

# **Newcastle Mitochondrial Disease Guidelines**

## **Epilepsy in Adult Mitochondrial Disease:**

## **Investigation and Management**

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## Introduction

Epilepsy is common to a number of mitochondrial diseases - in some a myoclonic epilepsy may be the defining clinical feature (e.g. MERRF), whereas in others, a focal epilepsy, often associated with encephalopathy and stroke-like episodes (e.g. MELAS), may predominate. MERRF and MELAS are most commonly associated with the m.8344A>G and the m.3243A>G mtDNA point mutations respectively. Many other point mutations have been reported to cause similar phenotypes, and disorders of mtDNA maintenance due to the nuclear POLG1 mutation may also cause a MELAS-like presentation or myoclonic epilepsy. The encephalopathy and stroke-like episodes associated with MELAS may result in seizures that are refractory to treatment leading to recurrent 'cerebral crises' that risk cumulative cortical damage and step-wise cognitive decline. The post-ictal (or apparently post-ictal) period should be monitored closely. Persistent electrical status may not be readily apparent, particularly in patients where encephalopathy, dementia or severe deafness co-exists. Focal neurology, and in particular visual field defects, may indicate ongoing seizure activity. A prolonged post ictal period with encephalopathic features may also represent non-convulsive status epilepticus and requires urgent assessment.

Seizures in mitochondrial disease are treated similarly to other forms of epilepsy; with the notable exception that sodium valproate is generally avoided due to potential hepatotoxicity. In our experience, early and adequate treatment of seizures in both the inpatient and outpatient scenario is beneficial in terms of minimizing or preventing irreversible and cumulative cortical damage, and thus preserving function. It is important that best practice includes liaison with a specialist centre in the treatment of mitochondrial diseases where this is practicable. Patients should have access to local neurology services as per the SIGN guidelines.

## **Patient Centred Care**

This guideline offers best practice advice on the care of people with mitochondrial disease. Treatment and care 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 a code of practice accompanying the Mental Capacity Act (summary 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 evidence tailored to the patient's 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 epilepsy arising as a result of mitochondrial disease should have access to a specialist with experience in this field. Seizures may be associated with encephalopathy or stroke-like episodes, and may be refractory to treatment. The experience of this group is that epilepsy in patients with mitochondrial disease should be treated actively from the outset, in order to minimize subsequent cerebral damage related to frequent or intractable seizures. Potential precipitants should be recognized, outpatient and inpatient treatment optimized, and non-convulsive status epilepticus actively excluded in the obtunded patient. This document is intended for guidance only, and should not replace patient specific management plans.

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

1.1. Recommendations for the diagnosis of epilepsy in patients with mitochondrial disease are as follows:

1.1.1. The diagnosis of epilepsy is best made by a neurologist or other epilepsy specialist as recommended in the SIGN guidelines.

1.1.2. Classification: the seizure type(s) and epilepsy syndrome should be identified if possible. A variety of seizure types may be seen in mitochondrial disease. Focal and myoclonic epilepsy may occur independently or coexist. In some patients with myoclonic epilepsy there may be a marked photoparoxysmal response (e.g. MERRF).

1.1.3. ECG should be performed in all patients (see Cardiac Guidelines).

1.1.4. EEG studies should be performed to help in the diagnosis and classification of suspected epilepsy. They should not be used to 'exclude' epilepsy. Patients with mitochondrial disease may have marked abnormalities of the inter-ictal EEG. Documentation of these abnormalities may be helpful for comparison at a future date.

1.1.5. MRI brain imaging is indicated as per the SIGN guidelines, and should employ epilepsy specific protocols (CT may be indicated in the emergency setting or if MRI is contraindicated). Alternative pathologies should be excluded. MRI changes consistent with acute metabolic infarction may accompany ongoing focal seizure activity and may require further investigation. Repeat imaging to assess the resolution of these changes is often helpful in providing a baseline for comparison in anticipation of future events.

1.2. Disease-specific assessments (over and above those recommended in the SIGN guidelines) are recommended as follows:

- 1.2.1. Exclude hyponatraemia – common in patients with MELAS phenotypes or the m.3243A>G mutation (either as a result of SIADH or renal disease). Hyponatraemia is a recognized side effect of carbamazepine and oxcarbazepine, but occurs more frequently in the groups above. Occasionally hyponatraemia can be marked (<125mmol/l) and may require withdrawal or a change in medication.
- 1.2.2. Serum lactate (uncuffed sample) – it is generally helpful to be aware of any significant lactic acidosis resulting from the underlying respiratory chain defect, if only to provide a baseline for future comparison. No convincing evidence exists to support attempts to correct the lactic acidosis detected in mitochondrial patients, and some believe it may be harmful to do so. In status epilepticus, the degree of acidosis should be assessed (as per SIGN guidelines) and severe derangements may require treatment.
- 1.2.3. Consider need for further cardiac evaluation – higher incidence of cardiomyopathy and arrhythmias (may coexist with epilepsy).
- 1.2.4. Assess respiratory and bulbar function in myopathic patients – may be increased risks of respiratory failure following seizures or administration of benzodiazepines (see Respiratory Guidelines).
- 1.2.5. Assess inter-ictal function and level of interaction. Chronic encephalopathy, dementia, and profound deafness may limit the patient's ability to manage their own condition and affect compliance. Assessment of post-ictal recovery is aided by comparison with accurate interictal assessments and may be particularly useful where no carer or relative is available.

