Chapter

Mitochondria and Eye

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Abstract

Mitochondria are essential subcellular organelles and important key regulators of metabolism. Mammalian mitochondria contain their own DNA (mtDNA). Human mtDNA is remarkably small (16,569 bp) compared to nuclear DNA. Mitochondria promote aerobic respiration, an important part of energy metabolism in eukaryotes, as the site of oxidative phosphorylation (OXPHOS). OXPHOS occurs in the inner membrane of the mitochondrion and involves 5 protein complexes that sequentially undergo reduction-oxygen reactions ultimately producing adenosine triphosphate (ATP). Tissues with high metabolic demand such as lungs, central nervous system, peripheral nerves, heart, adrenal glands, renal tubules and the retina are affected preferentially by this critical role in energy production by mitochondrial disorders. Eye-affected mitochondrial disorders are always primary, but the role of mitochondrial dysfunction is now best understood in acquired chronic progressive ocular diseases. Recent advances in mitochondrial research have improved our understanding of ocular disorders. In this chapter, we will discuss the mitochondria in relation to eye diseases, ocular tumors, pathogenesis, and treatment modalities that will help to improve the outcomes of these conditions.

Keywords: mitochondria, LHON, biomarkers, mutations, tumors

1. Mitochondria

Mitochondria are essential sub cellular mammalian organelles found in eukaryotes. It is surrounded by two lipid bilayers which is commonly associated with oxidative phosphorylation, a process that meets the majority of cellular energy demands. It is involved in many other cellular functions such as fatty acids oxidation, apoptosis, heme biosynthesis, metabolism of amino acids and lipids, and signal transduction [1]. They are central organelles controlling the life and death of the cell. Mitochondria contain their own DNA, which is maternally inherited. Mitochondrial density varies from one tissue to another [2]. Mitochondrial diseases are heterogeneous group of disorders, often characterized by morphological changes in the mitochondria, a defective respiratory chain and variable symptoms, ranging from severe metabolic disorders with onset in early infancy or childhood to late onset adult myopathies [3]. Mutations in mitochondrial DNA (mtDNA) are the most frequent cause of mitochondrial diseases in adults. However, the mtDNA encodes only a subset of proteins of the different complexes of the respiratory chain [4]. Nuclear genes encode all the other mitochondrial proteins and most of the mitochondrial disorders are caused by mutations in the nuclear genes [5].

Mitochondria are ~0.5 to ~3 μm long tubular organelles that undergo continuous remodeling of their network by fusion and fission events [6]. Mitochondria forms an extensive network preserved in many cells by an intricate balance between
fission and fusion, mitochondrial biogenesis and mitophagy [7, 8]. Mitochondria was identified as the main source of cell energy, and indeed mitochondria is a major site of ATP and macromolecule development. Equivalent-reducing electrons are fuelled by the ETC to produce an electrochemical gradient required for both the production of ATP and the active transport of selective metabolites, such as pyruvate and ATP, through the IMM [9]. Mitochondria, however, plays a variety of roles beyond energy production, including generation of reactive oxygen species (ROS), redox molecules and metabolites, control of cell signaling and cell death, and biosynthetic metabolism.

While mitochondria is best known for harvesting and storage of energy released by oxidation of organic substrates under aerobic conditions by respiration, their many anabolic functions are often ignored [7]. Biosynthetic functions of mitochondria are essential for tumorigenesis and tumor progression [10]. Tumor cells easily survive under hypoxic conditions by recycling NADH to NAD+ through lactate dehydrogenase (LDH) and plasma membrane electron transport (PMET) to enable continued production of glycolytic ATP [11].

2. Mitochondrial genetics

The human mitochondrial genome consists of 16,569 pairs of nucleotides of double-stranded, closed-circular molecules. It was first sequenced in 1981 and updated in 1999 [12, 13]. mtDNA contains no introns and only encodes 13 polypeptides, 22 transfer RNAs (tRNAs), and the mitochondrial protein synthesis genes 12S and 16S rRNA [14]. The 13 polypeptides of the respiratory complexes (RC) encode subunits (7 of 45 for RC-I, 1 of 11 for RC-III, 3 of 13 for RC-IV, and 2 of 16 for RC-V). Along with the remaining 85% of the other RC subunits, the four subunits that make up RC-II are nuclear-encoded [14]. About 22,000 proteins are encoded by nuclear DNA, about 1,500 of which contribute to the mitochondrial proteome. These nuclear encoded proteins include TCA cycle enzymes, amino acids, nucleic acid and lipid biosynthesis, mtDNA and RNA polymerases, transcription factors, and ribosomal proteins, in addition to all DNA pathway repair components. In the cytoplasm, these proteins are expressed and folded through the TOM/TIM complex upon entry through the mitochondrial outer membrane. From there, they find the outer mitochondrial membrane (OMM), the IMM, the intermembrane space (IMS) or the mitochondrial matrix at their specific positions [15]. There is no structural association of mtDNA with histones, as is nuclear DNA. Rather, it is closely associated with a variety of proteins, about 100 nm in diameter, in discrete nucleoids.

