

Newcastle Mitochondrial Disease Guidelines

Peripheral Neuropathy in Adult Mitochondrial Disease: Screening and Initial Management

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Introduction

Peripheral neuropathy is a common feature of mitochondrial disease, reported in up to 77% of patients in some studies¹. In many patients this can be attributed to other complications of mitochondrial disease such as diabetes and/or renal failure. Nevertheless, even when these factors are accounted for, approximately 35% of patients with mitochondrial disease have evidence of peripheral neuropathy attributable directly to the mitochondrial disease itself². The range of severity extends from asymptomatic neurophysiological changes to severe and disabling motor deficits or sensory ataxia. Both axonal³ and demyelinating forms^{4,5} are described. Typically the neuropathy takes the form of a symmetrical polyneuropathy; however, asymmetrical and patchy demyelinating neuropathy has been described.

Some authors have also suggested an increased risk of focal neuropathies⁶, although to date no systematic studies have been published.

In general, there is a poor correlation between genotype and the phenotype of the neuropathy. Exceptions include the predominant finding of sensory neuronopathy in POLG1⁷ and an axonal neuropathy in NARP syndrome secondary to m.8993T>G mutation⁸. In these syndromes, the neuropathy tends to be severe and progressive, leading to significant disability. Clinical vigilance and expert neurophysiological assessment are key to the diagnosis of neuropathy in mitochondrial disease. Management should focus on the exclusion of treatable factors and symptom control.

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

In view of the diverse phenotypes of mitochondrial disease, we recommend that all patients suspected to have a neuropathy should have access to a specialist with experience in the diagnosis and management of peripheral neuropathy/neuronopathy in mitochondrial disease. Access to an experienced neurophysiologist is vital in helping to determine the nature of the neuropathic involvement. This guidance also applies to those asymptomatic carriers deemed to be at significant risk of developing disease.

Further investigation and follow-up should be based on the initial evaluation and the likelihood of peripheral nervous system involvement, if known, for the specific genetic sub-type. This document is intended for guidance only, and should not replace patient-specific management plans.

1. Guidance for screening in patients with neuropathic symptoms in mitochondrial disease

1.1. Safety: patients with mitochondrial disease are at risk of cardiac arrhythmias, and on rare occasions may be fitted with implanted defibrillators. Nerve conduction studies pose a theoretical risk to these patients, especially if repetitive nerve stimulation at frequencies of 3Hz or above are employed. It is essential that the physician performing the investigation is aware of this situation in advance, so that these issues can be discussed with the patient's cardiologist prior to the test, and if necessary, the defibrillator switched off for the duration of the test.

1.2. Nerve conduction studies and electromyography should be performed in the following:

1.2.1. All patients with symptoms or signs suggestive of a peripheral neuropathy, entrapment neuropathy, or neuronopathy. Nerve conduction studies should ideally include motor studies on the following nerves: median; ulnar; common peroneal; tibial. Nerve conduction studies should ideally include sensory studies on the following nerves: median; ulnar; radial; sural; superficial peroneal. Conduction studies should include examination of sites of common nerve entrapment: ie carpal tunnel; cubital tunnel; fibular head. Electromyography should ideally include both proximal and distal limb muscles.

1.2.2. Repeat studies should be considered on clinical grounds. Routine follow up studies are not recommended unless these are felt likely to alter management (eg entrapment neuropathies). Repeat studies may

be indicated if there is deviation from the expected clinical course to exclude additional pathologies.

1.3. Exclude other causes: the importance of excluding other causes of neuropathy should not be overlooked merely because of the diagnosis of mitochondrial disease, even where the association with neuropathy is well described. Reversible causes should be screened for in all cases. The nature of the neuropathy (axonal, demyelinating, or dorsal root ganglionopathy) and the level of clinical suspicion will guide further investigations. For example – a patient with CPEO due to a single deletion of the mitochondrial DNA would not be expected to develop a symptomatic neuropathy or dorsal root ganglionopathy. Other causes should be actively excluded.

1.3.1. Routine blood screens - should include a fasting blood glucose, glycosylated haemoglobin, full blood count, erythrocyte sedimentation rate, vitamin B12 and folate, urea and electrolytes, creatinine, liver function tests, auto-antibodies, extractable nuclear antigens, serum (and urine) electrophoresis.

1.3.2. Chest X-Ray – should be performed to exclude neoplasia, lymphadenopathy or parenchymal abnormalities (e.g. sarcoid)

1.3.3. Nutrition – many patients with mitochondrial disease have problems with swallowing or gastric motility. Resultant deficiency states are rarely sufficient to cause a neuropathy but may contribute. Patient's nutritional status should be optimised wherever possible. Poor dietary intake (+/- alcohol excess) increase the likelihood of thiamine or a mixed B vitamin deficiency. Supplementation based on clinical

suspicion (and without laboratory confirmation) is generally recommended.

1.3.4. Drugs/Toxins – appropriate enquiries should be made for agents known to cause neuropathies. This should include prescribed/over the counter drugs, recreational drugs (including alcohol), and occupational exposure to potential toxic substances.

1.3.5. Other Pathologies – consider whether compressive disease in the cervical or lumbosacral spine might be providing significant contribution to symptoms/signs.

