

# **Newcastle Mitochondrial Disease Guidelines**

## **Ocular Involvement in Adult Mitochondrial Disease: Screening and Initial Management**

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## Introduction

Mitochondrial disease affects a minimum of 9.2 per 100,000 of the adult population with a further 16.5 per 100,000 at risk of developing disease.<sup>1</sup> Ocular involvement is a prominent feature of this group of disorders and it frequently results in significant visual disability.<sup>2-4</sup> The symptoms reported by patients with mitochondrial disease fall into three main groups: (i) visual loss, (ii) diplopia, and (iii) drooping of the upper eyelid (ptosis).

Visual loss is frequently due to optic nerve dysfunction, and in Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (DOA), the two most common mitochondrial optic neuropathies, it is the defining clinical feature.<sup>4</sup> Both LHON and DOA result in significant visual impairment and the majority of affected patients will become eligible for CVI (Certificate of Visual Impairment) registration.<sup>5,6</sup> Progressive visual failure with optic atrophy also occurs in other classical mitochondrial syndromes such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and myoclonic epilepsy and ragged-red fibres (MERRF).<sup>3,4</sup> Although variable, and a secondary clinical feature, the development of optic neuropathy further exacerbates the considerable neurological burden in this group of patients. Visual deterioration among patients with mitochondrial disease can also arise secondary to macular degeneration, a more generalised pigmentary retinopathy, early-onset cataracts, or vascular infarcts involving the retrochiasmatal visual pathways (e.g. the occipital lobes in MELAS).<sup>3</sup>

Chronic progressive external ophthalmoplegia (CPEO) affects over half of all patients with mitochondrial disease. This slowly-progressive extraocular muscle disorder is characterised by bilateral generalised limitation of eye movements (ophthalmoplegia) and ptosis.<sup>7</sup> CPEO is a characteristic ocular manifestation of the mitochondrial encephalomyopathies, but not infrequently, it occurs in isolation as a pure CPEO phenotype. The Kearns-Sayre syndrome (KSS) is a specific subtype where CPEO develops before the age of 20 years in association with pigmentary retinopathy and the early development of multi-system disease.<sup>2,3</sup>

Although the pattern of ophthalmoplegia in CPEO is usually symmetrical, asymmetry can occur early in the course of the disease. Patients can develop manifest ocular misalignment (squint) and persistent diplopia, with rates of 30-

60% in published case series.<sup>7</sup> The degree of ptosis in CPEO becomes functionally significant when the pupillary axis is involved, obstructing the patient's field of view. The cosmetic aspect is also an important element and the goals of ptosis management will vary depending on the patient's expectations.

## **Patient-centred Care**

This guideline offers expert consensus advice on the care of patients with mitochondrial disease. The care of these patients and their treatment should take into account patients' needs and preferences. People with mitochondrial disease should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines – 'Reference guide to consent for examination or treatment' (2001), available from [www.dh.gov.uk](http://www.dh.gov.uk). Healthcare professionals should also follow the code of practice accompanying the Mental Capacity Act (a summary of this code is available from [www.dca.gov.uk/menincap/bill-summary.htm](http://www.dca.gov.uk/menincap/bill-summary.htm)).

Good communication between healthcare professionals and patients is essential. It should be supported by the best available information tailored to the patients' needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English. If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care. Families and carers should also be given the information and support they need.

## Key Priorities for Implementation

Patients with mitochondrial disease should be referred for a comprehensive neuro-ophthalmological assessment if they report:

- (i) significant visual loss at first presentation or progressive visual failure during follow-up.
- (ii) diplopia ( $\pm$  limitation of eye movements)
- (iii) functionally disabling ptosis (e.g. severe enough to occlude the patient's visual axis)

Further investigation will be dictated by the specific clinical history, the patient's underlying molecular genetic defect (if known), and initial findings on slit-lamp biomicroscopy. These additional tests include (i) formal visual field perimetry, (ii) optical coherence tomography (OCT) imaging of the optic nerve and macular region, (iii) visual electrophysiology, and (iv) eye movement recordings. Patients with extraocular muscle involvement will usually undergo a full orthoptic assessment to document baseline motility measurements, and especially if future surgical intervention is being considered. All patients should have access to a specialist with experience of the management of ocular involvement in mitochondrial disease. This document is intended for guidance only, and should not replace patient-specific management plans.

