

#1

COMPLETE

Collector: Email Invitation 1 (Email)
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Page 2: SECTION A: Demographic Data

<p>Q1 Which of the following best describes your clinical practice in mitochondrial disease?</p>	<p>Regional Neuroscience Referring Centre/ University Teaching Hospital</p>
<p>Q2 What is your current job title?</p>	<p>Part-time clinical specialist (neurologist/paediatrics/geneticist/metabolic medicine)</p>
<p>Q3 Which of the following group of patients do you see in your routine clinical practice?</p>	<p>Adults</p>
<p>Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?</p>	<p>1-5</p>
<p>Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)</p>	<p>Patients are transferred from a satellite (or district) hospital to the hospital where you base but not necessarily directly under your care</p>
<p>Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)</p>	<p>Taught that way by your mentor(s) , Personal experience, Published literature</p>
<p>Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting.</p>	<p>Strongly agree</p>
<p>(no label)</p>	<p>I suggest this greatly improves the care of these patients. Proper drug choice, awareness of potential complications, etc.</p>
<p>Comments:</p>	
<p>Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes</p>	<p>Disagree, Comment: There is much to do in educating the patients and their families / caregivers.</p>
<p>Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.</p>	<p>Strongly Disagree, Comment: Unfortunately this remains an obscure area and considered by many as an extreme rarity</p>
<p>Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.</p>	<p>Agree, Comment : Neurologists are reasonably well aware of the existence of SLEs in MELAS and the classical brain imaging findings but the whole spectrum of clinical presentations and patient recognition (when no pre-existing diagnosis) are not that well developed</p>
<p>Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)</p>	<p>Part-time (25-50%)</p>

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label) **Strongly agree**

Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

- Acute/subacute onset, evolving neurological symptoms **Agree**
- Headache **Agree**
- Nausea and vomiting **Agree**
- Altered conscious level/ encephalopathy **Agree**
- Focal motor seizures (including epilepsy partialis continua) **Agree**
- Generalised seizures **Agree**
- Non-convulsive status epilepticus **Agree**
- Elementary visual hallucination e.g. coloured flashing light **Agree**
- Formed, complex visual hallucination **Neither disagree nor agree**
- Visual field defect **Agree**
- Focal motor weakness **Agree**
- Focal sensory symptoms **Agree**
- Dysphasia **Agree**
- Apraxia **Agree**
- Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance) **Agree**
- Lactic acidosis **Agree**

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head plus EEG**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes?Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Agree**
 Comment: I would be hesitant if brain MRI would not show abnormalities suggestive of SLE (ie, if only EEG finding + clinical presentation). If we include acute epileptic presentations of a mitochondrial energy crisis ("MRI negative SLE") then we end up with a partial misnomer?

Q16 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label) **Agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Agree**
 Comment: Agree when the mutation heteroplasmy level high enough to suggest potential risk

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Agree
Urea and creatinine (kidney function)	Agree
Liver function test (LFT)	Agree
Serum lactate (without tourniquet applied)	Agree
C-reactive protein (CRP)	Agree
Creatine kinase (CK)	Agree
Random glucose	Agree
HbA1c	Disagree
Coagulation screen	Agree
Urinalysis and urine culture	Agree
Blood culture	Agree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Neither disagree nor agree
Arterial blood gas (ABG)	Neither disagree nor agree

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Agree
Chest radiograph (if aspiration pneumonia suspected)	Agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Agree
Electrocardiogram (ECG)	Agree
Lumbar puncture	Neither disagree nor agree
Electroencephalogram (EEG)	Agree
MRI head (unless there is contraindication, then CT head)	Strongly agree
Other (please specify):	Abdominal CT may be preferable to X-ray, nowadays not that much more radiation but vastly more informative??

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Strongly agree**

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

**T1,
FLAIR,
DWI ,
ADC**

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Agree
Chest radiograph	Agree
Abdominal X-ray	Agree
Electrocardiogram (ECG)	Neither disagree nor agree
Lumbar puncture	Agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree
Other (please specify):	Abdominal x-ray vs CT please see above; investigations should be tailored individually according to clinical problem / findings

Q27 What access to EEG monitoring do you have in the acute setting?

Standard EEG recording (~30 mins)

Continuous single channel EEG monitoring

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label) **Agree**

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

Intravenous anti-epileptic drug

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	1
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	3
Phenobarbitone (15mg/kg)	4
Lacosamide (200-400mg)	2
Other	5

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

Other (please specify):
If no clinically evident epileptic activity I would perform EEG first, and start an antiepileptic if EEG suggests epileptic activity

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label) **Strongly agree**

Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label) **Agree**

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label) **Strongly agree**

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Strongly agree**
 Comment: In our experience this is the case

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Neither disagree nor agree**

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Strongly agree**

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus**
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Focal status epilepticus with retained consciousness >60 minutes failing to respond to IV AEDs**
- Occipital status epilepticus (and at risk of developing cortical blindness) which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	3
Propofol	1
Midazolam	2
Ketamine	4
Other	5

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Neither disagree nor agree**
 Comment: Consider change of anaesthetic if prolonged sleep needed

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Ketogenic diet or similar diet

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label)

Agree

Comment:

In generalized status epileptics requiring GA, yes

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label)

Agree

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label)

Agree

Comment:

Yes if EEG / clinical evidence (seizures) of NCSE

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

**Haloperidol,
Quetiapine,
Risperidone**

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label)

Neither disagree nor agree

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)

Neither disagree nor agree

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)

Agree

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label)

Neither disagree nor agree

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label)

Agree

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes?

Do not know

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label)

Neither disagree nor agree

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label)

Agree

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Agree**

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label) **Agree**

Comment: How many days can we let the patient stay on fluids?

