

Newcastle Mitochondrial Disease Guidelines

Stroke-Like Episodes in Adult Mitochondrial Disease: Investigation and Management

First published November 2012

Updated January 2013

Contents

Introduction	3
Patient-centered Care	4
Key priorities for implementation	5
1. Clinical features of stroke-like episodes	6
1.1. Onset	6
1.2. Headache	6
1.3. Encephalopathy	6
1.4. Seizures	6
1.5. Focal neurological deficits	7
1.6. Supporting evidence	7
2. Management of the acute episode	8
2.1. Exclude other causes	8
2.2. Observation	8
2.3. Treatment of seizures	8
2.4. Bloods tests	9
2.5. Exclude infection	9
2.6. Ensure adequate hydration	10
2.7. Ensure drug delivery and calorific/nutritional intake	10
2.8. Cerebral imaging	10
2.9. Cerebrospinal fluid	12
2.10. Genetic studies	12
2.11. Other considerations	13
3. Specific therapies for stroke-like episodes	13
4. Notes on the scope of this guidance	15
5. Implementation	16
6. Research recommendations	17
6.1. Natural history studies	17
6.2. Pharmaceutical therapies	17
6.3. Seizure control	17
7. Updating the guideline	17
Appendix A: The Guideline Development Group	18
References	19

Introduction

Stroke-like episodes have been synonymous with mitochondrial disease since the acronym MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes) was first coined. Despite this now accepted term, these episodes of focal cerebral metabolic crisis bear little resemblance to strokes of an atherosclerotic or thrombo-embolic aetiology, and this distinction is important to avoid misdiagnosis. Gradual evolution of headache, encephalopathy, seizures and focal deficits represent a 'full house' but the presence of headache and in particular seizures and/or focal deficits is highly variable. Even in the absence of a focal deficit there may be focal EEG and MRI abnormalities and resultant neuronal loss with step-wise reduction in cerebral function. Although mitochondrial disease clinically affects a minimum 9.2/100,000 of the adult population¹, stroke-like episodes are relatively rare across the broad spectrum of mitochondrial disease. Even in patients who harbour the m.3243A>G mutation (the commonest single cause of the MELAS phenotype), these events are infrequent and for many patients will never occur throughout their lifetime. Lower levels of heteroplasmy (in muscle or urinary epithelial cells) for mutated mitochondrial DNA (mtDNA) appear associated with lower risk of stroke-like episodes, but this rule of thumb is not infallible, possibly due to the lack of access to clinically relevant tissues. Furthermore, in pedigrees where the m.3243A>G mutation predominantly manifests as maternally inherited diabetes and deafness (MIDD) the incidence of such events is significantly less than in those where a family history of stroke-like episodes exists. It is therefore important that the familial phenotype is considered before referring to the m.3243A>G substitution as 'The MELAS mutation' as this may be phenotypically inaccurate and cause unnecessary anxiety for family members. Many other mtDNA mutations have been reported in association with stroke-like episodes but are all relatively rare². Autosomal recessive mutations within the polymerase gamma gene (POLG1) may also present in a similar manner yet usually follow a slightly different clinical course³. Seizures often predominate and may be intractable. These may present with focal seizures (eg epilepsy partialis continua) when the prognosis may be more favourable if progression to generalised status epilepticus can be prevented. This guideline aims to clarify the typical features that identify a stroke-like episode, the necessary investigations in the acute setting, and appropriate management to minimise any permanent neurological deficit.

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 suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed in the acute setting with the local neurology team and ideally a specialist mitochondrial centre where this is feasible. Other treatable causes need to be excluded. Transfer to a unit with EEG facilities is important where symptoms do not resolve rapidly and access to urgent 'out of hours' EEG may improve outcome where non-convulsive status epilepticus is suspected. Where access to EEG may delay treatment there should be a low threshold for empirical treatment on the assumption of non-convulsive status epilepticus. Stroke-like episodes are often undetectable on CT imaging, so access to MRI is important to support the clinical diagnosis. This document is intended for guidance only, and should not replace patient-specific management plans.

