

# **Newcastle Mitochondrial Disease Guidelines**

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

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# Contents

Introduction	3
Patient-centered Care	4
Key priorities for implementation	5
1. Guidance for Cardiac Screening	6
1.1. Standard 12-lead ECGs	6
1.2. Trans-thoracic echocardiograms	6
1.3. Holter (24-hour) monitoring	6
1.4. Cardiac magnetic resonance imaging	7
2. Guidance for Clinical Management	8
2.1. Cardiology referral	8
2.2. Conventional cardiac risk factors	8
2.3. Hypertrophic remodelling	8
2.4. Conduction block and pacemaker implantation	8
2.5. Pre-excitation syndromes	9
2.6. Atrial fibrillation	9
2.7. Implantable cardioverter-defibrillators (ICDs)	10
2.8. Left ventricular systolic dysfunction	11
2.9. Pre-operative assessment	11
2.10. Sudden adult death syndrome (SADS) and m.3243A>G specific guidance ( <i>New</i> )	12

4. Implementation	14
5. Research recommendations	15
5.1. Natural history studies	15
5.2. Energy-sparing medications in hypertrophic remodelling	15
5.3. Cardiac magnetic resonance imaging / spectroscopy	15
5.4. Exercise and mitochondrial disease / cardiomyopathy	15
6. Updating the guideline	16
Appendix A: The Guideline Development Group	17
Appendix B: Screening / management algorithm	18
References	19

## Introduction

Mitochondrial disease clinically affects a minimum 9.2/100,000 of the adult population with a further 16.5/100,000 at risk of developing disease. Cardiac involvement in mitochondrial disease is common and can include both conduction abnormalities and cardiomyopathy. Evidence exists for a link between genetic defect and the type of cardiac involvement with, for example, heart block frequently present in patients with large-scale mtDNA deletions; hypertrophic cardiomyopathy in patients with mtDNA point mutations and ventricular preexcitation in patients with two of the most prevalent pathogenic mtDNA mutations (m.3243A>G / m.8344A>G).

Importantly cardiac involvement in mitochondrial disease is often treatable, yet no guidelines exist. Treatment is more likely to be effective if initiated early and for this reason it is important to screen all patients with mitochondrial disease at the point of diagnosis. Cardiac disease in patients with mitochondrial disease may progress insidiously and rarely causes symptoms until advanced in severity. Morbidity and mortality may therefore be avoided if cardiac involvement is detected earlier through the implementation of organised screening programs.

Pacemaker implantation in patients with atrio-ventricular block may prevent sudden cardiac death, while the use of angiotensin converting enzyme (ACE) inhibitors in some patients may prevent early hypertrophic remodelling. Left ventricular systolic and diastolic dysfunction are both potent contributors to the occurrence of atrial fibrillation in a variety of clinical contexts. Additionally, hypertrophied hearts, such as are seen in some patients with mitochondrial disease, tolerate the abrupt onset of a rapid heart rate poorly. Beta-adrenergic receptor antagonists (beta blockers) or calcium channel blockers can help the heart function better in pathological hypertrophy by slowing heart rate and improving diastolic filling. Indirectly this can delay the onset of, or prevent, atrial fibrillation – a consequence of left ventricular diastolic dysfunction.

Addressing cardiac and respiratory involvement in other progressive genetic conditions (eg Duchenne and Becker muscular dystrophy) has been shown to provide significant benefits in terms of morbidity, mortality, and quality of life, and is likely to offer similar benefits in patients with mitochondrial disease. This is

best coordinated through a specialist mitochondrial centre, with subsequent care provided either centrally or locally depending on individual circumstances and patient preference.

### **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**

In view of the diverse phenotypes of mitochondrial disease, we recommend that all patients diagnosed with mitochondrial disease should have a minimum cardiovascular assessment at baseline. This guidance also applies to those asymptomatic carriers deemed to be at significant risk of developing disease. This should include a clinical assessment (cardiovascular history and

examination), standard 12-lead electrocardiogram (ECG) and transthoracic echocardiogram. Further investigation and follow-up should be based on the initial evaluation and the likelihood of cardiac involvement, if known, for the specific genetic sub-type. All patients should have access to a specialist with experience of the management of cardiac involvement in mitochondrial disease. This document is intended for guidance only, and should not replace patient-specific management plans influenced by other factors such as patient preference and pragmatism.

