American Journal of Ophthalmology Case Reports 22 (2021) 101073

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

# Ptosis, ophthalmoplegia and corneal endothelial disease – ocular manifestations of mitochondrial disease

Elizabeth M. McElnea [a,*], Zelda S. Pick [a], Aoife C. Smyth [a], Louis J. Stevenson [a], Penny A. McKelvie [b], Michael S. Loughnan [c], Alan A. McNab [a,d]

[a] Department of Orbit, Plastic and Lacrimal Surgery, Royal Victorian Eye and Ear Hospital, 32 Gisborne Street, East Melbourne, Victoria, Australia
[b] Department of Anatomical Pathology, St Vincent's Hospital, 41 Victoria Parade, Fitzroy, Victoria, Australia
[c] Eye Surgery Consultants, 100 Victoria Parade, East Melbourne, Victoria, Australia
[d] Department of Surgery, Royal Melbourne Hospital, University of Melbourne, 300 Grattan Street, Parkville, Victoria, Australia

ARTICLE INFO

*Keywords:*
Ptosis
Ophthalmoplegia
Mitochondrial disease
Corneal endothelial disease

ABSTRACT

*Purpose:* To describe two patients with bilateral ptosis, ophthalmoplegia, cataracts and corneal endothelial disease requiring corneal transplantation.
*Observations:* Histopathological analysis of muscle biopsy samples from both patients identified features consistent with a mitochondrial cytopathy. A single multigenic mitochondrial deoxyribonucleic acid (DNA) deletion was detected in the first patient. Pathogenic mutations in the POLG gene which codes for mitochondrial DNA polymerase, tasked with replicating the mitochondrial genome were identified in the second patient.
*Conclusion:* The collection of clinical features present in both cases described can be explained by a diagnosis of mitochondrial disease.
*Importance:* Corneal endothelial disease, in addition to ptosis, ophthalmoplegia, cataract, pigmentary retinopathy and optic atrophy should be recognised as a feature of mitochondrial disease.

## 1. Introduction

Mitochondrial diseases are a diverse group of disorders that result from mitochondrial dysfunction and can affect any organ. Brain, cardiac and skeletal muscle and ocular involvement occur most frequently.[1] The most common ocular manifestations of mitochondrial disease are ptosis, external ophthalmoplegia, pigmentary degeneration of the retina and optic atrophy.[2] More recently corneal endothelial involvement in mitochondrial disease has been recognised.[3]

## 2. Case 1

A 29-years old man presented with bilateral ptosis. He had had bilateral sequential Descemet's stripping automated endothelial keratoplasty (DSAEK) at age 27 years. As Fig. 1 shows, histopathological analysis of the stripped Descemet's membrane demonstrated a complete absence of endothelial cells. He was awaiting cataract surgery. He wore hearing aids for sensorineural deafness since age 11 years. He had a working diagnosis of Harboyan syndrome – congenital hereditary endothelial dystrophy (CHED) with progressive sensorineural deafness.

He had bilateral symmetrical ptosis with margin reflex 1 distance ($MRD_1$) of 0mm and levator palpebrae superioris function (LF) of 5mm bilaterally. Ocular movements were symmetrically reduced in all directions. Previous DSAEK surgery and bilateral posterior subcapsular cataracts were notable bilaterally. No fundal abnormalities were noted.

As can be seen from Fig. 2 histopathological analysis of a muscle biopsy sample identified cytochrome oxidase (COX) negative muscle fibres interspersed among normal-appearing fibres in a mosaic pattern - features of a mitochondrial cytopathy. Genetic analysis did not identify the genetic mutation associated with Harboyan syndrome. A single

*Abbreviations:* ATP, Adenosine triphosphate; CHED, Congenital hereditary endothelial dystrophy; COX, Cytochrome oxidase; CPEO, Chronic progressive external ophthalmoplegia; DNA, Deoxyribonucleic acid; DSAEK, Descemet's stripping automated endothelial keratoplasty; FECD, Fuchs endothelial corneal dystrophy; LF, Levator palpebrae superioris function; MELAS syndrome, Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke; MRD1, Margin reflex 1 distance; MT-TP, Mitochondrially encoded transfer ribonucleic acid proline; MT-ATP6, Mitochondrially encoded adenosine triphosphate synthase membrane subunit 6; RNA, Ribonucleic acid; SDH, Succinic dehydrogenase; TRNA, Transfer ribonucleic acid.

* Corresponding author. Ophthalmology Department, University Hospital Galway, Newcastle Road, Galway, Ireland.
*E-mail address:* mcelneaelizabeth@gmail.com (E.M. McElnea).

https://doi.org/10.1016/j.ajoc.2021.101073
Received 24 March 2020; Received in revised form 3 February 2021; Accepted 7 March 2021
Available online 17 March 2021

**Fig. 1.** Case 1. Haematoxylin and eosin. 200X. A double layer of Descemet's membrane with a marked reduction in endothelial cell density.