1. Clinical features of stroke-like episodes

- 1.1. Onset: Gradual. Often reported by relatives rather than patient (encephalopathic). Usually headache and obtundation before seizures or neurological deficit.
- 1.2. Headache: often of a non-specific or migrainous nature but usually lacking prominent photophobia or nausea. Positive visual phenomena variably reported. Visual field deficits may be present but usually not volunteered.
- 1.3. Encephalopathy: patients are usually drowsy and apathetic. Headache or neurological deficits are often underplayed. Agitation is rare but psychiatric features may be seen with temporal lobe involvement. Cerebellar signs and slurring dysarthria are common. Myoclonus may be observed and can be stimulus sensitive
- 1.4. Seizures: seizures are not uniformly present, but ongoing seizure activity represents a treatable factor in the acute stroke-like episode. Increased metabolic demand due to seizure activity may perpetuate the focal metabolic crisis and worsen neuronal loss and subsequent neurological outcomes. Physicians must be wary of non-convulsive status epilepticus arising from the occipito-parietal lobes. In these cases the obtundation may be slow to resolve and a careful examination of the patient may reveal a homonymous hemi or quadrantanopia. Access to EEG is vital in this scenario. Focal motor seizures or generalised tonic-clonic seizures may be observed. Temporal lobe involvement may result in complex

partial seizures or occasionally psychiatric symptoms, often with auditory hallucinations.

- 1.5. Focal neurological deficits: clear neurological deficits are frequently absent. Homonymous hemi or quadrantanopia is the most frequent neurological deficit, but is rarely volunteered by the patient and can be difficult to identify in the encephalopathic patient. Dysphasia may be subtle and hemiparesis (arm > leg) is rarely dense. A well demarcated deficit in a patient *without* encephalopathy is unlikely to be a mitochondrial stroke-like episode.
- 1.6. Supporting evidence: certain results (below) may support the diagnosis but are not uniformly present.
 - 1.6.1. Hyponatraemia is common (SIADH +/- background renal involvement)
 - 1.6.2. CSF lactate may be elevated and is a strong marker for mitochondrial disease. Serum lactate is often normal and false positive results common (samples should be taken uncuffed and analysed promptly).
 - 1.6.3. EEG is encephalopathic. Focal epileptic discharges or status epilepticus may be observed particularly in the occipito-parietal regions.
 - 1.6.4. MRI typically shows lesions on T2 weighted imaging which predominantly affects the cortex of the posterior parietal and occipital lobes and often crosses vascular territories. Cerebellar lesions are more common in POLG1 mutations than m.3243A>G (personal observation). Lesions often resolve within days, but residual gliosis or atrophy may develop.

2. Management of the acute episode

2.1. Always consider other causes. Even in patients with established mitochondrial disease other treatable causes of encephalopathy, seizures or neurological deficit should be considered. This may necessitate urgent imaging or CSF studies (see imaging and CSF below). A “stroke-like episode” in a mitochondrial genotype which is not typically associated with MELAS should be a diagnosis of exclusion.

2.2. Observation: maintain a low threshold for admission if a stroke-like episode is suspected. Even a brief overnight stay will often allow time to assess whether symptoms are resolving spontaneously, or worsening – a scenario that requires inpatient management.

2.3. Treatment of epilepsy: the EEG may be the most important tool in the acute management of stroke-like episodes in mitochondrial disease.

Identification and treatment of non-convulsive status epilepticus can significantly change management and overall outcome (see epilepsy guidelines).

2.3.1. Consider need for EEG early in the assessment. Many centres do not have “out of hours” EEG facilities so early liaison with the neurophysiology department is important.

2.3.2. Subsequent EEG monitoring may be required to guide treatment – particularly in non-convulsive status epilepticus.

2.3.3. Epilepsy management is described in detail in our epilepsy guidelines. Early and effective control is vital, especially in status epilepticus and patients with POLG1 mutations where seizures can become intractable. Sodium valproate is contraindicated in patients with POLG1 mutations and best avoided in other genotypes unless benefit has previously been documented. In our experience intravenous loading with phenytoin, levetiracetam, or both is often a sensible starting point. Addition of oral clobazam to new or existing AED regimes can be effective.

2.3.4. Where non-convulsive status epilepticus is suspected but limited access to EEG may delay treatment, empirical treatment should be strongly considered.

2.4. Blood tests: routine bloods are always indicated. Investigations worthy of specific mention are:

2.4.1. U+Es: Hyponatraemia may worsen obtundation or make seizures more likely. Slow correction may be necessary but strict fluid restriction is not advised as this may worsen dehydration or hypovolaemia.

2.4.2. Glucose: diabetes is common in the m.3243A>G mutation. Hyperglycaemia should be managed. Hypoglycaemia should be routinely excluded in any stroke-like episode.

2.4.3. Serum lactate: lactic acidosis may support the diagnosis and offer a possible explanation for unexplained dyspnoea and exercise intolerance. Arterial blood gases may be indicated in extreme cases.

- 2.4.4. Creatine kinase: Often normal even in myopathic phenotypes.
Modest elevation (<1000 IU) consistent with mitochondrial disease.
Not usually a clinical concern and rhabdomyolysis is rare.