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label) **Agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label) **Agree**

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Agree**

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Agree**

Comment: How aggressive bowel emptying do the patients tolerate in an acute SLE setting?

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Neither disagree nor agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Neither disagree nor agree**

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Agree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label)

Neither disagree nor agree

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label)

Neither disagree nor agree

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label)

Agree

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label)

Agree

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label)

Agree

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label)

Agree

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label)

Agree

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)

Neither disagree nor agree

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital?

One to two weeks

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?

Blood,
Muscle,
Other (please specify):
Muscle in mtDNA disease, blood in POLG disease. As a first line testing, WBC DNA analysis for both

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?

Yes,
Comments:
In our research lab yes, in the hospital lab not

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Agree**
 Comments: Yes when this analysis is available

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Neither disagree nor agree**
 Comment: Mostly yes, but more information and education is needed

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education** ,
- Cognitive impairment,**
- Social isolation** ,
- Financial hardship,**
- Dependence for activities of daily living** ,
- Caregiver burden of other family members** ,
- Depression**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label) **Disagree**
 Comments: Apart from those with pre-existing epilepsy / seizures or previous SLEs, I would not recommend prophylactic AED treatment

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Disagree**
 Comments: Same as above.

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

For men **levetiracetam**
 For women of childbearing age **levetiracetam**
 For children **levetiracetam**

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop.

Very useful survey. Consensus guidelines much needed but so are more studies - difficult to achieve a prospective SLE study even internationally. The prophylactic treatments are a difficult question, do we have any data indicating the usefulness of this approach? In many settings, educating the acute care neurologists and ICU physicians (who are not mitochondrial disease specialists) on mitochondrial stroke like episodes is the key, as well as contacting and consulting mitochondrial neurology experts early on.

#2

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Friday, February 16, 2018 12:21:28 PM
Last Modified: Monday, February 19, 2018 7:31:33 AM
Time Spent: Over a day

Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	National Referring Centre for Mitochondrial Disease
Q2 What is your current job title?	Clinical academics
Q3 Which of the following group of patients do you see in your routine clinical practice?	Adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	11-15
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	Patients are directly admitted under your care in a university/teaching hospital
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	Personal experience, Published literature, Adoption of other best practice guidelines
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting. (no label)	Strongly agree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Neither Agree nor Disagree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Strongly Disagree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Neither Agree nor Disagree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Part-time (25-50%)

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management. (no label)	Agree
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Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Agree
Headache	Agree
Nausea and vomiting	Agree
Altered conscious level/ encephalopathy	Agree
Focal motor seizures (including epilepsy partialis continua)	Agree
Generalised seizures	Agree
Non-convulsive status epilepticus	Agree
Elementary visual hallucination e.g. coloured flashing light	Agree
Formed, complex visual hallucination	Neither disagree nor agree
Visual field defect	Neither disagree nor agree
Focal motor weakness	Agree
Focal sensory symptoms	Neither disagree nor agree
Dysphasia	Agree
Apraxia	Agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Agree
Lactic acidosis	Agree

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes? Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Disagree**
 Comment: MRI is crucial; cannot be MRI head and/or abnormal EEG

Q16 Stroke-like episodes should be suspected irrespective of patient's age, although it is more common under age of 40.

(no label) **Agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Strongly agree
Urea and creatinine (kidney function)	Agree
Liver function test (LFT)	Agree
Serum lactate (without tourniquet applied)	Strongly agree
C-reactive protein (CRP)	Neither disagree nor agree
Creatine kinase (CK)	Agree
Random glucose	Agree
HbA1c	Disagree
Coagulation screen	Disagree
Urinalysis and urine culture	Disagree
Blood culture	Disagree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Neither disagree nor agree
Arterial blood gas (ABG)	Strongly agree

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Disagree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Strongly agree**
 Comment: including proton spectroscopy

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T1,
T2,
FLAIR,
DWI ,
MR ,
angiogram

Other (please specify):
 proton spectroscopy

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Strongly agree
Abdominal X-ray	Agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Disagree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Agree

Q27 What access to EEG monitoring do you have in the acute setting?

Standard EEG recording (~30 mins)	,
Ambulatory EEG monitoring	,
Continuous single channel EEG monitoring	

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	Agree
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Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

Oral anti-epileptic drug	,
Intravenous anti-epileptic drug	,
Intravenous L-arginine	

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	1
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	3
Phenobarbitone (15mg/kg)	5
Lacosamide (200-400mg)	4
Other	2

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

Intravenous L-arginine

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	Strongly agree
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Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	Strongly agree
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Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label)	Strongly agree
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Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Neither disagree nor agree**

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Neither disagree nor agree**

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Agree**

Q38 Indications for intensive care unit admission (more than one option is permitted):

Convulsive (generalised) status epilepticus ,

Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	2
Propofol	5
Midazolam	1
Ketamine	3
Other	4

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Neither disagree nor agree**

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Intravenous magnesium

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label) **Neither disagree nor agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label) **Strongly agree**

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label) **Strongly agree**

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

Benzodiazepine,
Haloperidol,
Quetiapine

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label)

Strongly agree

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)

Agree

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)

Strongly agree

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label)

Neither disagree nor agree

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label)

Strongly agree

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **No**

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label)

Neither disagree nor agree

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label)

Agree

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label)

Strongly agree

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label)

Strongly agree

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label)

Neither disagree nor agree

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label) **Strongly agree**

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Agree**

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Strongly agree**

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Neither disagree nor agree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **Yes**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **Yes**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Strongly agree**

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label) **Strongly agree**

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Strongly agree**

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label) **Strongly agree**

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label) **Strongly agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Agree**

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Strongly agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital?