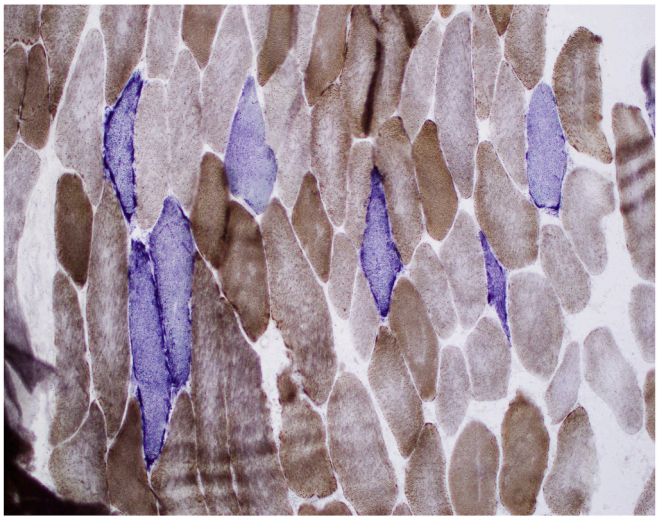

**Fig. 2.** Case 1. Cytochrome oxidase (COX), succinic dehydrogenase (SDH) stain. 200X. COX-negative muscle fibres staining blue interspersed among normal-appearing fibres to create a mosaic pattern. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

multigenic mitochondrial deoxyribonucleic acid (DNA) deletion of approximately 7.43 kilobases (m.8649_16084del), encompassing part of the mitochondrially encoded adenosine triphosphate (ATP) synthase membrane subunit 6 (MT-ATP6) gene through to the mitochondrially encoded transfer ribonucleic acid (TRNA) proline (MT-TP) gene and including part of the mitochondrial DNA control region was detected via whole mitochondrial DNA genome analysis and deemed to be consistent with the clinical diagnosis of a mitochondrial disorder.

## 3. Case 2

A 60-years old gentleman presented with recurrent bilateral ptosis. At 39 years he had had right penetrating keratoplasty (PK) for corneal endothelial decompensation thought secondary to Fuchs endothelial corneal dystrophy (FECD). He had right and subsequently left eye cataract surgery and then left PK.

At 45 years examination identified bilateral ptosis with $MRD_1$ of 0mm and - 2mm on the right and left sides respectively and LF of 14mm bilaterally. Ocular movements were considered normal. No fundal abnormalities were noted. He underwent bilateral levator advancement. These muscles were found to be infiltrated by fat. Further investigation regarding the possible presence of myopathy was encouraged but not undertaken. Upon his return with recurrence of ptosis, a decrease in ocular movements were noted.

Histopathological analysis of a muscle biopsy sample again identified features of a mitochondrial cytopathy. Further, DNA studies identified three pathogenic mutations in POLG – the gene which encodes mitochondrial DNA polymerase, responsible for the replication of the mitochondrial genome.

## 4. Discussion

Mitochondrial diseases are a diverse group of disorders.[1] They arise as the result of mutations in either mitochondrial DNA or nuclear DNA causing mitochondrial dysfunction and in either case result in inadequate cellular production of energy. Mitochondrial DNA mutations are transmitted by maternal inheritance while nuclear DNA mutations follow an autosomal dominant, autosomal recessive, or X-linked inheritance pattern of inheritance. New, non-inherited mutations in mitochondrial DNA also occur. In neither case described above was there a family history of mitochondrial disease.

Extraocular muscles and the levator palpebrae superioris, the corneal endothelium, the lens, the retina and the optic nerve are among the more metabolically active ocular tissues. The most common ocular signs of mitochondrial disease then are ophthalmoplegia and ptosis, cataract, pigmentary degeneration of the retina, and optic atrophy.[2]

Chronic progressive external ophthalmoplegia (CPEO) describes a group of disorders characterized by insidiously progressive ptosis and symmetrical limitation of ocular movements. Mitochondrial disease underlies CPEO in all its forms. CPEO may occur in isolation or form part of a recognizable clinical entity such as Kearns-Sayre Syndrome - the triad of CPEO, pigmentary retinopathy and cardiac conduction defects.[4]

Corneal endothelial cells maintain corneal stromal deturgescence and have large numbers of mitochondria to support the high metabolic activity that this function demands.[5] Despite this, corneal endothelial involvement in mitochondrial disease is not typical and to date only sporadically reported. An evaluation of the medical literature carried out by Kim et al. revealed 19 reports of corneal involvement in patients with a clinical phenotype of mitochondrial disease.[3] Nine of these patients had a diagnosis of Kearns-Sayre syndrome or features suggestive of the same.[3]

There may be several explanations for the apparent absence of corneal endothelial involvement in mitochondrial disease. Heteroplasmy - the existence of more than one genome within a cell i.e. wild type and mutant DNA, is characteristic of most mitochondrial diseases.[5] Biochemical defects and disease phenotype result only when a threshold of mutant DNA is met.[6] In the first case described here heteroplasmy was estimated at 80–90%. Even if present, subtle endothelial changes may not be readily discerned by either the patient, general physician or ophthalmologist.[3] Finally, even in homoplasmy wherein all mitochondrial DNA is mutant, phenotypic expression may be incomplete.[7]