Germline mutations resulting in reduced or lost expression of succinate dehydrogenase (SDH), fumarate hydratase (FH) and isocitrate dehydrogenase have been identified in inherited paragangliomas, gastrointestinal stromal tumors, pheochromocytomas, myomas, SDH, papillary renal cell cancer (FH) and gliomas [16]. mtDNA mutations have been involved in neuromuscular and neurodegenerative mitochondrial disease [17–19] and complex diseases such as diabetes [20], cardiovascular disease [21, 22], gastrointestinal disorders [23], skin disorders [24], aging [25, 26] and cancer. Different human populations have different human mtDNA haplotypes, each with a specific mtDNA polymorphism fingerprint, transmitted through the maternal germline. These haplotypes are associated with the geographic origin of the population. Some human haplotypes are at greater risk of developing a certain form of cancer or neurodegenerative disorder during their lifetime than others [27–29]. The 22 mitochondrial tRNA genes have more than 50 percent of the mtDNA mutations involved in carcinogenesis [29].
The single nucleotide polymorphism, 3243A > G, which alters leucine mt-tRNA and thus affects the translation of 13 respiratory subunits, leading to fewer mitochondrial subunits and impaired OXPHOS, is the most common mtDNA mutation [30, 31]. Individuals can develop maternally inherited diabetes and deafness with 10–30 percent defective copies of tRNALeu. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) are likely to occur in people with 50–90% defective copies [20, 30–35]. The mutation of tRNALeu results in variable types of mitochondrial RC deficiency in various patients. By far, complex I (RC-I) deficiency is the most common finding in MELAS, although some patients have combined RC-I, RC-III and RC-IV deficiencies [30, 36]. Other mutations in mt-tRNA that play a role in human disease include: tRNAlys, which is associated with myoclonal epilepsy, tRNAser with deafness, and tRNAlle with cardiomyopathy [21].

3. Drivers of mtDNA mutations

mtDNA mutations are caused by ROS-mediated oxidative damage [28, 37]. ROS generation in the respiratory chain is an inherent part of OXPHOS. ROS plays an important role in many signaling processes and their levels are regulated by the antioxidant enzyme systems in the mitochondrial matrix and the IMS. However, in situations where OXPHOS is compromised due to misshapen respiratory complexes resulting in increased leakage of electrons to oxygen, ROS levels can overwhelm the antioxidant protection system and damage to nearby mtDNA [38, 39]. DeBalsi and colleagues suggest that errors produced by mtDNA replication and repair machines may also cause mtDNA mutations [40].

Human cells contain 17 different human DNA polymerases, but in mtDNA replication and repair, only polymerase gamma (Pol-γ) functions. A catalytic subunit and an accessory subunit consist of a nuclear-encoded Pol-γ holo-enzyme [40]. Pol-γ replicates high fidelity mtDNA with one misinsertion in every 500,000 new base pairs due to nucleotide selectivity and proofreading capacity [41]. More than 300 Pol-γ mutations have been associated with human illness, some of which occur in adulthood and are associated with aging, including different types of progressive external ophthalmoplegia (PEO) and Parkinson’s disease (PD) [40]. The role of Pol-γ in restricting mtDNA mutations has been demonstrated by homozygous, but not heterozygous, mutator mice with re-reading-deficient Pol-g developing multiple age-related disorders and shortening their lifespan. As their antioxidant capacities were the same and the degree of oxidative damage was comparable to wild-type mice, they acquired mtDNA mutations that were not caused by oxidative damage.

Somatic point mutations, great deletions and several linear deleted mtDNA fragments were acquired by the mutator mice. The mtDNA-specific Twinkle helicase, which unwinds mtDNA for Pol-γ synthesis, is another n-mitoprotein involved in mtDNA replication [42]. Overexpression of Twinkle in transgenic mice resulted in increased copy number of mtDNA and OXPHOS and some twinkle mutations are associated with mitochondrial myopathy [40]. Oxidative damage and defective replication are both likely to add to the overall mutational load of the mtDNA cell, and the contribution of each mutational driver is likely to change over time. Inevitable respiratory electron leakage from complexes I and III results in the formation of superoxide, O₂⁻ that can react with lipids, proteins and DNA [43–46]. Superoxide can be quickly converted to H₂O₂ either naturally or through a manganese superoxide dismutase (MnSOD) dysmutation reaction, a resident of the mitochondrial matrix. In the presence of redox active metal ions, H₂O₂ can generate a highly reactive hydroxyl radical through the Fenton reaction (OH-) [47]. Multiple mtDNA
damage sites, including single and double-strand breaks, abasic sites and base changes, are responsible for the OH-radical. Another oxidative burden is caused by damage to mitochondrial protein centers caused by O$_2^-$ to Fe-S and involves sub-units of complexes I, II and III as well as aconitase [48–50]. A significant target for ROS is provided by Labile Fe-S enzymes such as mitochondrial aconitase.

Mitochondria located in cells exposed to visible light generate ROS through interactions with mitochondrial photosensitizers, such as cytochrome c oxidase, of particular relevance to the eye, to produce ROS and mtDNA damage [50, 51]. Transferring energy from photoactivated chromophores to oxygen contributes to the formation of singlet oxygen, $^1$O$_2$, which occurs in an excited state. $^1$O$_2$ can produce ROS, such as O$_2^-$ by interacting with diatomic oxygen and directly reacting with dual-bond electrons without the formation of free radical intermediates [52]. It is also important to remember that, from non-mitochondrial sources, various tissues within the eye may also produce substantial amounts of ROS. For instance, lipofuscin (an age-related pigment that accumulates with age in RPE cells) is a potent photoinducible ROS generator, and NADPH oxidase is considered to be a major source of superoxide in microvascular endothelial cells. Studies indicate that ROS may also contribute to exogenous mitochondrial oxidative damage, exacerbating mitochondrial dysfunction [51, 53, 54].

