Ocular manifestations of mitochondrial disease

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Abstract

Mitochondrial disease caused by mutations in mitochondrial DNA is recognized as one of the most common causes of inherited neurological disease. Neuro-ophthalmic manifestations are a common feature of mitochondrial disease. Optic atrophy causing central visual loss is the dominant feature of mitochondrial DNA diseases. Nystagmus is also encountered in mitochondrial disease.

Although optometrists are not involved with the management of mitochondrial disease, they are likely to see more patients with this disease. Ophthalmic examination forms part of the clinical as-sessment of mitochondrial disease. Mitochondrial disease should be suspected in any patient with unexplained optic neuropathy, ophthalmoplegia, pigmentary retinopathy or retrochiasmal visual loss. Despite considerable advances in the under-standing of mitochondrial genetics and the patho-genesis of mtDNA diseases, no effective treatment options are currently available for patients with mitochondrial dysfunction. (*S Afr Optom* 2012 **71**(1) 46-50)

Key Words: dominant optic atrophy, genes, Leb-er hereditary optic neuropathy, mitochondrial dis-ease, DNA mutation, neuro-ophthalmology.

Introduction

Mitochondrial diseases are a group of genetic dis-orders that affect organs which depend a lot on aero-bic metabolism[1-4]. They are recognized as a common cause of metabolic disease. The most common neuro-ophthalmic manifestations of mitochondrial disease are bilateral optic neuropathy, ophthalmoplegia, dom-inant optic atrophy, Kearn-Sayre syndrome and retro-chiasmal visual loss. Ocular features are not isolated and may coexist with neurological and/ or systemic symptoms[2]. Understanding of the neuro-ophthalmic manifestations of mitochondrial disease can help in diagnosis and treatment of patient and/ or counselling of close family members.

Optometrists are likely to see patients with mi-tochondrial disease in their practice, as they are the first clinician the patient consults. The purpose of this paper is to review the recent data on mitochondrial diseases with emphasis on their neuro-ophthalmic manifestations. There is still a lot to learn about the pathophysiology of mitochondrial diseases.

Basic mitochondrial genetics

Mitochondria are double-membrane cytoplasmic or subcellular organelles, present in all nucleated mammalian cells[2-4]. Their primary function is to sup-port aerobic respiration and they produce more than 90% of a cell's ATP through oxidation phosphoryla-tion (OXPHOS) and electron transfer[2-6]. It is stated that cells in highly metabolically tissues, such as the eye and optic nerve, cardiac system, oxidative mus-cles, pancreas, kidneys and liver, rely heavily on ATP and have increased numbers of mitochondria[7]. Although the production of ATP by OXPHOS is an essential task of mitochondria in the cell, other mi-tochondrial processes include the detoxification of reactive oxygen species (ROS), regulation of cellular apoptosis, the fission and fusion of organelle mem-branes among mitochondrial networks and aspects of iron metabolism, fatty acid oxidation and amino acid biosynthesis[8]. A disturbance of OXPHOS seems to be the main factor in the pathogenesis of mitochondrial disease since it generates energy.

Beside the 44 autosomes and two sex chromo-

somes that make up human nuclear DNA (nDNA), there is a small extrachromosomal double-stranded circle (cytosine-rich light and guanine-rich heavy strands) of DNA that is essential for life called the mitochondrial genome or DNA (mtDNA)[9]. Mitochondria are under dual genetic control of both nDNA and mtDNA. The human mitochondrial (mtDNA) genome comprises of 16 base pairs of nucleotides which contains 37 genes[3, 9-11]. The heavy strand encodes 28 genes while the light strand encodes 9 genes. Thirteen of these genes encode protein subunits of respiratory complexes I, III, IV and V. Only complex II is solely composed of protein encoded by nuclear genes (nDNA). The mtDNA genome also encodes 22 mitochondrial tRNAs and 2 rRNAs that are essential for translation of mtDNA transcripts[10, 11]. Nuclear genes encode the remaining OXPHOS components and all other proteins required for mitochondrial metabolism and maintenance, which are imported to mitochondria via specialized import system[12].

Concepts unique to mitochondrial genetics

mtDNA have unique characteristics that differ considerably from the Mendelian genetics[2, 13]. The genome is maternally-inherited and is polyploidy, with multiple copies of the mtDNA within each mitochondrion. Several hundreds, if not thousands, of mitochondria are present per cell. Normally, all of the mitochondrial genomes within the cells of an individual are identical, a situation called homoplasmy. However, a mutation occurring in one copy of mtDNA can eventually result in heteroplasmy, which is a dual population of wild-type and mutated mtDNA coexisting within the same cell[2, 3]. During mitosis, both mutate and wild-type mtDNA are randomly segregated to each daughter cell. This random segregation affects both expression and inheritance of the mitochondrial disease, thereby contributing to a wide range of clinical presentations seen in mtDNA disorder[1, 9].