Greater than two weeks

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?

Urine

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?

Yes

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Neither disagree nor agree**

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Neither disagree nor agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Disagree**

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education ,
- Cognitive impairment,
- Social isolation ,
- Dependence for activities of daily living ,
- Caregiver burden of other family members ,
- Depression

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label)

Neither disagree nor agree

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)

Neither disagree nor agree

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

Respondent skipped this question

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop.

We should also discuss if, during a stroke like episode, or even during the cronic phase of the disease, some drug (iei the ones listed in the IMP Table) are really contraindicated in those patients or not

#3

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Sunday, February 18, 2018 10:05:13 AM
Last Modified: Wednesday, February 21, 2018 9:31:46 AM
Time Spent: Over a day

Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	National Referring Centre for Mitochondrial Disease
Q2 What is your current job title?	Clinical academics
Q3 Which of the following group of patients do you see in your routine clinical practice?	Adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	Respondent skipped this question
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	<p>Patients are directly admitted under your care in a university/teaching hospital</p> <p>,</p> <p>Patients are transferred from a satellite (or district) hospital to the hospital where you base but not necessarily directly under your care</p>
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	<p>Personal experience,</p> <p>Published literature</p>
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting. (no label)	Strongly agree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Disagree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Disagree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Disagree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Full-time

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management. (no label)	Agree
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Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Strongly agree
Headache	Agree
Nausea and vomiting	Neither disagree nor agree
Altered conscious level/ encephalopathy	Strongly agree
Focal motor seizures (including epilepsy partialis continua)	Strongly agree
Generalised seizures	Strongly agree
Non-convulsive status epilepticus	Strongly agree
Elementary visual hallucination e.g. coloured flashing light	Neither disagree nor agree
Formed, complex visual hallucination	Agree
Visual field defect	Strongly agree
Focal motor weakness	Strongly agree
Focal sensory symptoms	Strongly agree
Dysphasia	Strongly agree
Apraxia	Strongly agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Strongly agree
Lactic acidosis	Agree

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes? Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Agree**

Q16 Stroke-like episodes should be suspected irrespective of patient's age, although it is more common under age of 40.

(no label) **Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Agree
Urea and creatinine (kidney function)	Agree
Liver function test (LFT)	Agree
Serum lactate (without tourniquet applied)	Neither disagree nor agree
C-reactive protein (CRP)	Agree
Creatine kinase (CK)	Neither disagree nor agree
Random glucose	Strongly agree
HbA1c	Agree
Coagulation screen	Neither disagree nor agree
Urinalysis and urine culture	Strongly agree
Blood culture	Neither disagree nor agree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Strongly agree
Arterial blood gas (ABG)	Neither disagree nor agree

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Strongly agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Strongly agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Neither disagree nor agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Strongly agree**

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T1,
T2,
FLAIR,
DWI ,
ADC

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph	Strongly agree
Abdominal X-ray	Strongly agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Neither disagree nor agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q27 What access to EEG monitoring do you have in the acute setting?

Standard EEG recording (~30 mins)

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)

Strongly agree

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

Intravenous anti-epileptic drug

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	2
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	1
Phenobarbitone (15mg/kg)	3
Lacosamide (200-400mg)	4
Other	5

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

Intravenous anti-epileptic drug

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)

Agree

Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)

Strongly agree

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label)

Strongly agree

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)

Strongly agree

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label)

Strongly agree

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label)

Strongly agree

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)
- Occipital status epilepticus (and at risk of developing cortical blindness) which fail to respond to IV AEDs (and titration of usual maintenance AEDs)

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	1
Propofol	5
Midazolam	2
Ketamine	3
Other	4

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Agree**

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

- Ketogenic diet or similar diet
- Neurostimulation (e.g. vagal nerve stimulator, transcranial magnetic stimulation, transcranial direct current stimulation)

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label) **Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label) **Strongly agree**

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label) **Strongly agree**

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

- Benzodiazepine

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label) **Agree**

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)

Agree

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)

Strongly agree

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label)

Agree

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label)

Strongly agree

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label)

Agree

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label)

Agree

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label)

Strongly agree

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label)

Agree

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label)

Strongly agree

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label)

Strongly agree

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label)

Strongly agree

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label)

Strongly agree

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label)

Strongly agree

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label)

Agree

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label)

Strongly agree

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label)

Strongly agree

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label)

Agree

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label)

Agree

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label)

Strongly agree

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label)

Disagree

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label)

Strongly agree

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label)

Agree

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label)

Agree

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label)

Strongly agree

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital? **72 hours to one week**

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Blood, Urine, Muscle**

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **Yes**

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Agree**

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Strongly agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Neither disagree nor agree**

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital? **Unemployment/ Drop out of education, Cognitive impairment, Social isolation, Financial hardship, Dependence for activities of daily living, Caregiver burden of other family members, Depression**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label)

Strongly agree

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)

Strongly agree

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

For men

Leviteracetam

For women of childbearing age

Leviteracetam

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop.