4. Ophthalmologic mitochondrial dysfunction

Mitochondrial disease can manifest in any organ at any age. In general terms, tissues and organs (retina, optic nerve, brain, heart, testis, muscle, etc.) that are heavily dependent upon oxidative phosphorylation bear the brunt of the pathology. It is also puzzling that many mitochondrial disorders affect multiple organ systems, whereas others have a highly stereotyped and organ specific phenotype. These subtle interactions between nuclear and mitochondrial genes in health and disease will have broader relevance for our understanding of many inherited and sporadic disorders.

Mitochondrial disorder can be categorized according to several different criteria in the manifestations of ophthalmology diseases. They may be defined as isolated or nonisolated, occurring in combination with other manifestations of the organ. The dominant trait of the phenotype or a nondominant attribute can be ophthalmologic manifestations. Mitochondrial disorders with ophthalmic manifestations may be caused either by mutations in mtDNA or nuclear DNA. Ophthalmologic symptoms may be unique to syndromic mitochondrial disorder (e.g. Leber hereditary optic neuropathy) or nonspecific to syndromic mitochondrial disorder (eg, cataract). The cornea, iris, lens, ciliary body, retina, choroid, uvea, or optic nerve may be the primary manifestations of ophthalmologic mitochondrial disorder. There is growing evidence supporting an association between mitochondrial dysfunction and a number of ophthalmic diseases causing defects in OXPHOS and increased production of ROS triggering the activation of cell death pathway.

5. Corneal dystrophy

Some evidence has been given in recent years that the cornea may be involved in mitochondrial disorders. However, systematic studies have not been performed on this matter. Astigmatism, corneal dystrophy, corneal clouding, or corneal endothelial dysfunction are corneal disorders associated with mitochondrial dysfunction [55, 56]. Loss of SLC4A11 gene activity which is localized to the inner
mitochondrial membrane of corneal endothelium, induces oxidative stress and cell death, resulting in Congenital Hereditary Endothelial Dystrophy (CHED) with corneal edema and vision loss [57]. Fuchs endothelial corneal dystrophy (FECD) is characterized by progressive and non-regenerative corneal endothelial loss. Variations in mtDNA affect the susceptibility of FECD. Mitochondrial variant A10398G and Haplogroup I were significantly associated with FECD [58]. There are few studies showing the role of mtDNA in the pathogenesis of FECD. Mitophagy activation leads to decrease in Mfn2 gene level and loss of mitochondrial mass in FECD [59]. In a study of 20 patients, keratoconus was related to increased oxidative stress due to mitochondrial respiratory chain complex-I sequence variation [60]. Progressive external ophthalmoplegia secondarily led to persistent conjunctivitis and keratitis in a patient with Kearns-Sayre Syndrome [61]. Corneal clouding has been documented occasionally in Kearns-Sayre syndrome due to structural changes in the endothelium or Descemet membrane [62]. Numerous distended mitochondria were present in the corneal epithelium in a child with Leigh syndrome due to the m.8993 T > G mutation [63]. There are also non-specific corneal alterations in a patient with Neurogastrointestinal mitochondrial encephalomyopathy [64]. Pathogenesis of type 2 granular corneal dystrophy (GCD2) is associated with alteration of mitochondrial features and functions that causes mutated GCD2 keratocytes, particularly in older cells [65].

6. Mitochondrial encephalomyopathy, lactic acidosis, and episodic stroke-like syndrome (MELAS)

Early onset of the disease and higher level of mtDNA heteroplasmy are associated with a worse prognosis in mitochondrial encephalomyopathy, lactic acidosis, and episodic stroke-like syndrome (MELAS). Iris involvement in mitochondrial disorders has been rarely mentioned in MELAS [66]. The m.3243A > G variant is the most common heteroplasmatic mtDNA mutation in MELAS and underlies a spectrum of diseases. Patchy iris stroma atrophy has been identified in a patient carrying the m.3243A > G mutation in the tRNA (Lys) gene [66]. MNRR1 (CHCHD2) is a bi-organellar regulator of mitochondrial function, found to be depleted in MELAS and significantly associated with m.3243A > G mutation (heteroplasmic) in the mtDNA at a level of ~50 to 90% [67]. Ability of the peroxisome proliferator-activated receptor γ (PPARγ) activator pioglitazone (PioG), in combination with deoxyribonucleosides (dNs), improves the mitochondrial biogenesis/respiratory functions in MELAS cybrid cells containing >90% of the m.3243A > G mutation that found to be novel therapies to treat this disease [68]. Induced pluripotent stem cells (iPSCs) are appropriate for studying mitochondrial diseases caused by mtDNA mutations in MELAS. Increase of autophagy inpatient-specific iPSCs generated from fibroblasts are associated with mtDNA mutations and OXPHOS defects in patients with MELAS [69]. Studies demonstrated that defective MRM2 gene causes a MELAS-like phenotype which suggests the genetic screening of the MRM2 gene in patients with a m.3243 A > G negative MELAS-like presentation [70]. Mutations caused by mitochondrial complex I deficiencies by alleviating ketone bodies are also associated with MELAS that leads to recurrent cerebral insults resembling strokes [71].