## **1. Guidance for Cardiac Screening in Patients with Mitochondrial Disease**

1.1. Standard 12-lead ECGs are recommended for patients as follows:

1.1.1. All patients, at the time of diagnosis.

1.1.2. All patients, at an interval of 12-months (or earlier if a change in clinical status or development of symptoms suggestive of cardiac involvement).

1.1.3. Extension of this 12-month interval should be considered only after discussion with a clinician experienced in the management of cardiac involvement in mitochondrial disease.

1.2. Trans-thoracic echocardiograms are recommended for patients as follows:

1.2.1. All patients at the time of diagnosis.

1.2.2. All patients at an interval of 12-months (or earlier if a change in clinical status or development of symptoms suggestive of cardiac involvement).

1.2.3. Extension of this 12-month interval should be considered only after discussion with a clinician experienced in the management of the cardiac manifestations of mitochondrial disease. It is usually acceptable to extend the interval to 3 years if the ECG and echocardiogram have remained within normal limits over a similar period.

1.3. Holter (24-hour) ECG monitoring is recommended for patients as follows:

- 1.3.1. All patients at high-risk of pre-excitation syndrome / conduction disease at diagnosis, even if asymptomatic (e.g. atrio-ventricular block  
in patients with single large scale deletion or ventricular pre-excitation in patients with m.8344A>G or m.3243A>G).
- 1.3.2. All patients with severely impaired LV systolic function (LVEF < 35%) to identify asymptomatic ventricular arrhythmias of prognostic importance (ie non-sustained ventricular tachycardia, NSVT).
- 1.3.3. As a first line investigation in all patients with very frequent paroxysmal symptoms suggestive of cardiac involvement; longer term monitoring may be considered, including implantable loop recorders.

1.4. Cardiac magnetic resonance imaging (MRI) is recommended for patients as follows:

- 1.4.1. All patients with inadequate echocardiographic images, to identify structural remodelling or to quantify abnormalities more precisely prior to starting or evaluating response to cardio-active therapies.
- 1.4.2. There is currently no clear clinical role for cardiac <sup>31</sup>P magnetic resonance spectroscopy.

## **2. Guidance for Clinical management in Patients with Mitochondrial Disease**

2.1. All patients with significant cardiac involvement should be reviewed by a cardiologist with awareness of the various manifestations of cardiac involvement in mitochondrial disease, even if currently asymptomatic.

2.2. Conventional cardiac risk factors and symptoms should be addressed promptly in keeping with existing guidelines for patients without mitochondrial disease.

2.3. Hypertrophic remodelling (left ventricular hypertrophy):

2.3.1. Treatment with conventional agents such as beta-adrenergic receptor antagonists or calcium channel blockers and ACE inhibitors or angiotensin receptor blockers should be initiated with any evidence of hypertrophic remodelling, regardless of symptomatic status. Doses should be optimised for patients' size, weight and age.

2.3.2. Further management of these patients should be considered by a cardiologist with awareness of the various manifestations of cardiac involvement in mitochondrial disease even if currently asymptomatic.

2.4. Conduction block and pacemaker implantation:

2.4.1. Patients fulfilling conventional guidelines (European Society of Cardiology or American College of Cardiology / American Heart Association) for implantation of permanent pacemakers should be offered this therapy without delay, due to the unpredictable nature of progression.

2.4.2. Permanent pacemaker implantation may additionally be considered prophylactically for patients with any degree of atrio-ventricular (AV) block (including first-degree AV block >300ms) or any fascicular block with or without symptoms, especially if there is evidence of progressive abnormalities.

2.5. Ventricular pre-excitation syndromes:

2.5.1. All patients with evidence of an accessory pathway should be offered an electrophysiological study (EPS) to define conduction properties and whether the pathway and AV-node can sustain AV-reentry tachycardia (AVRT).

2.5.2. Catheter ablation is indicated for accessory pathways capable of rapid antegrade conduction (ie pathway antegrade effective refractory period  $\leq$  230 ms) and in those able to support sustained re-entry tachycardia. The option of pathway ablation should be discussed with all patients undergoing invasive EPS since the success rate of this procedure is high (~ 95%) at very low risk.

## 2.6. Atrial fibrillation (AF):

2.6.1. Annual cardiac screening provides the best way of protecting patients with mitochondrial disease against the development of AF. By timely identification and appropriate treatment of asymptomatic left ventricular systolic and / or diastolic dysfunction, the occurrence of AF may be minimised.

2.6.2. The management of AF in patients with mitochondrial disease should be individualised to the patient and involve a cardiologist with awareness of the various manifestations of cardiac involvement in mitochondrial disease.