Respondent skipped this question

#4

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Friday, February 16, 2018 2:13:01 PM
Last Modified: Wednesday, February 21, 2018 10:53:05 AM
Time Spent: Over a day

Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	National Referring Centre for Mitochondrial Disease
Q2 What is your current job title?	Clinical academics
Q3 Which of the following group of patients do you see in your routine clinical practice?	Adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	11-15
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	<p>Patients are directly admitted under your care in a university/teaching hospital</p> <p>,</p> <p>Hub and spoke model (providing advice via telephone, video-link and/or email)</p> <p>,</p> <p>Patients are transferred from a satellite (or district) hospital to the hospital where you base but not necessarily directly under your care</p>
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	<p>Personal experience,</p> <p>Published literature ,</p> <p>Adoption of other best practice guidelines</p>
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting.	
(no label)	Strongly agree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Agree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Disagree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Disagree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Part-time (50%)

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label) **Strongly agree**

Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Strongly agree
Headache	Strongly agree
Nausea and vomiting	Strongly agree
Altered conscious level/ encephalopathy	Strongly agree
Focal motor seizures (including epilepsy partialis continua)	Strongly agree
Generalised seizures	Strongly agree
Non-convulsive status epilepticus	Strongly agree
Elementary visual hallucination e.g. coloured flashing light	Strongly agree
Formed, complex visual hallucination	Agree
Visual field defect	Strongly agree
Focal motor weakness	Agree
Focal sensory symptoms	Agree
Dysphasia	Neither disagree nor agree
Apraxia	Neither disagree nor agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Agree
Lactic acidosis	Agree

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head plus EEG**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes? Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Strongly agree**

Q16 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label) **Agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Strongly agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Strongly agree
Urea and creatinine (kidney function)	Strongly agree
Liver function test (LFT)	Strongly agree
Serum lactate (without tourniquet applied)	Strongly agree
C-reactive protein (CRP)	Strongly agree
Creatine kinase (CK)	Strongly agree
Random glucose	Strongly agree
HbA1c	Strongly agree
Coagulation screen	Strongly agree
Urinalysis and urine culture	Strongly agree
Blood culture	Strongly agree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Strongly agree
Arterial blood gas (ABG)	Strongly agree

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Strongly agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Strongly agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Strongly agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Strongly agree**

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T1,
T2,
FLAIR,
DWI ,
ADC,
T2 gradient
echo

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Agree
Chest radiograph	Agree
Abdominal X-ray	Strongly agree
Electrocardiogram (ECG)	Neither disagree nor agree
Lumbar puncture	Agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q27 What access to EEG monitoring do you have in the acute setting?

Standard EEG recording (~30 mins)	,
Ambulatory EEG monitoring	,
Continuous single channel EEG monitoring	,
Videotelemetry	

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	Strongly agree
------------	-----------------------

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

Oral anti-epileptic drug	,
Intravenous anti-epileptic drug	

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	2
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	1
Phenobarbitone (15mg/kg)	3
Lacosamide (200-400mg)	4
Other	5

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

Other (please specify):	
Supportive care	

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	Strongly agree
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Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	Agree
------------	--------------

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label)	Strongly agree
------------	-----------------------

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Strongly agree**

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Agree**

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Strongly agree**

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus**
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	4
Propofol	2
Midazolam	1
Ketamine	3
Other	5

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Agree**

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Strongly agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

- Ketogenic diet or similar diet**
- Intravenous methylprednisolone,**
- Intravenous magnesium**

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label) **Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label) **Agree**

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label) **Strongly agree**

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

**Benzodiazepine,
Olanzapine,
Risperidone**

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label) **Agree**

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Strongly agree**

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label) **Agree**

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label) **Strongly agree**

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Do not know**

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Agree**

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label) **Agree**

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label) **Agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label) **Strongly agree**

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Strongly agree**

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Agree**

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Strongly agree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label) **Agree**

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Agree**

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label) **Agree**

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label) **Agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Agree**

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Agree**

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Agree**

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital? **One to two weeks**

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Blood,
Urine,
Muscle**

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **Yes**

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Agree**

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label)

Disagree

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

Unemployment/ Drop out of education ,
 Cognitive impairment,
 Social isolation ,
 Financial hardship,
 Dependence for activities of daily living ,
 Caregiver burden of other family members ,
 Depression

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label)

Neither disagree nor agree

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)

Neither disagree nor agree

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

Respondent skipped this question

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop.

Respondent skipped this question

#5

COMPLETE

Collector: Email Invitation 1 (Email)
Started: Thursday, February 22, 2018 7:52:24 AM
Last Modified: Thursday, February 22, 2018 8:46:46 AM
Time Spent: 00:54:22

Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	Regional Neuroscience Referring Centre/ University Teaching Hospital
Q2 What is your current job title?	Clinical academics
Q3 Which of the following group of patients do you see in your routine clinical practice?	Adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	>15
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	Other (please specify): Patients are admitted as an emergency and I am contacted either at that time or the next day.
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	Personal experience
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting. (no label)	Strongly agree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Disagree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Agree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Disagree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Part-time (25-50%)

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management. (no label)	Agree
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Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Agree
Headache	Agree
Nausea and vomiting	Agree
Altered conscious level/ encephalopathy	Agree
Focal motor seizures (including epilepsy partialis continua)	Agree
Generalised seizures	Agree
Non-convulsive status epilepticus	Agree
Elementary visual hallucination e.g. coloured flashing light	Agree
Formed, complex visual hallucination	Agree
Visual field defect	Agree
Focal motor weakness	Agree
Focal sensory symptoms	Neither disagree nor agree
Dysphasia	Neither disagree nor agree
Apraxia	Neither disagree nor agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Agree
Lactic acidosis	Neither disagree nor agree

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head plus EEG**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes? Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label)	Neither disagree nor agree
Comment:	Think we can be more specific: Subacute onset, evolving neurological symptoms (including headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness and focal neurological deficit with preceding neuropsychiatric and or visual symptoms) with supporting MRI evidence of a lesion on diffusion weighted scans and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

Q16 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	Neither disagree nor agree
Comments:	differences between m3243 (younger) and POLG (young but can occur in older)

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label)	Agree
------------	--------------

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label)	Neither disagree nor agree
Comment:	Difficult. How many with m3243 develop SLE? Which factors indicate significant risk? Often the first episode