## 1. Guidance for Ophthalmological Screening in Patients with Mitochondrial Disease

1.1. Snellen visual acuities should be measured for patients as follows:

1.1.1. All patients, at the time of diagnosis.

1.1.2. All patients, at subsequent follow-up clinic visits (or earlier if there is a change in visual status).

1.1.3. For consistency, it is recommended that the Snellen chart is viewed by the patient at the same distance, either at 3m or 6m, depending on the clinic set-up. A pinhole (placed over the patient's own glasses if available) should be used to obtain the best possible vision. This simple procedure can correct an underlying refractive error and significantly improve the patient's Snellen visual acuity.

1.2. Eye movements should be assessed for patients as follows:

1.2.1. All patients at the time of diagnosis.

1.2.2. All patients, at subsequent follow-up clinic visits if clinically indicated (e.g. patients with CPEO), or if there is a change in clinical status (e.g. new onset of diplopia).

1.2.3. For consistency, and in a non-ophthalmological clinic setting, it is sufficient to record eye movements using a simplified diagram (i) for each eye, (ii) in the main cardinal positions; upgaze, downgaze, and in lateral gaze, and (iii) express the observed range of eye movements as a percentage of normal (i.e. 100%).<sup>8</sup>

1.3. The presence of ptosis should be documented at the time of diagnosis and at subsequent follow-up visits. In a non-ophthalmological clinic setting, it is sufficient to document the degree of ptosis with a simplified diagram

showing the relative position of the upper eyelid to the pupil and the pupillary axis.

1.4. Fundoscopy with a direct ophthalmoscope should be performed at the time of diagnosis and at subsequent follow-up visits. Although only a limited view is possible if the pupils are not dilated, fundoscopy may still reveal significant pathology of the lens, retina or optic nerve.

1.5. Visual field testing should be assessed in the clinic by confrontation where there is a history of seizures, encephalopathy, or stroke-like episodes. Transient field defects can occur as a result of occipital lobe status epilepticus and these are unlikely to be volunteered by the encephalopathic patient (e.g. MELAS). Stroke-like episodes may lead to permanent visual field defects, and bilateral lesions of the occipital lobes may result in cortical blindness.

## 2. Guidance for Clinical Management in Patients with Mitochondrial Disease

2.1. All patients with significant ocular involvement should be offered review by a neuro-ophthalmologist aware of the specific disease manifestations seen in mitochondrial disease and their management.

2.2. Leber hereditary optic neuropathy (LHON):

2.2.1. Only ~ 50% of male and ~10% of female LHON carriers will experience visual failure during their lifetime.<sup>9</sup> The peak age of onset is between 20 to 30 years, and the risk of disease conversion is low beyond the age of 50 years. Smoking is strongly associated with an increased risk of visual loss among LHON carriers, with the risk being much higher in heavy smokers compared to light smokers.<sup>10</sup> There is also an increased risk of visual failure among heavy drinkers, but this effect is not as strong as smoking.<sup>10</sup> LHON carriers should therefore be strongly advised not to smoke and to moderate their alcohol intake, especially avoiding binge drinking episodes.

2.2.2. Idebenone is a short-chain synthetic analogue of ubiquinone which promotes mitochondrial ATP synthesis in addition to having antioxidant properties.<sup>11</sup> A multicentre randomised placebo-controlled trial of idebenone (Catena®, Santhera Pharmaceuticals Ltd) in LHON was recently completed ([www.lhon.ncl.ac.uk](http://www.lhon.ncl.ac.uk)). The findings suggest that patients with discordant visual acuities (LogMAR > 0.2), and hence at highest risk of further deterioration in the least affected eye, were more likely to benefit from treatment with idebenone.<sup>12</sup> High-dose oral idebenone appears safe and well-tolerated and it is likely to represent an important treatment option among affected LHON carriers, especially those with recent disease onset. At the time of writing,



Catena® has not yet been approved for clinical use by the European Medicines Agency (EMA). A decision is expected in 2012.

### 2.3. Cataract surgery:

2.3.1. Patients with mitochondrial disease can develop either early-onset lens opacities as part of their disease phenotype, or age-related cataracts unrelated to their genetic diagnosis. In both situations, the development of cataracts can lead to progressive visual loss and impact negatively on the patient's quality of life.

2.3.2. If clinically indicated, the patient can be offered routine cataract surgery (phacoemulsification with intraocular lens implantation), with the majority of these being performed as day-case procedures under local anaesthesia.

### 2.4. Management of ptosis:

2.4.1. Only a proportion of patients with ptosis will require active treatment. There are two indications for intervention; for functional reasons if the degree of ptosis is severe enough to impair the patient's field of vision; and/or for cosmetic reasons. The management plan needs to be carefully discussed and re-evaluated, taking into consideration the possible surgical options and the patient's expectations.

