Newcastle Mitochondrial Disease Guidelines

Respiratory Involvement in Adult Mitochondrial Disease:

Screening and Initial Management

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Introduction

Patients with mitochondrial disease are at increased risk of respiratory problems. It is important that such involvement is recognised so that appropriate advice may be offered, screening arranged, and treatment provided in a timely fashion. Proximal myopathy often seen in mitochondrial disease may also involve the axial and respiratory muscles. The degree of respiratory muscle weakness (and hence respiratory impairment) tends to correlate with the extent of the myopathy, but this is not always the case. It is often overlooked by physicians, and unappreciated by patients, as the tendency for a sedentary lifestyle in patients afflicted with a significant myopathy may conceal respiratory symptoms under normal conditions. Those that do occur are often considered physiological rather than pathological. Such patients may develop chronic respiratory insufficiency, or decompensate acutely as a result of cardiopulmonary disease, general anaesthesia, or post operative complications. Diaphragmatic weakness is not always appreciated, but can be particularly dangerous in the surgical patient as both supine posture and splinting of the diaphragm in abdominal surgery may result in a dangerous reduction in respiratory excursion. Patients and their doctors should be made aware of the potential anaesthetic risks. Diaphragmatic weakness may contribute to nocturnal hypoventilation and bulbar weakness may predispose to obstructive sleep apnoea, even in the absence of a typical body habitus. Aspiration pneumonia may occur due to an unsafe swallow. This is usually due to bulbar weakness, cerebellar disease, or a combination of the two. A weak cough may lead to basal atelectasis, reduced lung volumes and predispose to recurrent chest infections.

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. 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).

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

All patients with mitochondrial disease should be screened for respiratory muscle weakness at diagnosis. This practice aims to define a baseline and thereafter to establish the trajectory of pulmonary function over time. Additional consideration should be given to other factors affecting respiratory function (e.g. aspiration pneumonia with bulbar dysfunction). The possibility of respiratory involvement should be considered at times of illness or in the pre-operative assessment. All patients with respiratory involvement should be offered access to relevant vaccination programs (e.g. influenza vaccine, pneumovaccine). Patients should have access to a specialist in respiratory medicine and local support, particularly where non-invasive ventilation is a requirement. This document is intended for guidance only, and should not replace patient-specific management plans.

1. Guidance for Respiratory Screening in Patients with Mitochondrial Disease

1.1 Forced Vital Capacity (FVC) and Forced Expiratory Volume (FEV1) measurements should be performed in both the erect and supine position. They are recommended for patients as follows:

1.1.1. All patients, at the time of diagnosis.

1.1.2. All patients as part of any pre-operative assessment.

1.1.3. Spirometry should ideally be performed daily in patients suffering respiratory symptoms or signs of respiratory impairment whilst an inpatient in a hospital environment. Where spirometry is not readily accessible, clinicians should remain vigilant for signs of respiratory failure or exhaustion.

1.1.4. Patients with clinically detectable myopathy, at 12-monthly intervals (or earlier if a change in clinical status or development of symptoms suggestive of respiratory involvement).

1.1.5. Patients with documented respiratory muscle weakness, at 12-monthly intervals (or earlier if a change in clinical status or development of symptoms suggestive of respiratory involvement).

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

1.1.7. Facial/bulbar weakness may impair a patient's ability to perform satisfactory pulmonary function. A mouthpiece and nose-clip, or a mask, can be used depending on how well a patient can create a seal.

1.2. Formal pulmonary function tests (PFTs) may be required including spirometry (Forced Expiratory Volume in 1 second or FEV1 and Forced or relaxed Vital Capacity or VC), flow volume loop, lung volumes, transfer factor, erect and supine VC, MIPS/MEPS or SNIP's. Where this level of assessment is required, referral to a respiratory physician is recommended.

1.3. Chest X-ray (CXR) is recommended for patients as follows:

1.3.1. All patients who report respiratory symptoms, at the time of diagnosis. Future radiographs may be required in response to new or recurrent symptoms.