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Neither disagree nor agree**

Comment:

Not sure what you are asking here. We usually take a history of presenting complaint and I would expect this to cover these aspects. The problem can be, however, that with an emergency admission, history is curtailed. so if you are asking if we should retrospectively ask or if we should do this as a study then I agree

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Agree
Urea and creatinine (kidney function)	Agree
Liver function test (LFT)	Agree
Serum lactate (without tourniquet applied)	Agree
C-reactive protein (CRP)	Agree
Creatine kinase (CK)	Agree
Random glucose	Agree
HbA1c	Neither disagree nor agree
Coagulation screen	Agree
Urinalysis and urine culture	Agree
Blood culture	Agree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Agree
Arterial blood gas (ABG)	Agree
Other (please specify):	Spinal fluid

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Agree
Chest radiograph (if aspiration pneumonia suspected)	Agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Neither disagree nor agree
Electrocardiogram (ECG)	Agree
Lumbar puncture	Agree
Electroencephalogram (EEG)	Agree
MRI head (unless there is contraindication, then CT head)	Agree
Other (please specify):	What are you asking here?

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Agree**

Comment:

Need diffusion/ADC t1, t2 as minimum

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T1,
T2,
DWI ,
ADC,
Other (please specify):
The others will be necessary if the question of real stroke is also taken

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Neither disagree nor agree
Chest radiograph	Neither disagree nor agree
Abdominal X-ray	Neither disagree nor agree
Electrocardiogram (ECG)	Neither disagree nor agree
Lumbar puncture	Neither disagree nor agree
Electroencephalogram (EEG)	Agree
MRI head (unless there is contraindication, then CT head)	Agree

Q27 What access to EEG monitoring do you have in the acute setting? **Videotelemetry**

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label) **Agree**

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted) **Intravenous anti-epileptic drug**

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	2
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	1
Phenobarbitone (15mg/kg)	3
Lacosamide (200-400mg)	4
Other	5

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

Other (please specify):
With failure of phenytoin/Keppra I would move to full sedation first with propofol and (reluctantly) to barbiturates, together with colloing (33degrees) +/- ketamine

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label) **Agree**

Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label) **Agree**

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label) **Agree**
 Other (please specify): But if in doubt iv.

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Agree**

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Agree**
 Comment: I would expect this patient (particularly if POLG) to be on AED. The better question is what would I do in a patient who did not have a previous episode. Answer: treat on the most minimal suspicion

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Agree**
 Comment: I would probably manage the patient there from the beginning

Q38 Indications for intensive care unit admission (more than one option is permitted):

Convulsive (generalised) status epilepticus
Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)
 ,
 Other (please specify):
 the others would be indications. see above

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	2
Propofol	1
Midazolam	4
Ketamine	3
Other	5

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Disagree**
 Comment: Have used it repeatedly (POLG) without this occurring

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

**Intravenous magnesium,
Ketamine,
Hypothermia,
Folinic acid**

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label)

Agree

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label)

Agree

Comment:

m3243 and POLG

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label)

Neither disagree nor agree

Comment:

Only before investigating if unavailable

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

**Benzodiazepine,
Quetiapine**

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label)

Agree

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)

Agree

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)

Agree

Comment:

NB: cardiac complications/m3243

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label)

Neither disagree nor agree

Comment:

differences between POLG & m3243

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label)

Agree

Comment:

above

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Neither disagree nor agree**

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Neither disagree nor agree**

Comment: Bicarb works once maybe twice. prolonged severe LA requires other interventions (dialysis?)

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Agree**

Comment: m3243

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label) **Agree**

Comment: timing important

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label) **Agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label) **Neither disagree nor agree**

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Agree**

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Agree**

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Neither disagree nor agree**

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Agree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Neither disagree nor agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label) **Agree**

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Neither disagree nor agree**

Comment: Have used it without severe side effects (ISCU)

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label) **Disagree**

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label) **Agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Agree**

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Agree**

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Agree**

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital? **Within 72 hours**

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Blood,**
Other (please specify):
blood POLG; urine m3243

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **No**

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Agree**

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Neither disagree nor agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Neither disagree nor agree**

Comment: Do not understand the basis of the question, work up is required if we do not have a diagnosis

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Agree**

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education** ,
- Cognitive impairment,**
- Dependence for activities of daily living** ,
- Depression**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label) **Neither disagree nor agree**

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Agree**

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

For men **keppra**

For women of childbearing age **keppra**

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop. **Respondent skipped this question**

#6

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Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	National Referring Centre for Mitochondrial Disease
Q2 What is your current job title?	Full-time clinical specialist (neurologist/paediatrics/geneticist/metabolic medicine)
Q3 Which of the following group of patients do you see in your routine clinical practice?	Both paediatrics and adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	>15
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	Hub and spoke model (providing advice via telephone, video-link and/or email)
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	Taught that way by your mentor(s) Adoption of other best practice guidelines
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting. (no label)	Strongly agree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Disagree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Disagree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Agree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Part-time (<25%)

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management. (no label)	Agree
---	--------------

Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Strongly agree
Headache	Agree
Nausea and vomiting	Agree
Altered conscious level/ encephalopathy	Strongly agree
Focal motor seizures (including epilepsy partialis continua)	Strongly agree
Generalised seizures	Strongly agree
Non-convulsive status epilepticus	Agree
Elementary visual hallucination e.g. coloured flashing light	Agree
Formed, complex visual hallucination	Agree
Visual field defect	Agree
Focal motor weakness	Agree
Focal sensory symptoms	Agree
Dysphasia	Agree
Apraxia	Agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Agree
Lactic acidosis	Neither disagree nor agree