7. Cataract

Cataracts are the most common lenticular defects of mitochondrial disorders. In mitochondrial disorders, cataract is typically of the posterior subcapsular type [66].
Autophagic dysfunction and abnormal oxidative stress are associated with cataract. Cataract may be a phenotypic characteristic of MELAS syndrome, but a patient with nonsyndromic mitochondrial disorder due to mtDNA deletion has also been documented as an initial manifestation [66, 72, 73]. Oxidative stress plays an important role in cataractogenesis [74, 75]. Mitochondria are found in the epithelium and superficial fiber cells of the lens and it is extremely sensitive to ROS. Interestingly, mitochondria have been confirmed as the main source of ROS generation in these cell types [76]. A number of in vitro studies have shown that human lens cells are particularly sensitive to oxidative insults, where antioxidant activity was inversely proportional to the severity of cataracts [77]. Proteins, lipids and DNA oxidation have been found in cataract lenses [78–80]. Under high glucose conditions, fluctuations in autophagy and oxidative stress are found in mouse lens epithelial cells (LECs) that might attenuate high glucose-induced oxidative injury to LECs [81]. Cataract proteins lose sulfhydryl groups, contain oxidized residues, produce aggregates of high molecular weight and become insoluble [75]. In addition, cataract has been shown to be a symptom of a newly identified mitochondrial disorder called autosomal recessive myopathy, caused by growth factor mutations, increased liver regeneration gene, which affects protein levels of mitochondrial intermembrane space region [82].

8. Leigh syndrome

In mitochondrial disorders, involvement of ciliary body has rarely been reported. Leigh's syndrome is the most common pediatric syndrome, characterized by symmetrical brain lesions, hypotonia, motor and respiratory deficits, and premature death are associated with pathways involved in mitochondrial diseases [83]. A case report showed ocular histopathological finding such as 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, non-pigmented cilia are associated with the m.8993 T > G mutation in the ATPase6 gene of mtDNA in patient with Leigh's syndrome [63]. In addition, ciliary epithelium was also found to be impaired by a long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency [84]. Dysfunction of mitochondrial complex I are also associated with many brain pathologies including Leigh's syndrome. Mitochondrial complex I activity facilitates organismal survival by its regeneration potential of NAD+, while optimal motor regulation involves mitochondrial complex I bioenergetic function in Leigh's syndrome [85].

9. Retinitis pigmentosa

Retinitis pigmentosa is a central characteristic of Kearns-Sayre syndrome and neuropathic ataxia retinitis pigmentosa syndrome [72]. Typical for Kearns-Sayre syndrome is ‘salt and pepper’ retinitis, with areas of increased and decreased pigmentation, especially in the equatorial fundus [62]. Pigment retinopathy is only an uncommon characteristic of progressive external ophalmoplegia and can be milder than in Kearns-Sayre syndrome [72, 86]. Only certain patients with MELAS or MERRF syndrome have mild posterior pole pigment retinopathy [72]. Mild pigmentary defects were also observed in 2 of 20 patients with Leber hereditary optic neuropathy due to mutation m.11778G > A [72]. Small pigment retinal defects have been identified in a 4-year-old female with a COX deficiency [87]. In addition, because of the mutation m.8993 T > GG retinitis pigmentosa has been identified in patients with Leigh syndrome [88].
In a sample of 44 Korean Leigh syndrome patients, pigmentary retinopathy was also observed in 22% of Korean patients [89]. In a study of 14 patients with pontocerebellar hypoplasia, 4 patients presented with retinopathy without disclosing information [90]. Occasionally, retinal dystrophy can manifest with photophobia. In a report of 46 mitochondrial disease patients, 4 had photophobia. Two patients had Leigh syndrome, 1 of which had rod-cone dystrophy on electroretinography, 1 had Kearns-Sayre syndrome with regular electroretinography, and 1 had MERRF syndrome with isoelectric electroretinography [91].

10. Diabetic retinopathy

It has been shown that mitochondrial dysfunction plays a significant role in diabetic retinopathy [92, 93]. Hyperglycemia causes retinal mitochondrial damages that plays a central role in the development of diabetic retinopathy. Retinal mitochondria undergo elevated oxidative stress in diabetes, and complex III is one of the key causes of increased $O_2^-$ [94]. Superoxide levels are elevated in the retina of diabetic rats and in retinal vascular endothelial cells incubated in high-glucose media [95] and the content of hydrogen peroxide is also increased in the retina of diabetic rats [96]. In diabetes, membrane lipid peroxidation and oxidative DNA damage, the effects of ROS-induced injury, are elevated in the retina [97]. Chronic overproduction of ROS in the retina results in aberrant mitochondrial functions in diabetes [92]. Overproduction of superoxide by the mitochondrial electron transport chain caused by hyperglycemia is considered to cause major hyperglycemic damage pathways by inhibiting the action of GAPDH. However, it is not yet fully understood the mechanism by which hyperglycemia induces an increase in mitochondrial ROS, with some suggesting a direct effect and others an indirect function via high-glucose-induced cytokines [98–101].