- 2.5. Exclude infection: even minor infections can precipitate/perpetuate attacks.
 - 2.5.1. FBC and CRP. Blood culture if pyrexial.
 - 2.5.2. Exclude urinary tract infections.
 - 2.5.3. CXR if respiratory symptoms/signs or history of aspiration
 - 2.5.4. Look hard for other causes – ear infections, dental caries, toe/nailbed infections (especially in diabetic patients).

- 2.6. Ensure adequate hydration: patients often neglect oral intake during encephalopathy. Nausea and vomiting may contribute.
 - 2.6.1. Low threshold for intravenous hydration – even where U+Es are normal. Prompting sufficient oral intake is difficult in encephalopathic patients. Gastric dysmotility and/or vomiting may limit rehydration via nasogastric tube.
 - 2.6.2. Achieving correct balance can be difficult, and factors such as hyponatraemia, diabetes, and cardiac function (risk of coexistent cardiomyopathy) need to be considered.

- 2.7. Ensure optimum drug delivery and sustained calorific/nutritional provision. In addition to reduced oral intake in encephalopathy, patients with the m3243A>G mutation in particular are prone to gastrointestinal dysmotility and ileus.

- 2.7.1. NGT should be considered if oral calorific/nutritional intake is suboptimal. Dietetic advice is recommended.
 - 2.7.2. Anti-epileptic drugs should ideally be given intravenously during acute episodes where seizures are a feature. Absorption from the gastrointestinal tract may be unpredictable (see epilepsy guidelines).
 - 2.7.3. Diabetic medications may need to be adjusted taking into account current calorific input and available routes of drug administration.
- 2.8. Cerebral imaging: MRI is the preferred modality but CT imaging plays an important role in the acute setting where MRI may be unavailable. The urgency and type of cerebral imaging depends on whether the patient is presenting for the first time (undiagnosed) or attending with recurrent events in the context of a known MELAS phenotype. Because no specific therapies for mitochondrial stroke-like episodes exist, urgent imaging is primarily to exclude other treatable causes, and thereafter has an important role in supporting the clinical diagnosis:
- 2.8.1. Rapidly resolving migrainous symptoms in known MELAS phenotypes may not require cerebral imaging. Atypical or prolonged episodes will require imaging, the urgency of which will depend upon the clinical features (e.g. urgent CT if symptoms consistent with subarachnoid haemorrhage). Unless urgent, cerebral imaging should not delay investigation or treatment of possible non-convulsive status epilepticus.
 - 2.8.2. CT brain: helps exclude certain pathologies (eg cerebral haemorrhage, space occupying lesions etc) but may not identify parenchymal change in stroke-like episodes and will rarely offer sufficient information to confidently differentiate between these and

other pathologies. Basal ganglia calcification suggests mitochondrial disease but can be idiopathic or occur in other disorders.

- 2.8.3. CT angiogram: should be requested urgently (with the initial CT scan request) if a thromboembolic stroke is suspected and the onset lies within the time window for intravenous thrombolysis (In accordance with NICE guidelines (www.nice.org.uk/guidelines/CG68)). This also applies to patients with known mitochondrial disease.
- 2.8.4. CT venogram: should be requested urgently (with the initial CT scan request) if a cerebral venous sinus thrombosis is suspected on clinical grounds.
- 2.8.5. MRI brain: urgently required where the diagnosis is unknown. MR angiogram or venogram may be required to exclude other pathologies. MRI is a diagnostic tool, but beyond this rarely changes acute management once the diagnosis of MELAS is known. Comparative and prognostic information may be helpful in future management.
- 2.8.6. MRS: may be normal or show non-specific abnormalities. Demonstration of raised lactate concentrations may suggest mitochondrial disease but MRS is rarely necessary for diagnosis.

2.9. Cerebrospinal Fluid:

- 2.9.1. may be required urgently to exclude other causes.
- 2.9.2. For diagnostic purposes CSF lactate may be elevated and is highly suggestive of mitochondrial disease.
- 2.9.3. Unnecessary for typical episodes where diagnosis of MELAS is known.
- 2.9.4. In MELAS CSF is typically unremarkable. Protein may be mildly raised. Glucose normal. CSF is usually acellular. Very rarely a mildly raised white cell count is observed (personal observation).

2.10. Genetic studies:

2.10.1. Analysis for m.3243A>G or POLG1 may be available with a rapid turn-around from your specialist mitochondrial centre if discussed directly and likely to alter management. Negative results do not exclude other pathogenic mutations.

2.10.2. MELAS due to the m.3243A>G mutation may be undetectable in blood samples for genetic analysis. Blood *and* urine is preferred for exclusion purposes.

2.10.3. Muscle biopsy: sequential COX/SDH staining of muscle tissue may provide a rapid diagnosis of mitochondrial disease but can appear normal. Subsequent respiratory chain analysis and genetic testing is required to clarify the genotype and inheritance pattern.