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head plus EEG**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes? Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Agree**

Q16 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label) **Agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Disagree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Strongly agree
Urea and creatinine (kidney function)	Strongly agree
Liver function test (LFT)	Strongly agree
Serum lactate (without tourniquet applied)	Strongly agree
C-reactive protein (CRP)	Agree
Creatine kinase (CK)	Agree
Random glucose	Strongly agree
HbA1c	Agree
Coagulation screen	Strongly agree
Urinalysis and urine culture	Strongly agree
Blood culture	Strongly agree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Strongly agree
Arterial blood gas (ABG)	Agree

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Strongly agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Agree
Electrocardiogram (ECG)	Agree
Lumbar puncture	Agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	Disagree
Comment:	Ideally a seizure protocol

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T1,
T2,
FLAIR,
DWI

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Agree
Chest radiograph	Neither disagree nor agree
Abdominal X-ray	Neither disagree nor agree
Electrocardiogram (ECG)	Neither disagree nor agree
Lumbar puncture	Agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Agree

Q27 What access to EEG monitoring do you have in the acute setting?

- Standard EEG recording (~30 mins)
- Ambulatory EEG monitoring
- Continuous single channel EEG monitoring
- Videotelemetry

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label) **Strongly agree**

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

- Intravenous anti-epileptic drug
- Oral L-arginine

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

- | | |
|---|---|
| Levetiracetam (20-40mg/kg, maximum 4500mg) | 1 |
| Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg) | 2 |
| Phenobarbitone (15mg/kg) | 3 |
| Lacosamide (200-400mg) | 4 |
| Other | 5 |

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

- Oral L-arginine

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label) **Agree**

Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label) **Neither disagree nor agree**

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label) **Neither disagree nor agree**
 Other (please specify): IVs preferable in this case due to risk of aspiration

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Neither disagree nor agree**

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Agree**

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Strongly agree**

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus**
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Focal status epilepticus with retained consciousness >60 minutes failing to respond to IV AEDs**
- Occipital status epilepticus (and at risk of developing cortical blindness) which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	1
Propofol	4
Midazolam	3
Ketamine	2
Other	5

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Agree**

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Neither disagree nor agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Other (please specify):
N/A

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label) **Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label) **Agree**

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label) **Agree**

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

Do not use any antipsychotic drug

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label)

Agree

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)

Strongly agree

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)

Strongly agree

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label)

Agree

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label)

Strongly agree

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes?

Do not know

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label)

Strongly agree

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label)

Agree

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label)

Strongly agree

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label)

Agree

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label)

Agree

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label)

Strongly agree

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Agree**

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Agree**

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Agree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

Comment: **Not sure**

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Agree**

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label) **Agree**

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label) **Agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

Comment: **Not sure of the evidence**

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Agree**

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital? **Greater than two weeks**

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Blood, Urine, Buccal, Fibroblast, Muscle**

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **Yes**

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Neither disagree nor agree**

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Neither disagree nor agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Disagree**

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education ,
- Cognitive impairment,
- Social isolation ,
- Financial hardship,
- Dependence for activities of daily living ,
- Caregiver burden of other family members ,
- Depression

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label) **Neither disagree nor agree**

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Neither disagree nor agree**

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

- For men N/A
- For women of childbearing age N/A
- For children N/A

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop.

The management for adult SLE and paediatric SLE needs to be considered separately.

#7

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Last Modified: Thursday, February 22, 2018 6:18:37 PM
Time Spent: 02:34:38
IP Address: 138.245.1.1

Page 2: SECTION A: Demographic Data

<p>Q1 Which of the following best describes your clinical practice in mitochondrial disease?</p>	<p>National Referring Centre for Mitochondrial Disease</p>
<p>Q2 What is your current job title?</p>	<p>Clinical academics</p>
<p>Q3 Which of the following group of patients do you see in your routine clinical practice?</p>	<p>Both paediatrics and adults</p>
<p>Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?</p>	<p>>15</p>
<p>Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)</p>	<p>Patients are directly admitted under your care in a university/teaching hospital , Hub and spoke model (providing advice via telephone, video-link and/or email) , Patients are transferred from a satellite (or district) hospital to the hospital where you base but not necessarily directly under your care</p>
<p>Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)</p>	<p>Personal experience, Published literature</p>
<p>Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting.</p>	<p>Strongly agree otherwise often treated like a normal vascular insult (ie, with ASS but without AED)</p>
<p>(no label)</p>	
<p>Comments:</p>	
<p>Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes</p>	<p>Disagree</p>
<p>Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.</p>	<p>Strongly Disagree</p>
<p>Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.</p>	<p>Disagree</p>
<p>Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)</p>	<p>Part-time (25-50%)</p>

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label) **Strongly agree**

Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Strongly agree
Headache	Neither disagree nor agree
Nausea and vomiting	Neither disagree nor agree
Altered conscious level/ encephalopathy	Neither disagree nor agree
Focal motor seizures (including epilepsia partialis continua)	Neither disagree nor agree
Generalised seizures	Neither disagree nor agree
Non-convulsive status epilepticus	Neither disagree nor agree
Elementary visual hallucination e.g. coloured flashing light	Neither disagree nor agree
Formed, complex visual hallucination	Neither disagree nor agree
Visual field defect	Strongly agree
Focal motor weakness	Strongly agree
Focal sensory symptoms	Strongly agree
Dysphasia	Strongly agree
Apraxia	Strongly agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Neither disagree nor agree
Lactic acidosis	Neither disagree nor agree
Other (please specify):	SLE is foremost a phenomenological concept, and it is not restricted to mitochondrial disease. In my view, it should therefore be defined as "acute, subacute or gradual onset of a focal neurological deficit which is not due to a vascular insult of atherosclerotic, thrombo-embolic or haemorrhagic aetiology". According to this logic, all other symptoms named above can accompany (or in the case of seizures even trigger) SLE but are not part of the phenomenological definition.

