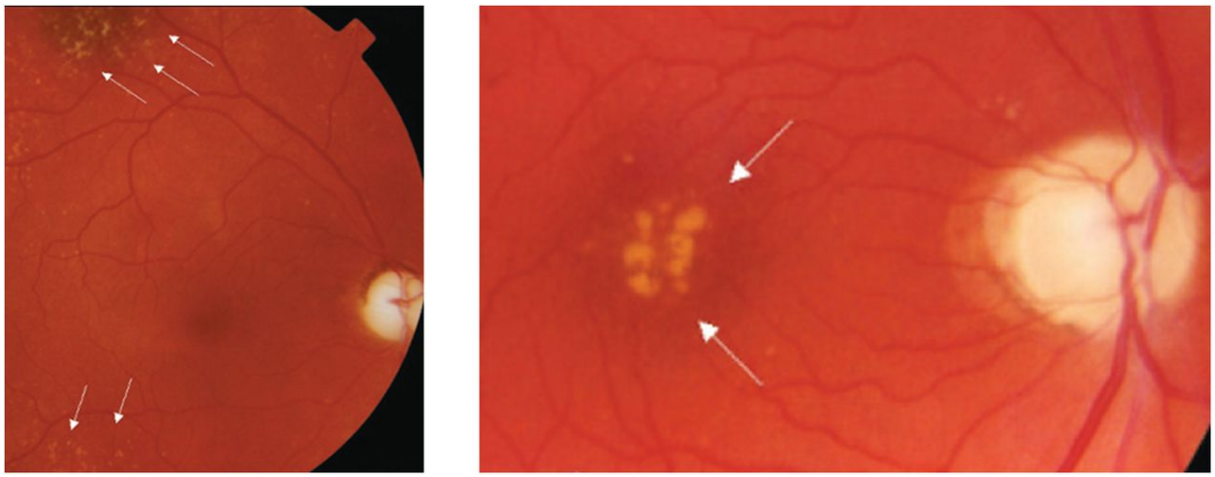
Fluorescein angiography showing blocking of background fluorescence in areas of hyperpigmentation and hyperfluorescence due to a retinal pigment epithelium window defects in the depigmented areas (A, B). On spectral domain optical coherence tomography scans taken through the planes indicated by the green arrows, hyperpigmented areas corresponding to a hyperreflective dome-shaped lesion that seemed to originate from the retinal pigment epithelium are shown (blue arrows) (C, D).

Figure 2. A 58-year-old man with genetically unconfirmed Kearns-Sayre syndrome who had developed slowly progressive bilateral ptosis since age 32 years.



A 58-year-old man with genetically unconfirmed Kearns-Sayre syndrome who had developed slowly progressive bilateral ptosis since age 32 years. He had undergone a first surgical ptosis correction at age 46 years but experienced a relapse already 1 year later. He underwent a second ptosis correction on the right side at age 58 years.

Figure 3. Funduscopy of a patient carrying the mitochondrial DNA mutation m.13042G>A in the ND5 gene showing complete optic atrophy and retinopathy characterized by yellowish dots in the retinal pigmented epithelium with peripheral distribution (left).



Funduscopy of a patient carrying the mitochondrial DNA mutation m.13042G>A in the ND5 gene showing complete optic atrophy and retinopathy characterized by yellowish dots in the retinal pigmented epithelium with peripheral distribution (left). Complete optic atrophy and retinopathy with confluent yellowish dots at the fovea and macula were also seen in the patient's brother (right). In addition to the Leber hereditary optic neuropathy–like optic neuropathy and retinopathy, the phenotype included cataract, strokes, miscarriages, and sudden death.