2.6.3. Management may incorporate: control of ventricular response rate (in persistent or permanent AF) with the target heart rates of < 100 bpm at rest and < 130 bpm on moderate activity; anti-arrhythmic drug therapy or direct current cardioversion to restore sinus rhythm; or maintenance anti-arrhythmic drug therapy to maintain sinus rhythm (in paroxysmal or persistent AF).

2.6.4. The most appropriate anti-arrhythmic agent for an individual patient will need to take account of the extent of other cardiac involvement (ie severity of left ventricular systolic or diastolic dysfunction; degree of left ventricular hypertrophy; comorbidities and interactions with other medications).

2.6.5. Patients with established cardiomyopathy and AF are at risk of thrombo-embolic disease and should receive anti-platelet or anticoagulant therapy according to conventional guidelines for stroke prevention (eg CHADS2 or equivalent).

## 2.7. Implantable cardioverter-defibrillators (ICDs)

2.7.1. There is no current clinical evidence that patients with mitochondrial disease have an increased risk of ventricular tachyarrhythmia, in the absence of significant left ventricular dysfunction or conduction system disease.

2.7.2. Conventional guidelines (eg NICE Technology Appraisal 95) for the implantation of ICDs for both primary and secondary prevention should be followed – using left ventricular function, QRS width +/- Holter (24-hour) ECG recording and EPS to assess the risk of ventricular tachyarrhythmia.

## 2.8. Left ventricular systolic dysfunction:

2.8.1. While some patients with mitochondrial disease may present with cardiac involvement, other patients may develop left ventricular systolic dysfunction over time so that screening investigations remain a cornerstone of disease management.

2.8.2. Conventional guidelines for the management of clinical heart failure and symptomatic left ventricular systolic dysfunction should be followed including the use of specialist services, complex devices and consideration of cardiac transplantation, where appropriate.

2.9. Pre-operative assessments:

2.9.1. All patients with mitochondrial disease should have a standard 12lead ECG as part of routine pre-operative assessment.

2.9.2. An up-to-date echocardiogram (within the preceding 12 months) should be available for review or should be repeated.

2.9.3 A separate Newcastle expert-opinion guidelines on anaesthesia and pre-operative care in adult patients with mitochondrial disease is available on our website.

2.9.4. Further pre-operative assessment should be performed on an individualised basis, consistent with conventional guidelines (eg European Society of Cardiology or American College of Cardiology / American Heart Association).

2.9.5. Liaison with the mitochondrial specialist responsible for the patient is strongly recommended prior to any intervention, unless this would incur an unacceptable delay to treatment.

2.10. Sudden adult death syndrome (SADS) and m.3243A>G specific guidance

2.10.1. Please refer to this open access publication (Ng et al. 2015) published in the *European Heart Journal*.

[\(<http://eurheartj.oxfordjournals.org/content/early/2015/07/16/eurheartj.ehv306.short>\)](http://eurheartj.oxfordjournals.org/content/early/2015/07/16/eurheartj.ehv306.short)

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

The guideline was developed by experts in mitochondrial disease and cardiac disease 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 cardiac 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 no randomized controlled trials or high quality case-control or cohort studies.
- 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 multidisciplinary 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 cardiac screening, and the potential impact of screening and early intervention on prognosis.
- Access to specialist clinics allows relevant genetic counselling and family tracing to facilitate the identification of those at risk of developing disease. The potential for significant cardiac disease to develop in asymptomatic relatives highlights the importance of this programme.
- Close liaison is required both with cardiology services at the specialist centre itself, but also local cardiology services who may be closely involved with future follow up and management of patients 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 cardiac disease on morbidity and mortality.

### 5.2. Energy-sparing medications in hypertrophic remodelling

Current use of beta adrenergic receptor antagonists or calcium channel blocker medications and angiotensin-converting enzyme inhibitors or angiotensin receptors blockers in mitochondrial disease patients with hypertrophic remodelling is empirical, based on results from animal studies, other genetically determined causes (predominantly sarcomeric hypertrophic cardiomyopathy), and large registries of nongenetic hypertrophic remodelling. An assessment of the clinical utility of this approach is urgently needed.

### 5.3. Cardiac magnetic resonance imaging / spectroscopy (MRS) Cardiac

MRS represents a novel technique for studying abnormal cardiac bioenergetics in vivo. An assessment of the interaction between cardiac bioenergetics and hypertrophic remodelling is urgently needed and may allow for the future clinical assessment of interventions.