2. Guidance for Clinical management in Patients with Mitochondrial Disease

2.1. All patients diagnosed with a significant peripheral neuropathy should have access to specialist mitochondrial services.

2.2. All patients with significant peripheral neuropathy should be given advice on avoiding complications:

2.2.1. Advice should be given regarding foot care (e.g. well-fitting shoes).

2.2.2. All patients should have access to local podiatry services.

2.2.3. Patients with significant visual impairment and/or significant peripheral analgesia should have regular podiatry review.

2.3. Peripheral neuropathy attributable to diabetes:

Patients with diabetes and peripheral neuropathy should ensure optimum glycaemic control. No other interventions have been shown to reduce the rate of progression.

2.4. Peripheral neuropathy attributable to renal impairment / liver disease:

Management centres on the treatment of the renal impairment / liver disease. As with diabetes, no other specific measures have been demonstrated to reduce the rate of progression.

2.5. Physiotherapy: patients with functional deficits as a result of the neuropathy/neuronopathy may benefit from a physiotherapy assessment. Where possible this should be by a physiotherapist with experience of neuropathies and neurological disease. Myopathy and cerebellar ataxia may coexist which can create a complex dynamic that requires regular review and specialist input.

2.6. Occupational Therapy: this should be offered to patients with impaired function as a consequence of their neuropathy/neuronopathy, or to those where it is contributing to difficulties attributable to multi-system disease.

2.7. Orthotics: focussed assessment is recommended where a neuropathy or neuronopathy has lead to a functional deficit (usually motor). Use of an ankle foot orthosis may be beneficial in patients with foot drop and wrist supports may benefit patients with weakness of the wrist extensors. Proprioceptive loss and weakness in patients with dorsal root ganglionopathy may lead to instability at the ankle joint. Appropriate supports may be beneficial.

2.8. Surgical interventions: very rarely corrective surgery for achilles tendon contractures or other foot deformities may be indicated. Such interventions should not be dismissed or delayed due to the diagnosis of mitochondrial disease alone. Consideration, however, must be given to

additional contributing neurological factors (eg myopathy, ataxia, spasticity or dystonia) and other comorbidities when considering the overall benefit of the procedure.

2.9. Drugs to avoid:

2.9.1. Drugs known to cause peripheral neuropathy, for example vincristine, isoniazid, and nitrofurantoin should be avoided if possible.

2.9.2. Dichloroacetate has been used for the treatment of mitochondrial disease in the past, but randomised controlled trials were halted due to the observation of an excess of peripheral neuropathy⁹.

Dichloroacetate should therefore be avoided in patients with mitochondrial disease in all but the most exceptional circumstances.

2.9.3. Sodium valproate is not recommended by NICE for the treatment of neuropathic pain and should not be used for this purpose in mitochondrial disease due to potential mitochondrial toxicity.

2.10. Drug treatment:

2.10.1. No specific data exists on the treatment of neuropathic symptoms in mitochondrial disease. Drugs commonly used for the treatment of neuropathic pain (e.g. carbamazepine, amitriptyline, gabapentin) may offer symptomatic relief but can also produce side-effects.

Comorbidities (e.g. ataxia) should be taken into account when choosing which treatment is most appropriate.

2.10.2. No evidence exists that pharmacological treatments can prevent or slow the development of peripheral neuropathy in mitochondrial disease. Agents such as co-enzyme Q10, and creatine have been used but evidence of benefit is not available.

2.10.3. Stem cell therapy and dialysis have been used in the treatment of MNGIE syndrome. Although some evidence exists that these treatments reduce gastrointestinal symptoms, there is currently no evidence that they prevent or reverse the associated peripheral neuropathy.

2.11. Entrapment neuropathy:

Anecdotal evidence suggests an increased incidence of entrapment neuropathy in mitochondrial disease. Surgical decompression can lead to both symptomatic and neurophysiological improvement. Early neurophysiological testing is recommended where clinical features of entrapment neuropathy exist. In patients with a documented polyneuropathy, new deficits should be assessed and the possibility of super-added entrapment neuropathies considered. Compressive disease within the cervical or lumbosacral spine may also produce focal deficits of a lower motor neurone nature and this possibility should also be considered.

3. Notes on the scope of this guidance

The guideline was developed by experts in mitochondrial disease and neurophysiology 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 peripheral nervous system 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 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. The Newcastle Mitochondrial Centre is currently negotiating provision of outreach clinics in other centres to facilitate easier access for patients who do not reside within a reasonable distance of the existing centres.
- 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 causes, consequences, and potential complications of neuropathies in mitochondrial disease.
- 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 peripheral nervous system disease to develop in hitherto asymptomatic relatives highlights the importance of this programme.
- Close liaison is required with neurophysiology services at the specialist centre.

5. Research recommendations

3.1. 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 peripheral neuropathy on morbidity. This is particularly important in the paediatric population, in which little evidence is available.

3.2. The incidence of entrapment neuropathies

Although no specific treatment exists for polyneuropathies associated with mitochondrial disease, some evidence suggests an increased incidence of entrapment neuropathy. Further research is needed to determine the true incidence and optimum management of this potentially treatable complication.

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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Appendix A: The Guideline Development Group

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