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes?Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Strongly disagree**

Comment: SLE is foremost a phenomenological concept, and it is not restricted to mitochondrial disease. In my view, it should therefore be defined as "acute, subacute or gradual onset of a focal neurological deficit which is not due to a vascular insult of atherosclerotic, thrombo-embolic or haemorrhagic aetiology". In my view, there is no semantic logic in labelling an episode without a focal neurological deficit SLE. I agree that your above described scenario is common in MELAS but maybe we need another term for this, eg something like "mitochondrial encephalopathic crisis"

Q16 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label) **Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Strongly agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Strongly agree
Urea and creatinine (kidney function)	Strongly agree
Liver function test (LFT)	Strongly agree
Serum lactate (without tourniquet applied)	Strongly agree
C-reactive protein (CRP)	Strongly agree
Creatine kinase (CK)	Strongly agree
Random glucose	Strongly agree
HbA1c	Strongly agree
Coagulation screen	Strongly agree
Urinalysis and urine culture	Strongly agree
Blood culture	Strongly disagree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Strongly disagree
Arterial blood gas (ABG)	Strongly disagree

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Strongly agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Strongly agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Neither disagree nor agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Disagree**
 Comment: for diagnosis, any T2 will do ...; standardised MRI head protocol would be good for science and international harmonization

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T1,
T2,
FLAIR,
DWI ,
ADC,
MR
angiogram

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Electroencephalogram (EEG) **Strongly agree**
 MRI head (unless there is contraindication, then CT head) **Strongly agree**

Q27 What access to EEG monitoring do you have in the acute setting?

Standard EEG recording (~30 mins) ,
Videotelemetry

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label) **Strongly agree**

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

Oral anti-epileptic drug ,
Intravenous anti-epileptic drug ,
Intravenous L-arginine

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg) **1**
 Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg) **2**
 Phenobarbitone (15mg/kg) **4**
 Lacosamide (200-400mg) **3**
 Other **5**

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

Oral anti-epileptic drug ,
Intravenous L-arginine

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label) **Strongly agree**

Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label) **Strongly agree**

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label) **Strongly agree**

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Agree**

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Strongly agree**

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Strongly agree**

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus**
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Occipital status epilepticus (and at risk of developing cortical blindness) which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	3
Propofol	2
Midazolam	1
Ketamine	4
Other	5

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Agree**

Comment: I agree but sometimes propofol is needed, should then be used for a limited time

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Strongly agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Intravenous methylprednisolone

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label)

Neither disagree nor agree

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label)

Strongly agree

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label)

Strongly agree

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

Benzodiazepine,

Haloperidol,

Quetiapine,

Olanzapine,

Risperidone,

Other (please specify):

I would consider any antipsychotic medication, depending on kind and severity of symptoms

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label)

Strongly agree

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)

Agree

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)

Strongly agree

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidaemia in patients with mitochondrial disease.

(no label)

Agree

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label)

Strongly agree

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes?

Do not know

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label)

Strongly agree

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label)

Strongly agree

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label)

Strongly agree

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label)

Strongly agree

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label)

Strongly agree

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label)

Strongly agree

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label)

Agree

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label)

Strongly agree

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label)

Strongly agree

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label)

Strongly agree

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label)

Neither disagree nor agree

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label)

Agree

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **Yes**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **Yes**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label)

Strongly agree

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label)

Strongly agree

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label)

Strongly agree

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label)

Neither disagree nor agree

Comment:

What do you mean by "patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency."?

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label)

Strongly agree

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label)

Strongly agree

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label)

Strongly agree

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label)

Strongly agree

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)

Strongly agree

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital?

Greater than two weeks

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?

Urine

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?

Yes

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label)

Neither disagree nor agree

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Neither disagree nor agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Neither disagree nor agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Agree**
 Comment: but that's a different topic

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Disagree**

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education** ,
- Cognitive impairment,**
- Social isolation** ,
- Dependence for activities of daily living** ,
- Caregiver burden of other family members** ,
- Depression**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label) **Neither disagree nor agree**
 Comments: it would be unusual to treat anybody before a first seizure. After a first seizure in a mitochondrial Patient, I would start life-long treatment.

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Neither disagree nor agree**
 Comments: it would be unusual to treat anybody before a first seizure. After a first seizure in a mitochondrial Patient, I would start life-long treatment.

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED? **Respondent skipped this question**

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop. **Respondent skipped this question**

#8

COMPLETE

Collector: Web Link 1 (Web Link)
Started: Thursday, February 22, 2018 11:22:17 PM
Last Modified: Friday, February 23, 2018 12:12:26 AM
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Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	National Referring Centre for Mitochondrial Disease
Q2 What is your current job title?	Clinical academics
Q3 Which of the following group of patients do you see in your routine clinical practice?	Both paediatrics and adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	>15
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	<p>Patients are directly admitted under your care in a university/teaching hospital</p> <p>,</p> <p>Hub and spoke model (providing advice via telephone, video-link and/or email)</p> <p>,</p> <p>Patients are transferred from a satellite (or district) hospital to the hospital where you base but not necessarily directly under your care</p>
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	<p>Taught that way by your mentor(s) ,</p> <p>Personal experience</p>
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting. (no label)	Strongly agree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Agree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Strongly Disagree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Disagree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Part-time (50%)