Elevated levels of $O_2^-$ activate caspase 3 in retinal capillaries contributes to cell death [92]. Upregulation of superoxide dismutase (SOD2) inhibited increased mitochondrial O2-induced diabetes, restored mitochondrial function, and prevented both in vitro and in vivo vascular pathology [94, 102–104]. However, the timing of such therapies is important because animal studies have shown that oxidative stress not only leads to the development of diabetic retinopathy, but also to the resistance of retinopathy to reversal [105]. The resistance to reversal of diabetic retinopathy may be due to the accumulation of weakened mitochondrial molecules and ROS-induced damage that is not readily removed even after the restoration of high glycemic control. However, the accumulation of advanced glycation end products is also involved in metabolic memory [106]. The mtDNA variation has also been associated with resistance to type 1 diabetes. A single nucleotide modification (C5173A) is associated with resistance to type 1 diabetes in the Japanese population, resulting in a leucine-to-methionine amino acid substitution in the mitochondrially encoded NADH dehydrogenase subunit 2 gene [107]. Similarly, in comparison with the diabetes-prone nonobese diabetic mouse strain, orthologous polymorphism (C4738A), resulting in L-to-M substitution, offers resistance against the development of spontaneous diabetes [108]. Gusdon et al., have shown that the replacement of methionine results in a lower level of development of ROS from complex III [109].

The product of mtDNA mutations is also known to result in many syndromic central nervous system diseases. The most common retinal pathology is pigmentary retinopathy, while optic neuropathy is an uncommon finding in these disorders. Neurogenic atrophy and retinitis pigmentosa syndrome results from point mutations in the mtDNA ATPase-6 gene, usually T8993G variation. Patients usually
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present with retinitis pigmentosa with or without optic neuropathy and may
develop dystonia [110]. Several mtDNA point mutations may result from MELAS,
although the A3243G mutation in the tRNALeu gene is the most common. Patients
with MELAS undergo stroke-like episodes leading to recurrent retrochiasmal vision
loss, but sometimes even to pigmentary retinopathy without optic atrophy [111].
Its contribution to the pathogenesis of maternally inherited diabetes and deaf-
ness is also evidenced by the spectrum of disease resulting from the A3243G point
mutation [112–114]. This is a multisystemic disease characterized by sensorineural
deafness, retinal defects and diabetes, generally occurring in the third to fourth
decades of life [115]. The second phenotype is a pattern dystrophy, with diffuse
granularity and pigment clumping, marked by relative sparing of the fovea, and
retinal pigment epithelium within the vascular retinal arcades. However, with a
strong prognosis, visual acuity is retained, despite the degree of atrophy [116, 117].

11. Macular degeneration

Age-related macular degeneration is a neurodegenerative late-onset disorder that
shares certain characteristics of Alzheimer’s disease. In most cases, the build-up of
protein plaques, known as drusen, in the central macular area of the retina involves
age-related macular degeneration. Both age-related macular degeneration and
Alzheimer’s disease pathogenesis can be driven by stress stimuli, including oxidative
stress, aging, genetic factors and inflammation, including the deposition of protein
plaques in the retina or brain [98]. Similarities in these two disorders are also found
in the risk factor gene polymorphisms, APOE, associated with age-related macular
degeneration [99, 100] and Alzheimer’s disease [101, 102]. The APOE gene controls
the homeostasis of triglycerides and cholesterol [103], and the loss of function of
APOE has been correlated with the deposit of senile plaques, consisting mainly
of amyloid beta peptide [104], which is produced in drusen [105, 106] and is also
associated with an additional risk factor for age-related macular degeneration, i.e.
complement protein [107, 108]. Evidence shows that the APOE genotype can dictate
the risk of stress stimuli, including oxidative stress, aging, genetic factors and
inflammation, including the deposition of protein plaques in the retina or brain, can
drive both age-related macular degeneration and Alzheimer’s disease pathogenesis.
Alzheimer’s disease and other chronic disorders, primarily because of its effect on
regulation of oxidative stress [109]. Age-related macular degeneration is split into
two main forms, i.e. the “wet” form induced by leakage into the subretinal space
from choroidal neovascularization and the more common “dry” form associated
with the accumulation of drusen in the macula [75]. In patients with age-related
macular degeneration, there is an increased incidence of large-scale mtDNA rear-
rangements and deletions in blood [76] and retinas [77, 78]. In the non-coding
mtDNA control area (d-loop) in retinas with age-related macular degeneration,
which has been found in Alzheimer’s disease and other conditions of oxidative
stress, there are also increased rates of single nucleotide polymorphisms [79]. An
increased rate of mtDNA deletions and single nucleotide polymorphisms are likely
to decrease the amount and density of mitochondria [80].

Other than pigmentary retinopathy or macular degeneration, retinal anomalies
include retinal dystrophy, retinal hypertrophy, and pigmentary maculopathy.
Patients with Kearns-Sayre syndrome, Leigh syndrome, MELAS syndrome,
MERRF syndrome, and Leber hereditary optic neuropathy will find retinal
dystrophies that are most easily measured by electoretinography [91]. Retinal
hypertrophy has been identified in patients with autosomal recessive spastic
ataxia with leukoencephalopathy and autosomal recessive spastic ataxia with
Charlevoix-Saguenay (ARSAL/ARSACS) [118]. Six affected males in a family with Mohr-Tranebjaerg syndrome had blindness resulting from unexplained retinal degeneration [119]. Treatment options for retinopathy are usually limited.