2.4.2. Ptosis eyelid props mounted onto the upper rim of a pair of spectacles is a non-invasive treatment option, which can benefit some patients with CPEO.

2.4.3. The main treatment option for ptosis is surgical lifting of the upper eyelids.<sup>13</sup> Ptosis surgery for patients with CPEO should only be performed by experienced surgeons because of the increased risk of

complications such as corneal exposure secondary to poor orbicularis oculi function and impaired Bell's phenomenon.

## 2.5. Management of diplopia:

2.5.1. Patients with symptomatic ocular misalignment can benefit from simple conservative measures such as Fresnel prisms or fogging of one lens of their glasses with occlusive transparent tape.<sup>7</sup>

2.5.2. Strabismus surgery on the extraocular muscles to increase the field of binocular single vision is not frequently performed due to the progressive nature of the disease. When indicated, this should only be performed by experienced surgeons.<sup>14</sup>

## 2.6. Visual impairment:

2.6.1. The treatment options for patients with mitochondrial disease and visual loss remain limited. However, there are several practical steps that can be taken as part of a multi-disciplinary team to improve the patient's quality of life and to minimise long-term morbidity. Clinicians should facilitate access to rehabilitative services such as low visual aids (LVA) clinics, and if the patient is eligible, they should consider CVI (Certificate of Visual Impairment) registration. The criteria for CVI registration can be accessed using the following links:

- (i) <http://www.rcophth.ac.uk/page.asp?section=165&search=>
- (ii) [http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/documents/digitalasset/dh\\_078294.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_078294.pdf)

2.6.2. Ophthalmology services will often have dedicated eye clinic liaison officers on site, affiliated with charities such as the Royal National Institute for the Blind (RNIB). These liaison officers provide an important link with the community, supporting patients and their

families in gaining practical assistance from their local social services, such as access to occupational therapy and talking books.

2.6.3. Patient with mitochondrial disease and visual impairment should be carefully counselled regarding their ability to drive. This should be clearly documented in the medical notes. The DVLA has the ultimate responsibility as to whether a patient can retain their driving licence, and the current rules can be accessed using the following links:

- (i) <http://www.rcophth.ac.uk/page.asp?section=293&search>, Accessed 28<sup>th</sup> of May 2011.
- (ii) <http://www.dft.gov.uk/dvla/medical/ataglance.aspx>, Accessed 28<sup>th</sup> of May 2011.

### 3. Notes on the scope of this guidance

The guideline was developed by experts in mitochondrial disease and ophthalmology based at the Newcastle Mitochondrial Centre and the Newcastle upon Tyne Hospitals NHS Foundation Trust. This group specified which aspects of the screening, diagnosis and management of ophthalmological involvement in patients with mitochondrial disease was to be included and excluded.

#### 3.1. Audience

These guidelines are intended for use by the following people or organisations:

- all healthcare professionals
- people with mitochondrial disease and their carers
- patient support groups
- commissioning organisations
- service providers

#### 3.2. Guideline Limitations

Limitations of these guidelines include:

- Lack of a firm evidence base for reference. Guidelines in mitochondrial disease are currently unable to adopt the evidence-based approach used by organisations such as NICE, and at present are predominantly based on consensus expert opinion.
- Overall, the evidence review identified one published randomized controlled trial.<sup>12</sup>
- Further studies are needed (see research recommendations below).
- Specialist Mitochondrial Centres are located in Newcastle, London, and Oxford. The development of these centres represents an important advance in the care of patients with mitochondrial disease.

## 4. Implementation

Integral to this guideline is publication of the benefits of access to a specialist clinic with experience in mitochondrial disease.

- Specialist mitochondrial clinics are provided by selected centres with the support of the NHS Highly Specialised Services. The accumulation of experience within these centres, and access to focussed multi-disciplinary team input is designed to offer the best available care for patients with mitochondrial disease.
- Centres are currently located in Newcastle, London and Oxford.
- Patient education is an important aspect of the initial consultation, but also as a vital component of future care. We aim to provide an understanding of the role of ophthalmological screening, and the potential benefits of timely medical and surgical interventions.
- Access to specialist clinics allows relevant genetic counselling and family tracing to facilitate the identification of those family members at risk of developing ophthalmological disease, or to formally diagnose those who may already be affected.
- Close liaison is required both with neuro-ophthalmology services at the specialist centre itself, but also with local general ophthalmology services which may be closely involved with future follow up and management of patients, especially where frequent central review is impractical.