The majority of deleterious mtDNA mutations are heteroplasmic, with clinical manifestation only becoming evident when the number of mutated mtDNA molecules exceeds a critical threshold. This threshold represents the incapacity of the remaining wild-type mtDNA to compensate for the mutated mtDNA, resulting in impaired OXPHOS and consequently in cellular and organ dysfunction. Commonly, the threshold is reached when 60-90% of the cell's mtDNA is mutated, but the proportion varies between organs depending on their metabolic requirements[14]. For most diseases, the clinical phenotype is not simply a direct consequence of the relative abundance of mutated mtDNA. Other factors, such as nuclear genetic background, age, sex and environment contribute to the disease process[1]. Furthermore, the mitochondrial disease may also be caused by mutations in the nuclear genes, which are involved in the synthesis of various subunits of the mitochondrial respiratory-chain complexes[3].

Mutations in mtDNA or nDNA may cause mitochondrial disease due to disturbed mitochondrial respiratory function. mtDNA mutations that cause mitochondrial diseases were first documented in 1988 by Holt *et al*[15] and Wallace *et al*[16] and now there are many mutations associated with oxidative phosphorylation diseases[10]. Over the past 20 years, mitochondrial dysfunction has been increasingly recognized as an important contributor to a range of neuromuscular and neurodegenerative diseases.

Ocular features of mitochondrial disease

Bilateral optic neuropathy

The most common mitochondrial disease with bilateral optic atrophy is Leber's hereditary optic neuropathy (LHON). LHON was the first human disease to be etiologically associated with a point mutation in mtDNA and is maternally inherited[15-19]. LHON target the retinal ganglion cell layer with sparing of the retinal pigment epithelium and photoreceptors[20]. In most LHON patients, visual loss is the only manifestation of the disease[4]. Why the LHON affects the retinal ganglion cells is not clear but the abnormal OXPHOS and deficient generation of ATP may play a role. It presents with painless central visual loss in one eye with the other eye becoming affected in the next two months[5, 21, 22]. The visual loss usually occurs between the ages of 20 and 40 and is more common in men. Since mitochondrial diseases are maternally inherited, there will be no male-to-male transmission of LHON. Affected males do not transmit the genetic mutation to any of their children. Affected or carrier women transmit their LHON mutation to all of their children. It is not known why males are more suscep-

tible to visual loss in LHON. This gender bias could result from a combination of anatomical, hormonal and physiological variations between males and females. Pupillary functions are spared and patients report no pain on eye movements[20]. Funduscopic abnormalities may include hyperemia of the optic nerve head, dilation and tortuosity of vessels, haemorrhages or pseudo edema[4]. LHON does not occur alone but is associated with some neurological illness. At the moment there is no treatment proven benefit for LHON. Tobacco, alcohol consumption and head trauma has been suggested as some of the triggers to the development of LHON[21]. Ancillary tests are of limited value but may be used to monitor progress. Fluorescein angiography may help distinguish the LHON optic disc from disc edema. Optical coherence tomography can be used for more detailed study of retinal nerve fibre layer thickness. Three point mutations in mtDNA known as the primary LHON mutations are located at mtDNA nucleotide positions 11778, 14484 and 3460, which all involve genes encoding complex I subunits of the mitochondrial respiratory chain[1-5].

Dominant optic atrophy (DOA)

Dominant optic atrophy is the most common autosomal hereditary optic neuropathy. It is characterized by a slow progressive painless, bilateral, symmetrical visual loss[2, 23]. The onset of symptoms is relative insidious. DOA exhibits no gender bias unlike LHON which is more common in men. The onset is usually within the first two decades of life[23]. Visual loss is usually detected between the ages of four and six years. Defects in colour vision are thought to result from a generalized dyschromatopsia, involving both the blue-yellow and red-green axes, with a minority of patients having pure tritanopia[24]. There are central field defects. The peripheral fields are usually full. There may be optic disc cupping which might be misdiagnosed as glaucoma[3, 20]. Retinal ganglion cells appear to be the primary target. Magnetic resonance imaging (MRI) data from patients with DOA have also show significant tissue loss and thinning of the optic nerve along its entire length[4]. Optical coherence tomography and visual electrophysiological tests can be carried out to exclude retinal pathology and confirm optic nerve dysfunction. The majority of cases of DOA are caused by mutations in the OPA1 gene[4].