12. Choroidal dystrophy

Choroid and uvea are occasionally affected by mitochondrial disorders. Choroid atrophy is the most common manifestation of mitochondrial disorders [66]. Choroidal atrophy was especially identified in the sense of MELAS syndrome [66]. Choroid pigment epithelium atrophy also occurs in maternally inherited deafness and diabetes [120]. Central choroidal dystrophy was identified in 1 patient with Mohr-Tranebjaerg syndrome as confirmed by electroretinography [119]. In addition, chorioretinal dystrophy was reported in a single patient with a significant deletion of mtDNA [121].

13. Uveitis

A significant causative factor causing blindness from retinal photoreceptor degeneration is intraocular inflammation, also referred to as uveitis. Activated macrophages, which generate various cytotoxic agents, including inducible nitric oxide generated by inducible nitric oxide synthase, O$_2$· and other ROS, are responsible for oxidative retinal damage in uveitis [122]. Oxidative stress plays an important role in the early stages of experimental autoimmune uveitis (EAU) in the photoreceptor mitochondria. mtDNA damage has been shown to occur early in the EAU; interestingly, nDNA damage occurred later in the EAU [123]. In addition, peroxynitrite-mediated nitration modifies mitochondrial proteins in the inner segments of the photoreceptor, which, in turn, contributes to increased mitochondrial ROS generation [124]. MnSOD has been shown to be upregulated during EAU to promote an increased state of mitochondrial oxidative stress, possibly to combat ROS [125]. In the early phase of the EAU, before leukocyte infiltration, recent data seem to indicate a causative function of oxidative mtDNA harm. Such mitochondrial oxidative damage can be the initial event that contributes to retinal degeneration in uveitis [123].

14. Optic atrophy

Optic atrophy is the principal mitochondrial dysfunction manifestation of the optic nerve. Optic atrophy is a prevalent manifestation of mitochondrial disorder but is often overlooked or misinterpreted. This is due to the difficulties of optic atrophy diagnosis. Funduscopy can more reliably determine optic atrophy if the distal portion of the optic nerve is impaired, or if the more proximal portions of the nerve are affected by orbital magnetic resonance imaging (MRI). A decreased amplitude of visually evoked potential is a sign of optic nerve atrophy [126]. Optic atrophy has been specifically identified in Leber hereditary optic neuropathy and autosomal dominant optic atrophy among syndromic mitochondrial disorders, conditions in which optic atrophy is the dominant phenotypic function [127]. MELAS syndrome, Kearns-Sayre syndrome, Pearson syndrome, pontocerebellar hypoplasia, Mohr-Tranebjaerg syndrome, Alpers-Huttenlocher disease or Wolfram syndrome have been documented more rarely, with optic atrophy [62, 90, 91, 127]. In patients with MERRF syndrome, partial or complete optic atrophy has also been
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identified [72, 91, 128]. Optical atrophy is a common phenotypic characteristic of inherited motor and sensory neuropathy type VI (HMSN-IV) due to MFN1 mutations [127]. In addition, C12orf65 (COXPD7) mutations manifest phenotypically with optical atrophy and Leigh-like phenotype [129]. Optical atrophy associated with neuropathy ataxia retinitis pigmentosa syndrome due to m.8993 T > G mutation in the ATPase6 gene was only seen in a single family [110]. In a study of 44 Korean patients with Leigh Syndrome, 22.5 per cent of optical atrophy was identified [89]. Optical disk alterations have been observed only in a single patient with mitochondrial neurogastrointestinal encephalomyopathy [64]. Optical atrophy can also be a characteristic of childhood-onset spinocerebellar ataxia [130] or mitochondrial depletion syndrome. Non-syndromic mitochondrial optic atrophy disorders is attributed to AC11 mutation [131], due to ND5 mutation with cataract and retinopathy [132].

15. Glaucoma

Increased intraocular pressure (Glaucoma) is an unusual phenotypic characteristic of mitochondrial disorders. There are two primary types of glaucoma that can be distinguished, open-angle glaucoma and closed-angle glaucoma. In addition, normotensive and hypertensive glaucoma are distinguished. Open-angle glaucoma is seldom observed in patients with Leber inherited optic neuropathy or autosomal dominant optic atrophy. Funduscopic findings can indicate a mixture of abnormalities common for glaucoma retinopathy and an inherited Leber optic neuropathy fundus [133]. In a single patient with mitochondrial neurogastrointestinal encephalomyopathy, glaucomatous changes in the optic disc were observed by visual field assessment and optical coherence tomography [64]. In a study of 14 patients with pontocerebellar hypoplasia, one presented with glaucoma [90]. Normal pressure glaucoma is associated with polymorphism in the OPA1 gene [134].

Glaucoma has also been identified in a family with Wolfram Syndrome. There are signs that ND5 mutations are associated with the development of open-angle glaucoma. Glaucoma in mitochondrial disorders may be eligible for treatment with drugs or surgery [135, 136]. There is evidence in glaucoma that mitochondrial dysfunction can reduce the bioenergetic status of retinal ganglion cells, leading to increased susceptibility to oxidative stress and apoptotic cell death [93, 137]. Light exposure may also be an oxidative risk factor, reducing mitochondrial function and increasing the development of ROS in ganglion cells [138]. A defective mitochondria has been highly implicated in neuronal apoptosis in the experimental models of glaucoma [139, 140]. The mtDNA abnormalities further support the importance of mitochondrial dysfunction-associated stress as a risk factor for glaucoma patients [141].