1.3.2. All patients with a documented reduction in the FVC, at the time of diagnosis. Future radiographs may be required if the FVC drops unexpectedly. A CXR may identify a domed diaphragm, lobar collapse due to aspiration, or other unrelated pathologies.

1.4. Fluoroscopy of the diaphragm should be considered if features of diaphragmatic weakness are present (e.g. exertional or postural breathlessness, drop in supine VC, elevated hemidiaphragm, reduction in MIPs)

1.5. Computed tomography (CT) of the chest is not routinely indicated to assess respiratory involvement in mitochondrial disease. It may be indicated where other pathologies are being considered and under these circumstances liaison with a respiratory physician is advised.

1.6. Referral to a specialist in respiratory medicine is indicated as follows:

1.6.1. All patients with significant respiratory impairment based on clinical features and measurements of pulmonary function. Even in relatively mild cases it is important that reversible components are identified and treated appropriately from an early stage as other pulmonary pathologies (e.g. asthma) may coexist.

1.6.2. All patients with symptoms suggestive of nocturnal hypoventilation or obstructive sleep apnoea (e.g. excessive snoring with/without witnessed apnoeas, excessive daytime sleepiness). Formal sleep studies and trials of non-invasive ventilation may be required.

2. Alternative or contributory pathologies

It is important that other causes are considered, and excluded if there is clinical suspicion of an alternative or contributory pathology. Such scenarios include:

2.1. Anaemia – acute or chronic anaemia may present with dyspnoea and should be excluded.

2.2. Pulmonary – parenchymal lung disease (e.g. COPD) may coexist and its contribution requires assessment. A respiratory opinion is advised to ensure optimum management. Pulmonary embolism should be considered, particularly in the immobile patient or where dyspnoea develops rapidly and unexpectedly.

2.3. Cardiac – cardiac causes of dyspnoea should be excluded where a clinical suspicion exists (see Cardiac Guidelines).

2.4. Swallowing – swallowing assessments are recommended where bulbar or cerebellar dysfunction exists, or patients complain of dysphagia, choking or frequent chest infections.

2.5. Gastrointestinal – occasionally gastro-oesophageal reflux of stomach acid may precipitate recurrent attacks of bronchospasm. This appears more frequently in myopathic patients, probably as a result of weakness of the cardiac sphincter. Referral to a gastroenterologist for oesophageal studies, endoscopy or a trial of a proton pump inhibitor may be indicated.

2.6. Metabolic – Hyperventilation and apparent dyspnoea may occur as a compensatory mechanism in the presence of a significant metabolic acidosis. Lactic acidosis may occur in several mitochondrial disease phenotypes (e.g. MELAS). Diabetic ketoacidosis, acute renal failure and toxic causes require exclusion. Arterial blood gases, blood glucose, urea and electrolytes, and an uncuffed venous sample for lactate analysis represent the necessary initial investigations.

3. Education

3.1. Smoking: advise complete cessation.

3.2. Vaccinations: recommended as per national guidelines (see 'Treatment' below).

3.3. Patient awareness: patients should be made aware of significant respiratory muscle weakness and its implications (see below). Patients are encouraged to share this information with relatives, carers and other doctors involved in their care. The use of alert bracelets or information letters from a specialist is also helpful.

3.4. Medical awareness: other doctors involved in the care of the patient should be made aware of any significant respiratory disease and its implications (see below). It is important that they are included in all relevant future correspondence.

3.5. Early treatment: patients are encouraged to seek medical advice early in the course of any illness and particularly in the presence of worsening respiratory symptoms.

3.6. General anaesthesia: Patients and health professionals should be aware of the potential risks related to surgery, particularly if requiring general anaesthesia. In most cases this does not contra-indicate surgery, and should not unduly delay non-elective surgery.

4. Guidance for Clinical Management in Patients with Mitochondrial Disease

4.1. Vaccination: patients with respiratory impairment should be offered access to relevant vaccination programmes as per national guidelines. Mitochondrial disease does not constitute a contra-indication and in most cases the benefits are felt to outweigh any potential risks. Where concern exists we recommend liaison with the specialist responsible for the patient's care.