There is no specific treatment.

Ophthalmoplegia

This is one of the most common presentations of mtDNA in adults. It is characterized by painless bilateral progressive loss of extraocular muscle mobility leading to impaired eye movement and ptosis[2, 5, 9, 24-26]. Ptosis is frequently the presenting symptom. Patients may be unaware of their extraocular muscle limitations until the disease is severe, where the ptotic eyelids occlude the pupils interfering with vision and patients may then adopt a backward head tilt. When the patient adopts a backward head tilt, the frontalis muscles may be elevated to compensate for the ptotic eyelids occluding the pupils. Even the orbicularis oculi muscles may get involved by becoming weak and result in lagophthalmos and ectropion. This may cause exposure keratopathy[26]. Visual acuity is usually not affected. Pupillary function is always spared[27]. Pain and proptosis are not features of this disease. The typical cause of ophthalmoplgia is multiple mtDNA deletions.

Kearns-Sayre syndrome (KSS)

Kearns-Sayre syndrome is associated with the development of retinitis pigmentosa and ophthalmoparesis occurring before the age of twenty years[5, 9, 25]. It is also called pigmentary retinopathy. The cause is thought to be the degeneration of the retinal pigment epithelium with secondary disturbance of cones, rods and the choriocapillaris[28]. mtDNA is prone to damage retinal pigment epithelium cells, possibly due to a high degree of oxidant stress during phagocytosis of photoreceptor outer segments. KSS is a result of point mutations of mtDNA[29]. Clinical examination will show a "salt and pepper" retinopathy[30]. This presents as fine pigment dusting in the periphery. To evaluate this condition one will need to perform an indirect ophthalmoscopy for accurate detection.

Retrochiasmal visual loss

Patients with mitochondrial disease may have visual loss not ascribable to optic nerve or retinal dysfunction, but rather a reflection of the disruption of the retrochiasmal visual pathways. Retrochiasmal visual loss is commonly associated the MELAS syndrome[2]. MELAS is an abbreviation for mitochondrial en-

cephalomyopathy with lactic acidosis and stroke-like episode. MELAS is defined as stroke-like episode in the parieto-occipital regions[9] and is characterized by recurrent, abrupt attacks of headaches, vomiting, focal and generalized seizures[4]. It results in damage to the visual pathways and causes homonymous hemianopsia or cortical blindness[3]. This visual loss is not due to optic neuropathy or pigmentary retinopathy. Ophthalmoscopic examination and pupillary reflexes are normal. Patients on either ethambutol or vigabatrin should have visual fields tested at baseline and at periodic intervals[31, 32]. If visual field defects are seen, ethambutol or vigabatrin should be discontinued.

Diagnosis of mitochondrial diseases

The clinical presentation of mitochondrial disease is varied and can occur at any stage in life[9]. Mitochondrial disease often presents with involvement of an unusual combination of organs. More information on mitochondrial disease can be obtained from the family history. A more detailed eye examination is necessary in which the optic nerve is involved. Optical coherence tomography could be used to measure the progression of the LHON and dominant optic atrophy[33, 34].

Treatment

No specific pharmaceutical drugs have been clearly shown in large-scale clinical trials to treat mitochondrial disease effectively[35]. Exercise has been tested as a treatment for mitochondrial disease and has shown some success in patients[36]. Endurance training of patients with mitochondrial disease has shown some benefits, including improved OXPHOS and tissue perfusion[36-38]. However, these benefits are lost once the patient stops exercising. This means that the physiotherapist also has a role to play in the management of mitochondrial disease. The treating physiotherapist will advise patients on appropriate exercises. Pyruvate has been proposed as a treatment option[39]. So far, case reports on pyruvate therapy for mitochondrial diseases are very limited and the efficacy of this treatment still remains inconclusive. Vitamins are frequently prescribed but their effectiveness is unknown or limited[40, 41].

Conclusion

Mitochondrial dysfunction can result from abnormalities in either the mtDNA or nDNA which encode mitochondrial proteins. Diagnosis can be made on clinical grounds if ophthalmoscopic features are present. Maternal history also aids diagnosis. Molecular genetic testing is the best method to confirm if a patient has one of the DNA mutations. There is no generally accepted treatment for mitochondrial disease. For general health reasons DNA mutation carriers should be advised to limit alcohol intake and stop smoking[19]. The administration of various pharmacological and biochemical agents, such as vitamins, cofactors, metabolites and electron acceptors, to correct or bypass the underlying respiratory chain defect has met with limited success.

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