16. Nystagmus

The central nervous system or vestibular involvement in mitochondrial disorders may cause nystagmus or roving eye movements and are the most common ophthalmological manifestations as a symptom in patients with pediatric mitochondrial disorder [142]. A Gaze-evoked nystagmus identified in a single patient with “Leber hereditary optic neuropathy plus” who not only possessed the “m.11778G > A” mutation in the hereditary Leber hereditary optic neuropathy gene but also the “m.3394 T > C” mutation [143]. Since patients with MELAS may display irregular eye movements on an eye movement cueing task, ultrasound records of
eye movement may show abnormally slow saccadic reactions, prolonged saccades, impaired suppression of reflex eye movements, prolonged reaction during antisaccades, square-wave jerks, or impaired chase [144]. Patients have epilepsy due to MELAS may have epileptic nystagmus, disrupted smooth pursuit, or transient eye divergence, none of which are outward signs [145]. In addition, nystagmus was documented in a patient carrying a point mutation in the DGUOK gene who also had retinal blindness. Nystagmus, which is a common symptom of the disease along with 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 [146]. Nystagmus was part of the phenotype in a study of 7 Czech patients with autosomal dominant optic atrophy [147]. Nystagmus is also a common characteristic of ARSAL/ARSACS [148]. Nystagmus was observed in 14 percent in a study of 44 Korean patients with Leigh syndrome [88].

17. Strabismus

Strabismus was the most common ophthalmologic abnormality in a study of 44 Korean patients with Leigh syndrome and was present in 41% of patients [89]. Of the strabismus patients, 13 had exotropia and 5 had esotropia [89]. In some patients with X-linked sideroblast anemia with ataxia, strabismus has also been identified [149]. In 25 percent of juvenile mitochondrial disorders, divergent strabismus has been identified as the presenting manifestation [150]. In a study of 14 patients with pontocerebellar hypoplasia, of whom 13 had a CASK mutation, 2 had strabismus. 9 Strabismus was also identified without knowing the underlying mutation in other patients with pontocerebellar hypoplasia [151, 152]. The initial presentation at birth was cataract and strabismus in a child with a significant mtDNA deletion. Later on, he experienced Leigh-like pathologies and episodes of stroke [153]. In certain instances, surgery can have a beneficial effect on strabism.

18. Progressive external ophthalmoplegia

In mitochondrial disorders, affectation of the extraocular muscles results in progressive external ophthalmoplegia. The recurrent ophthalmologic manifestation of mitochondrial disorders is progressive external ophthalmoplegia. It may be complete, resulting in, or partial, walled-in bulbs. Both directions of bulb movements or only some of them can be affected. One eye or both eyes can be affected by it. Single or multiple mtDNA deletions are most often associated with progressive external ophthalmoplegia. Progressive external ophthalmoplegia, Kearns-Sayre syndrome or Pearson syndrome can cause single mtDNA deletions [154]. Multiple deletions of mtDNA may be due to mutations in nuclear genes such as PEO1, POLG1, SLC25A4, RRM2B, POLG2, or OPA1, along with progressive external ophthalmoplegia [154]. In addition, progressive external ophthalmoplegia, especially in the transfer of RNA (eg, tRNA(Lys)) genes, may be due to mtDNA point mutations [154]. Transfer RNA mutations with progressive external ophthalmoplegia are mostly sporadically similar to mtDNA deletions and can only be observed in muscle deletions [155]. The sole manifestation of the m.3243A > G mutation, which often manifests as MELAS syndrome, may be progressive external ophthalmoplegia [156]. In a patient with mitochondrial neurogastrointestinal encephalomyopathy, progressive external ophthalmoplegia was a phenotypic feature [64], Wolfram syndrome [157], Leigh syndrome, autosomal dominant optic atrophy, and mitochondrial recessive ataxia.
syndrome. In MERRF syndrome, progressive external ophthalmoplegia has also been described [158].

Infantile-onset spinocerebellar ataxia is a Finnish disorder, with some of the 24 cases identified to date developing ophthalmoplegia [130]. Ophthalmoparesis is a hallmark of sensory ataxic neuropathy with ophthalmoparesis syndrome and dysarthria [159]. Sensory ataxic neuropathy with dysarthria and ophthalmoparesis is due to mutations in either the POLG1 or PEO1 gene resulting in multiple mtDNA deletions [159]. Furthermore, ophthalmoparesis can be observed in patients with mitochondrial depletion syndrome [160] or nonsyndromal mitochondrial disorders [161]. In patients with Leber inherited optic neuropathy and progressive external ophthalmoplegia, ultrastructural variations in muscle biopsy from the extraocular muscles clearly differ [162].

19. Eyelid

Ptosis is one of the most common forms of mitochondrial dysfunction. It can occur unilaterally at onset, but during the course of the disease, it usually becomes bilateral. Ptosis can be the sole manifestation, particularly at the onset of the disease, of a mitochondrial disorder or associated with other manifestations. Particularly at the onset of the disease, ptosis can show dynamic alterations, leading to misinterpretation as myasthenia gravis [163]. Ptosis may be discrete, especially at initiation, so that it is missed on clinical review. Progressive external ophthalmoplegia or other ocular symptoms of mitochondrial disease can be associated with ptosis. Ptosis of syndromic as well as nonsyndromic mitochondrial disorders may be a phenotypic manifestation. In particular, ptosis was identified in progressive external ophthalmoplegia, MELAS, MERRF, Kearns-Sayre syndrome, sensory ataxic neuropathy with dysarthria and ophthalmoparesis [164], Pearson syndrome, mitochondrial neurogastrointestinal encephalomyopathy, and autosomal dominant optic atrophy, among the syndromic mitochondrial disorders [91]. Ptosis was present in 16 percent in a group of 44 Korean patients with Leigh syndrome [89]. Ptosis was also present in isolated cases of maternally inherited deafness and diabetes [156], mitochondrial neurogastrointestinal encephalomyopathy [64], or mitochondrial depletion syndrome [160]. Poor lid closure was found in a Persian Jew with mitochondrial myopathy, lactic acidosis, and sideroblastic anemia due to a PUS1 mutation [165].