2.11. Other considerations:

2.11.1. DVT prophylaxis: usual guidelines for DVT prophylaxis should be followed. LMW heparin is not contraindicated in mitochondrial disease.

2.11.2. Constipation is common and gastrointestinal dysmotility can become a major clinical issue. The need for aperients (eg movicol) and/or enemata should be assessed at admission and regularly thereafter.

2.11.3. SALT assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

2.11.4. Cardio-respiratory disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask

pre-existing cardiac conduction defects or ventricular impairment. Reduced respiratory drive due to encephalopathy or drugs may precipitate respiratory failure in the presence of existing respiratory muscle weakness.

3. Specific therapies for stroke-like episodes:

- 3.1. There are currently no specific treatments with proven efficacy in stroke-like episodes of mitochondrial origin.
- 3.2. Studies have been hampered by small numbers and a lack of natural history data. There is difficulty in defining what constitutes a stroke-like episode, and the tendency for variable degrees of spontaneous resolution means that the true effect of acute therapies is difficult to prove without large trials. Prior to the recent development of a disease specific clinical rating scale⁴ there was difficulty in measuring accrued disability against natural history data.
- 3.3. L-arginine has been reported to provide benefit, but the non-randomised, open label study design employed excluded this study from the recent Cochrane review of treatments for mitochondrial disorders^{5,6}. Most experts are of the opinion that further studies are required to prove this assertion.
- 3.4. Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits⁷.
- 3.5. Supplements such as ubiquinone, riboflavin, or creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes⁶.

4. Notes on the scope of this guidance

The guideline was developed by experts in mitochondrial 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 stroke-like episodes in patients with mitochondrial disease was to be included and excluded.

4.1. Audience

This guideline is 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

4.2. 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.

5. 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 potential precipitants for stroke-like episodes, the warning signs of an impending event, and the necessary action required.
- Access to specialist clinics allows relevant genetic counselling and family tracing to facilitate the identification of those at risk of developing disease. This allows relevant screening programs to be initiated, a patient specific management plan to be devised, and, in the event of symptoms, hastens appropriate treatment and minimises the risks of misdiagnosis.
- Close liaison is required between the specialist centre itself and local neurology services who may oversee acute admissions and remain closely involved with future follow up and management of patients where frequent central review is impractical.

6. Research recommendations

6.1. Natural history studies

Studies documenting the natural history of the m.3243A>G mutation are required, and in particular those patients exhibiting the MELAS phenotype. The development of disease specific clinical rating scales (ref) makes this an achievable goal in the foreseeable future.

6.2. Pharmaceutical therapies

Adequately powered, randomised, double blind control trials are required in MELAS to assess the effect of L-arginine and other agents on stroke-like episodes in the acute setting but also on subsequent disability using validated clinical rating scales. This may require multicentre trials to ensure adequate numbers.

6.3. Seizure control

Adequately powered, randomised, double blind control trials are required in MELAS to assess the effect of early and effective seizure control on stroke-like episodes in the acute setting but also on subsequent disability using validated clinical rating scales. This may require multicentre trials to ensure adequate numbers.

7. 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.

Last updated 22/1/2013

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 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

References

1. Schaefer AM, McFarland R, Blakely EL, He L, Whittaker RG, Taylor RW, Chinnery PF, Turnbull DM. Prevalence of mitochondrial DNA disease in adults. *Ann Neurol*. 2008 Jan;63(1):35-9.
2. McFarland R, Taylor RW, Turnbull DM. A neurological perspective on mitochondrial disease. *The Lancet Neurology*. 2010. 9(8), 829-840.
3. Horvath R, Hudson G, Ferrari G, et al. Phenotypic spectrum associated with mutations of the mitochondrial polymerase gamma gene. *Brain*. 2006;129(Pt 7):1674–1684.
4. Schaefer AM, Phoenix C, Elson JL, McFarland R, Chinnery PF, Turnbull DM. Mitochondrial disease in adults: a scale to monitor progression and treatment. *Neurology*. 2006 Jun 27;66(12):1932-4.
5. Koga Y, Akita Y, Nishioka J, Yatsuga S, Povalko N, Tanabe Y, et al. L-arginine improves the symptoms of stroke-like episodes in MELAS. *Neurology* 2005;64(4):710–2.
6. Pfeffer, G., Majamaa, K., Turnbull, D. M., Thorburn, D., & Chinnery, P. F. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev*. 2012(4):CD004426
7. Kaufmann P, Engelstad K, Wei Y, Jhung, S, Sano MC, Shungu, DC, ... & De Vivo DC. Dichloroacetate causes toxic neuropathy in MELAS A randomized, controlled clinical trial. *Neurology*. 2006; 66(3), 324-330.