## 5. Research recommendations

### 5.1. Natural history studies

Comprehensive assessment of a large cohort of mitochondrial disease patients from a variety of genotypic and clinical groups is required to document the effects of ophthalmological disease on morbidity and mortality.

### 5.2. Optic nerve involvement in mitochondrial disease

The primary mitochondrial encephalomyopathies encompass several distinct phenotypes such as MELAS, MERRF, and maternally inherited Leigh syndrome (MILS). However, the clinical manifestations resulting from specific mitochondrial DNA (mtDNA) mutations can be extremely varied. Nuclear disorders of mtDNA maintenance (e.g. *POLG1* mutations) are also being recognised more frequently, with new causative genes being identified. Although variable and not a disease-defining feature, the occurrence of optic atrophy is well described in these groups of patients. Additional studies are therefore required to determine the true prevalence of both clinical and subclinical optic neuropathy in these mitochondrial disorders, and whether specific genotypes or phenotypes are linked with an increased risk of optic nerve involvement.

### 5.3. Functional MRI studies in patients with CPEO

It is not yet entirely clear whether the ophthalmoplegia in CPEO is a pure extraocular muscle problem (myopathic) or whether there is evidence of a higher disorder of brainstem function (supranuclear) in a subgroup of patients, especially those who are more severely affected.<sup>15</sup> This clinically-relevant question could be explored further using a combination of high-resolution functional MRI and eye movement recordings.

## **6. Updating the guideline**

The Newcastle Mitochondrial Guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence every 2 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may update the guidance prior to any scheduled changes.

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## References

1. Schaefer AM, McFarland R, Blakely EL et al. Prevalence of mitochondrial DNA disease in adults. *Annals of Neurology*. 2008;63:35-39.
2. McFarland R, Taylor RW, Turnbull DM. The neurology of mitochondrial DNA disease. *Lancet Neurology*. 2002;1:343-351.
3. Fraser JA, Biousse V, Newman NJ. The neuro-ophthalmology of mitochondrial disease. *Survey of Ophthalmology*. 2010;55:299-334.
4. Yu-Wai-Man P, Griffiths PG, Chinnery PF. Mitochondrial optic neuropathies - disease mechanisms and therapeutic strategies. *Progress in Retinal and Eye Research*. 2011;30:81-114.
5. Kirkman MA, Korsten A, Leonhardt M et al. Quality of life in patients with Leber hereditary optic neuropathy. *Investigative Ophthalmology & Visual Science*. 2009;50:3112-3115.
6. Yu-Wai-Man P, Griffiths PG, Burke A et al. The prevalence and natural history of dominant optic atrophy due to OPA1 mutations. *Ophthalmology*. 2010;117:1538.
7. Richardson C, Smith T, Schaefer A et al. Ocular motility findings in chronic progressive external ophthalmoplegia. *Eye*. 2005;19:258-263.
8. Vivian AJ, Morris RJ. Diagrammatic representation of strabismus. *Eye*. 1993;7:565-571.
9. Yu-Wai-Man P, Griffiths PG, Hudson G, Chinnery PF. Inherited mitochondrial optic neuropathies. *J. Med. Genet*. 2009;46:145-158.
10. Kirkman MA, Yu-Wai-Man P, Korsten A et al. Gene-environment interactions in Leber hereditary optic neuropathy. *Brain*. 2009;132:2317-2326.
11. Haefeli RH, Erb M, Gemperli AC et al. NQO1-dependent redox cycling of idebenone: effects on cellular redox potential and energy levels. *PLoS One*. 2011;6:e17963.
12. Klopstock K, Yu-Wai-Man P, Dimitriadis K et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. *Brain*. 2011; In Press.
13. Ahn J, Kim NJ, Choung HK et al. Frontalis sling operation using silicone rod for the correction of ptosis in chronic progressive external ophthalmoplegia. *British Journal of Ophthalmology*. 2008;92:1685-1688.
14. Tinley C, Dawson E, Lee J. The management of strabismus in patients with chronic progressive external ophthalmoplegia. *Strabismus*. 2010;18:41-47.
15. Ritchie AE, Griffiths PG, Chinnery PF, Davidson AW. Eye movement recordings to investigate a supranuclear component in chronic progressive external ophthalmoplegia: a cross-sectional study. *British Journal of Ophthalmology*. 2010;94:1165-1168