1.3. Post-ictal assessment is essential and should address the following scenarios:

1.3.1. Clear ongoing seizure activity requires urgent treatment – irrespective of whether this is partial or generalised.

1.3.2. Confused or obtunded patients may be suffering non-convulsive status epilepticus. If the post-ictal period appears prolonged or unusual urgent EEG is indicated; or a trial of treatment (if EEG monitoring is unavailable) after liaison with a neurologist or specialist centre.

1.3.3. New focal neurological deficits may be the result of stroke-like episodes (metabolic cerebral infarcts) and/or focal status epilepticus. These are often, but not exclusively, associated with headache and obtundation. Visual field defects are the most common defects and must be looked for closely as they are rarely volunteered. Urgent EEG is indicated to exclude focal status. MRI is recommended to clarify the nature and extent of parenchymal involvement. CT may be used in the acute setting if MRI is not available, though its role is limited to the exclusion of other pathologies such as intracerebral haemorrhage.

1.3.4. Patients attending emergency departments following a seizure should be admitted for observation during the post-ictal period to confirm satisfactory resolution.

1.3.5. It is vital that the patient's usual anti epileptic drugs (AEDs) are continued during the post-ictal period, and alternative routes of administration should be sought if the patient is unable to take medications by mouth. See Table 1.

- 1.4. Status epilepticus. The treatment of generalised tonic-clonic status epilepticus should be treated in accordance with the existing SIGN guidelines. Exceptions and additional considerations are as follows:
- 1.4.1. Sodium Valproate should be avoided in patients with mitochondrial disease due to potential toxic effects.
  - 1.4.2. Benzodiazepines are indicated as per the 'immediate measures' outlined in the SIGN guidelines, however, they should be used with caution in patients with severe respiratory muscle weakness in view of the increased risks of respiratory suppression or arrest. Anaesthetic support is advised.
  - 1.4.3. Exclude non-convulsive status epilepticus irrespective of level of sedation. This is common in patients with mitochondrial encephalopathy. Low threshold for bi-spectral index monitoring (if available) and/or regular EEG (N.B. Interictal EEG may be grossly abnormal – comparison is advised to aid interpretation).
  - 1.4.4. Consider treatment with folinic acid supplements in addition to anaesthesia and AEDs. CSF may be sent for 5-MTHF levels prior to supplementation. Supplementation is safe but evidence for its efficacy is limited.
  - 1.4.5. Metabolic acidosis is more likely to occur in patients with mitochondrial disease due to excessive production of lactic acid. Other causes should be considered. The degree of acidosis should be assessed as per SIGN guidelines and treatment considered in severe cases.
  - 1.4.6. Creatine kinase levels should be checked in the presence of convulsive status epilepticus. Mitochondrial patients may have an



elevated baseline CK (<1000) and may be more prone to significant rhabdomyolysis.

1.4.7. Cardiomyopathy is more common in mitochondrial patients and LV function may deteriorate in the presence of acute stress, metabolic acidosis, anaesthetic agents, or excessive fluid replacement. Close cardiac monitoring is advised.

1.4.8. Consider diaphragmatic or generalised respiratory muscle weakness if difficulty weaning from assisted ventilation.

1.4.9. Bowel management is important. Patients with mitochondrial disease are at risk of pseudo-ileus (smooth muscle involvement) which may hamper recovery or affect enteral AED absorption.

#### 1.5. Anti-epileptic drugs in mitochondrial disease

1.5.1. Sodium Valproate should be avoided where possible. Absolute contraindication in patients with POLG mutations. Fulminant hepatotoxicity has been reported.

1.5.2. Long-term treatment with phenytoin is discouraged but may be unavoidable in difficult epilepsies. Long term usage may contribute to cerebellar atrophy. Phenytoin remains a very effective anti epileptic agent in the acute setting.

1.5.3. Focal epilepsy: Favoured agents are similar to those used in epilepsies due to other causes, with the exception of sodium valproate. Tolerability is often a major factor. Drowsiness, cerebellar and psychiatric symptoms can be problematic. For benefits and cautions see Table 1.

1.5.4. Myoclonic epilepsy: Favoured agents are similar to those used in epilepsies due to other causes, with the exception of sodium valproate.

We have found levetiracetam particularly helpful in controlling myoclonus. For benefits and cautions see Table 1.

1.5.5. Benzodiazepines should be used with caution in patients with severe respiratory muscle weakness, particularly where large individual dosages are used as 'rescue therapy'. Respiratory failure may result and anaesthetic support is advised under these circumstances. For benefits and cautions see Table 1.