### 5.4. Exercise in patients with mitochondrial disease and cardiomyopathy

Currently available evidence would support the benefits of exercise therapy in mitochondrial disease and also in patients with cardiomyopathy of different aetiologies. There is however no current evidence of safety and/or benefit of this approach in mitochondrial disease patients with coexistent cardiomyopathy.

## **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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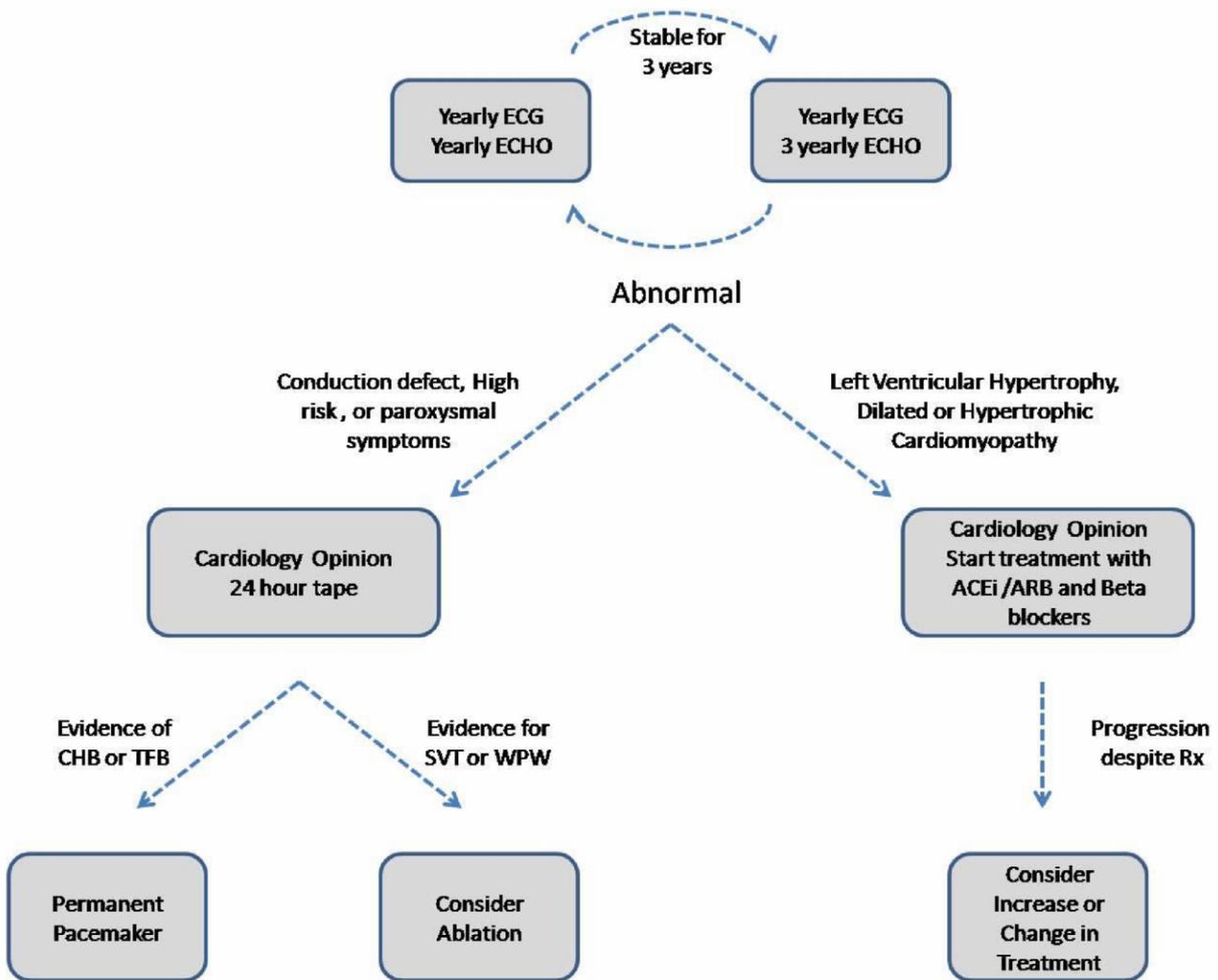
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Appendix B: Screening / management algorithm

# Mitochondrial Disease: Cardiology Guidance



<b>Key:</b>	ACEi	angiotensin converting enzyme inhibitor
	ARB	angiotensin II receptor blocker
	CHB	complete heart block
	TFB	trifascicular block
	SVT	supra-ventricular tachycardia
	WPW	Wolff-Parkinson-White syndrome

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