4.2. Lower respiratory tract infections: a policy of early intervention may be adopted in the presence of significant respiratory muscle weakness or where infections are known to precipitate deterioration in the patient's mitochondrial disease (eg MELAS). Most antibiotics may be used without caution in mitochondrial disease (see Drug Guidelines). Exceptions include **Linezolid** which can precipitate or worsen lactic acidosis, and aminoglycosides which may induce deafness in carriers of mutations within the *MT-RNR1* (e.g. m.1555A>G) and *MT-TS1* genes. Aminoglycosides are **not** contra-indicated in other forms of mitochondrial disease.

4.3. Co-existent respiratory disease (eg COPD): this should be treated in the usual manner, though a policy of early intervention should still be applied. It is worth noting that spirometry and inhaler technique may be adversely affected by weakness or incoordination of the upper limbs, facial or bulbar musculature. In such cases spirometry may be unreliable and the full benefit from inhaled medications may not be realised. Complications (eg candidiasis) may occur as a result of inhalers dispensing steroids to the

mucosa of the oropharynx rather than the lungs. Spacer devices or nebulisers may be useful alternatives.

4.4. Respiratory muscle weakness: this should be assessed by a respiratory physician. A low threshold for referral should be employed in all cases, but particularly in the presence of symptoms or a significant drop in the FVC from predicted norms or previous measurements. Specialist involvement allows for appropriate guidance, exclusion of other treatable pulmonary pathologies, and the assessment and provision of non-invasive ventilation where indicated.

4.5. Obstructive sleep apnoea – the opinion of a respiratory physician with experience in neuromuscular disease and non-invasive ventilatory techniques will guide appropriate treatment.

4.6. Posture: significant drops in the FVC while supine should prompt consideration of diaphragmatic weakness. Supine positioning should be avoided where possible and education offered to relatives, carers, and doctors involved in the care of the patient. Occasionally severe weakness of the neck extensors may lead to a sufficient head drop such that it contributes to upper airway obstruction. A soft collar may offer symptomatic improvement.

4.7. Physiotherapy: early involvement is recommended in cases of respiratory muscle weakness or where recurrent chest infections are documented.

4.8. Speech and language therapy: early assessment of the swallow is recommended in cases of respiratory muscle weakness where bulbar dysfunction might predispose to aspiration. In selected cases early consideration of PEG feeding may be appropriate. This should not necessarily be seen as a last resort (see Speech and Swallowing Guidelines).

5. Notes on the scope of this guidance

The guideline was developed by experts in mitochondrial disease and respiratory 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 respiratory involvement in patients with mitochondrial disease was to be included and excluded.

5.1. 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

5.2. 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.

6. 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 NHS 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 respiratory 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 disease to develop in the absence of respiratory symptoms highlights the importance of this programme.
- Close liaison is required both with respiratory services at the specialist centre itself, but also local respiratory services who may be closely involved with future follow up and management of patients where frequent central review is impractical.

7. Research recommendations

7.1. 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 respiratory disease on morbidity and mortality.

7.2. Non-invasive ventilation in mitochondrial patients with respiratory failure

7.3. Incidence of obstructive sleep apnoea and its treatment

8. 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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Appendix A: The Guideline Development Group

Dr Andrew M Schaefer
Consultant Neurologist
Newcastle Mitochondrial Centre, NHS Specialised Services for Rare Mitochondrial Disorders of Adults and Children

Dr Gerard Meachery
Consultant in Thoracic Medicine
Freeman Hospital
Newcastle upon Tyne

Dr Robert McFarland
DoH/HEFCE Clinical Senior Lecturer
Newcastle Mitochondrial Centre, NHS Specialised Services for Rare Mitochondrial Disorders of Adults and Children

Professor Douglass M Turnbull
Professor of Neurology
Newcastle Mitochondrial Centre, NHS Specialised Services for Rare Mitochondrial Disorders of Adults and Children