## 1.6. Other treatments for epilepsy

1.6.1. Vagal Nerve Stimulation: No good evidence exists for this treatment in patients with mitochondrial disease.

1.6.2. Epilepsy Surgery: No good evidence exists for this treatment in patients with mitochondrial disease. Although focal areas of high signal may appear on T2, FLAIR and DWI MR images during 'stroke-like episodes', these are often transient and may recur in multiple regions within either hemisphere. Residual gliotic scarring is rarely the sole source of future epileptic activity. The risk of neurosurgery in such patients is unknown.

## 1.7. Additional recommendations

1.7.1. Infections or dehydration may precipitate seizures in mitochondrial patients with a diagnosis of/or at risk of epilepsy. Both scenarios should be avoided if possible and treated promptly.

1.7.2. Patients with diabetes should make this known to carers and relatives. Hypoglycaemia should be actively excluded in the event of seizures or post-ictal confusion.

1.7.3. Clear management plans should be discussed with patients and carers for seizures occurring at home.

#### 1.8. Screening asymptomatic patients at risk of epilepsy (eg m.3243A>G)

1.8.1. No indication for EEG.

1.8.2. No indication for cerebral imaging

1.8.3. No indication for 'prophylactic' AEDs

#### 1.9. Driving and safety

1.9.1. DVLA regulations apply and patients should be advised accordingly.

1.9.2. Additional comorbidities need to be taken into account (e.g. visual impairment, myopathy, dementia etc).

1.9.3. Common sense safety advice should be provided to patients and carers.

1.10. Advice for women – this is as recommended in the SIGN guidelines

## 2. Notes on the scope of this guidance

The guideline was developed by experts in mitochondrial disease and epilepsy 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.

## 2.1.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

## 2.2.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.

### 3. 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 epilepsy in mitochondrial disease and the potential benefits of improved seizure control.
- Access to specialist clinics allows relevant genetic counselling and family tracing to facilitate the identification of those at risk of developing disease, or to formally diagnose those who may already be affected.
- Close liaison is required between the specialist centre itself and local services. We recommend local neurology follow up where frequent or emergency central review is impractical.

## 4. Research recommendations

### 4.1. 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 epilepsy on morbidity and mortality.

### 4.2. Frequency of SUDEP in mitochondrial disease

Sudden unexpected death in epilepsy (SUDEP) is well recognised, but is extremely rare when looking at unselected epilepsy cohorts.

Unexpected deaths in mitochondrial disease may be reduced with better seizure control and this possibility requires further study.

### 4.3. Appropriate Seizure Management

Prolonged focal or generalised seizure activity often results in focal neurological deficits or cognitive decline. The potential neuro-protective effects of prompt and adequate seizure control are unknown but may minimize neuronal loss and maintain function.

### 4.4. Neuro-Protective Agents

Permanent neuronal loss may occur during prolonged seizure activity or during stroke like episodes. Neuro-protective agents employed during these metabolic crises may preserve neuronal function and prevent cell loss. Agents such as L-arginine have failed to show clear benefit, but it remains important that research continues in this area.

## **5. 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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Table 1

| AED             | Epilepsy           | Mode administration   | Advantages  | Disadvantages  |
|-----------------|--------------------|---|---|--|
| Phenytoin       | Focal              | Capsules<br>Chews<br>Suspension<br>IV                             | Efficacy in localisation related epilepsy<br>IV use in status   | Narrow therapeutic index<br>Acute cerebellar toxicity<br>Chronic cerebellar toxicity |
| Carbamazepine   | Focal              | Tablets<br>Chews<br>Suspension<br>Suppository<br>Modified release | Efficacy in localisation related epilepsy<br>Option for short term suppository use                        | Acute cerebellar toxicity<br>Hyponatraemia   |
| Oxcarbamazepine | Focal              | Tablets<br>Suspension   | Tolerability (vs CBZ)   | As CBZ but to lesser extent  |
| Topiramate      | Focal              | Tablets<br>Sprinkle capsules                                      | Additional anti-migraine action   | Potential weight loss (low BMI patients)<br>Mood/concentration                       |
| Lamotrigine     | Focal<br>Myoclonic | Tablets<br>Chews<br>Dispersibl                                    | Broad spectrum efficacy – all seizure types<br>Tolerability   | No specific disadvantages  |
| Levetiracetam   | Focal<br>Myoclonic | Tablets<br>Suspension<br>IV                                       | Broad spectrum efficacy – all seizure types<br>Control of myoclonus<br>IV use in status<br>Tolerability   | Mood/irritability  |
| Clonazepam      | Myoclonic          | Tablets   | Control of myoclonus  | Sedation<br>Tolerability over time   |
| Clobazam        | Focal<br>Myoclonic | Tablets   | Broad spectrum efficacy – all seizure types<br>Temporary cover when necessary – eg illness, AED titration | Sedation<br>Tolerability over time   |