Mitochondrial dysfunction has however already been implicated in FECD.[8,9] The mitochondrial DNA deletion most commonly seen in Kearns-Sayre syndrome, the deletion of the 4977 base pair, has also been identified in patients with FECD.[2] Mitochondrial DNA analysis had been completed in four of the patients reviewed by Kim et al.[3] One patient had this 'common' deletion and two patients had mutations which encompassed it. The last of these had a large deletion 6000 to 7000 base pairs in length, the location of which was not determined.[3]

Up to two-thirds of patients with mitochondrial disease will have hearing impairment.[10] As with CPEO this may be isolated or occur as part of a defined clinical entity, for example MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke). CPEO

*and* sensorineural hearing loss were features of seven of those cases of corneal involvement in patients with a clinical phenotype of mitochondrial disease identified by Kim et al.[3]

The first patient described herein was thought to have Harboyan syndrome wherein CHED is accompanied by acquired progressive sensorineural deafness. A very limited number of such cases have been described. More than 50% are associated with parental consanguinity.[11] The patient we describe was the offspring of a non-consanguinous relationship. In Harboyan syndrome, diffuse bilateral corneal oedema is apparent at birth or within the neonatal period, producing vision loss and nystagmus.[11] Our patient had a much milder phenotype of corneal disease. Critically, ptosis and ophthalmoplegia have never been described in Harboyan syndrome. Harboyan syndrome is caused by mutations in the SLC4A11 gene located at the CHED2 locus on chromosome 20p13-p12 - CHED2 and Harboyan syndrome are allelic disorders.[11,12] Genetic analysis excluded the presence of mutations at this locus. Rather, a single, large, multigenic, mitochondrial DNA deletion which encompassed part of the MT-ATP6 gene and included part of the mitochondrial DNA control region was detected. The MT-ATP6 gene provides information for making the MT-ATP6 protein which forms one subunit of the ATP synthase enzyme, responsible for the final step of oxidative phosphorylation and so essential for normal mitochondrial function. The mitochondrial DNA control region is the main non-coding area of the mitochondrial genome and so contains the mitochondrial origin of DNA replication and transcription to ribonucleic acid (RNA).

In the second case mutations in the POLG gene were confirmed. The POLG gene at chromosomal locus 15q25 encodes the mitochondrial DNA polymerase ϒ that is responsible for replication of the mitochondrial genome.[13] POLG is thus one of several nuclear genes associated with mitochondrial DNA disorders. POLG related disorders comprise a continuum of overlapping phenotypes with onset from infancy to late adulthood. POLG mutations are now thought to be the most common cause of inherited mitochondrial disorders - mutations in POLG accounted for 10% of all adult mitochondrial disease cases in one large Australian cohort.[14]

In 2001 Van Goethem et al. described four mutations in POLG that were associated with either autosomal dominant or autosomal recessive progressive external ophthalmoplegia, the former characterized by progressive ptosis and ophthalmoplegia in association with generalized myopathy and variable degrees and combinations of sensorineural hearing loss, axonal neuropathy, ataxia, depression, parkinsonism, hypogonadism and cataract and the latter by progressive ptosis and ophthalmoplegia without associated systemic involvement.[15] Those disorders most commonly caused by POLG mutations are now known to include these two conditions.[16] POLG mutations were found to explain 10 and 25% of CPEO in a United Kingdom and Italian cohort respectively.[17,18]

Of note however most patients with POLG related disease, particularly those with adolescent or adult-onset disorders, do not present with a discrete clinical syndrome.[16] No direct genotype - phenotype correlations are evident for POLG mutations i.e. the same mutation can lead to mitochondrial DNA depletions, deletions or both making it difficult to predict the phenotype on the basis of observed mutations. Further, the age of onset and progression of POLG related disease in patients with the same POLG mutations can span several decades. These enigma of presentation suggest that there are factors which can modify the POLG disease phenotype which might include genetic, immune and environmental effects such as viral infection and/or toxins.[19]

In the cases described here the diagnosis of a mitochondrial disorder could account for all the patients' clinical features – CPEO, corneal endothelial dystrophy, cataract and, in the first case sensorineural deafness. Ophthalmologists should consequently be cognisant of the possibility of corneal endothelial involvement in mitochondrial disease.

## Patient consent

Consent for publication of this manuscript was obtained from the patients described.

## Funding

The authors received no funding for this work.

## Ethical considerations

This document was produced according to the principles of the Declaration of Helsinki.

## CRediT authorship contribution statement

**Elizabeth M. McElnea:** Data curation, Formal analysis, Project administration, Writing – original draft. **Zelda S. Pick:** Supervision, Writing – review & editing. **Aoife C. Smyth:** Project administration, Supervision, Software, Writing – review & editing. **Louis J. Stevenson:** Project administration, Supervision, Writing – review & editing. **Penny A. McKelvie:** Supervision, Writing – review & editing. **Michael S. Loughnan:** Supervision, Writing – review & editing. **Alan A. McNab:** Conceptualization, Data curation, Formal analysis, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors have no conflicts of interest to report.

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