20. Leber hereditary optic neuropathy

Leber hereditary optic neuropathy is a maternally inherited blindness condition caused by gene mutations encoding the respiratory-chain complex I subunits. Nearly 90 percent of all cases of Leber inherited optic neuropathy contain mutations in 3 genes [128]. The m.3460A > G mutation in the ND1 gene, the m.11778G > A mutation in the ND4 gene and the m.14484 T > C mutation in the ND6 gene are the 3 most common Leber hereditary optic neuropathy mutations (primary Leber hereditary optic neuropathy mutations) [128]. Leber inherited optic neuropathy is clinically characterized as bilateral, painless, subacute vision impairment that occurs during young adult life [134].

Compared with women, Leber hereditary optic neuropathy is 4 to 5 times more common in males. Individuals affected are usually completely asymptomatic until they experience visual blurring in 1 eye affecting the central visual field [134]. On average, 2 to 3 months later, similar signs develop in the other eye. In most cases,
visual acuity is greatly diminished or even worse when counting fingers, and visual field examination reveals an expanded central or ceco-central thick scotoma [134]. After the acute process, the optical disks become atrophic. Funduscopic findings characteristic of Leber inherited optic neuropathy include microangiopathy, hyperemic disks, retinal telangiectasis (ectatic capillaries), peripapillary microangiopathy, and tortuosity of vessels (twisted vessels). The orbital MRI can display atrophy of the nerve with a compensated widening of the space below the optic sheath. Mutations in mitochondrial ND3, ND4, or ND6 genes can cause hereditary Leber optic neuropathy with dystonia [166].

21. Autosomal dominant optic atrophy

Autosomal dominant optic atrophy is a blindness condition which does not display a gender disparity, unlike Leber inherited optic neuropathy [127]. It is caused by mutations in the nuclearly encoded OPA1 gene [127]. Autosomal dominant optic atrophy can also be due to OPA3 mutations that are associated with cataract [167]. Progressive, painless, bilateral symmetrical vision loss clinically characterizes autosomal dominant optic atrophy [154]. Central, ceco-central, or para-central scotomas, consistent with early involvement of the papillo-macular bundle, are the most common visual field anomalies in autosomal dominant optic atrophy [154]. OPA1 mutations can manifest not only with optic atrophy in some families, but also with progressive external ophthalmoplegia, ptosis, and hypoacusis [168]. Since glaucoma neuropathy, autosomal dominant optic atrophy, and Leber hereditary optic neuropathy often have similar changes in the topographic optic disc, they cannot be discriminated against alone by disc evaluation [169]. There is currently no appropriate treatment available.

22. Retinoblastoma

Retinoblastoma (Rb) is the most common intraocular cancer in children that arise from retinal precursor cells. Electron microscopy revealed numerous morphological and pathological changes in mitochondria of retinoblastoma patients. Cristolysis and degenerated mitochondria were the most frequently observed features in Rb [170]. A study suggested that T16519C, C16223T, A263G and A73G mtDNA D-Loop mutations plays a significant role in the etiology of retinoblastoma. This was the first study to examine the mtDNA D-loop mutation in retinoblastoma and its correlation with various parameters and patient outcome [171]. Their findings imply a strong inhibition of mitochondrial oxidative phosphorylation complexes in these patients. Loss of mitochondrial complex I was found in majority of the cases whereas expression of mitochondrial complex III, IV and V were found in more than 50% of the cases. Expression of mitochondrial complex I was associated with good prognosis and better overall survival [172]. Another consequence of alteration in OXPHOS complexes is an increased production of reactive oxygen species (ROS). NADPH oxidases (NOX4) are a major intracellular source of ROS and it was found to be overexpressed in retinoblastoma [173]. Increased expression of ROS and decreased expression of OXPHOS complexes modulates the apoptotic pathway involved in mitochondria by altering BCl-2 family proteins. Singh et al. showed a differential expression of apoptotic regulatory proteins (Bax, BCI-2, PUMA and p53) where they found increased expression of BCI-2 and PUMA along with loss of Bax and p53, which might contribute to carcinogenesis in Rb [174].
23. Conclusion

Researchers found that these findings are important because they indicate that mtDNA damage can be caused by both spontaneous ROS and by inherited mtDNA mutations. Continued study in this clinically important area would certainly provide a better understanding of how deficiencies/mutations of the mitochondrial genome contribute to the pathogenesis of ocular diseases. The biggest problems with the future of mitochondria are the advancement of therapeutic strategies to target mitochondria and modify its DNA using nucleotide precursors to retain mitochondrial integrity. These therapeutic strategies can potentially be used to block or slow down the effects of mitochondrial disease in future.
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