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label) **Strongly agree**

Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Strongly agree
Headache	Agree
Nausea and vomiting	Agree
Altered conscious level/ encephalopathy	Agree
Focal motor seizures (including epilepsy partialis continua)	Strongly agree
Generalised seizures	Agree
Non-convulsive status epilepticus	Disagree
Elementary visual hallucination e.g. coloured flashing light	Strongly agree
Formed, complex visual hallucination	Strongly agree
Visual field defect	Strongly agree
Focal motor weakness	Strongly agree
Focal sensory symptoms	Strongly agree
Dysphasia	Agree
Apraxia	Agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Strongly agree
Lactic acidosis	Agree

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head plus EEG**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes? Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Strongly agree**

Q16 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label) **Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Strongly agree
Urea and creatinine (kidney function)	Strongly agree
Liver function test (LFT)	Strongly agree
Serum lactate (without tourniquet applied)	Strongly agree
C-reactive protein (CRP)	Strongly agree
Creatine kinase (CK)	Neither disagree nor agree
Random glucose	Strongly agree
HbA1c	Strongly agree
Coagulation screen	Agree
Urinalysis and urine culture	Strongly agree
Blood culture	Agree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Strongly agree
Arterial blood gas (ABG)	Strongly agree

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Strongly agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Strongly agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Disagree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Strongly agree**

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T2,
DWI ,
ADC,
 Other (please specify):
 The question confines itself to 'essential' but that will depend on what you are trying to achieve - diagnosis, assessment of atrophy, etc

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph	Neither disagree nor agree
Abdominal X-ray	Neither disagree nor agree
Electrocardiogram (ECG)	Neither disagree nor agree
Lumbar puncture	Neither disagree nor agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree
Other (please specify):	Some of these responses would be modified depending on precisely how the clinical picture evolves. For example, no bowel opening and abdominal distension might suggest IPO, in which case repeat abdominal x-ray may be warranted or indeed abdominal MRI.

Q27 What access to EEG monitoring do you have in the acute setting?	Standard EEG recording (~30 mins) Continuous single channel EEG monitoring
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Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	Strongly agree
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Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)	Intravenous anti-epileptic drug Other (please specify): Need to include option for buccal emergency medication (Midazolam). Nasogastric tube insertion. Intravenous access and fluid rehydration.
---	--

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	1
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	2
Phenobarbitone (15mg/kg)	3
Lacosamide (200-400mg)	4
Other	5

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)	Intravenous anti-epileptic drug
---	--

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	Strongly agree
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Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	Neither disagree nor agree
Comment:	Too many other variables here. Compliance, gastrointestinal upset etc that limited availability of prescribed dose.

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label) **Strongly agree**

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Strongly agree**

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Strongly agree**

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Strongly agree**

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus**
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Focal status epilepticus with retained consciousness >60 minutes failing to respond to IV AEDs**
- Occipital status epilepticus (and at risk of developing cortical blindness) which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	1
Propofol	4
Midazolam	2
Ketamine	3
Other	5

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Agree**

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Strongly agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Neurostimulation (e.g. vagal nerve stimulator, transcranial magnetic stimulation, transcranial direct current stimulation)

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label) **Strongly agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label) **Strongly agree**

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label) **Neither disagree nor agree**

Comment:

What is your distinction between non-convulsive status epilepticus and epileptic encephalopathy?

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

Quetiapine,
Olanzapine

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label) **Agree**

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Strongly agree**

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label) **Strongly agree**

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Strongly agree**

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Strongly agree**

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label) **Strongly agree**

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label) **Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label) **Strongly agree**

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Strongly agree**

Comment: NG tube will not drain small bowel contents.

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Strongly agree**

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Strongly agree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Strongly agree**

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label) **Strongly agree**

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label)

Strongly agree

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label)

Agree

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label)

Strongly agree

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label)

Strongly agree

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label)

Strongly agree

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label)

Strongly agree

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)

Strongly agree

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital?

Within 72 hours

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?

**Blood,
Urine,
Muscle**

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?

Yes

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label)

Disagree

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label)

Strongly agree

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label)

Strongly agree

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Disagree**

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education** ,
- Cognitive impairment,**
- Social isolation** ,
- Financial hardship,**
- Dependence for activities of daily living** ,
- Caregiver burden of other family members** ,
- Depression**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label) **Agree**

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Strongly agree**

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

- For men **Levetiracetam/Brivacetam**
- For women of childbearing age **Levetiracetam/Brivacetam**
- For children **Levetiracetam**

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop. **Respondent skipped this question**

#9

COMPLETE

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Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	National Referring Centre for Mitochondrial Disease
Q2 What is your current job title?	Full-time clinical specialist (neurologist/paediatrics/geneticist/metabolic medicine)
Q3 Which of the following group of patients do you see in your routine clinical practice?	Adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	>15
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	Patients are directly admitted under your care in a university/teaching hospital
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	Personal experience, Published literature
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting. (no label)	Strongly agree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Disagree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Disagree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Disagree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Other (please specify): Heavily (clinical input) but not recognised in jobplan

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management. (no label)	Strongly disagree
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Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Strongly agree
Headache	Agree
Nausea and vomiting	Neither disagree nor agree
Altered conscious level/ encephalopathy	Agree
Focal motor seizures (including epilepsy partialis continua)	Agree
Generalised seizures	Agree
Non-convulsive status epilepticus	Strongly agree
Elementary visual hallucination e.g. coloured flashing light	Strongly agree
Formed, complex visual hallucination	Agree
Visual field defect	Agree
Focal motor weakness	Agree
Focal sensory symptoms	Neither disagree nor agree
Dysphasia	Agree
Apraxia	Agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Disagree
Lactic acidosis	Neither disagree nor agree
Other (please specify):	Agitation unusual - usually obtunded. Exceptions exist - eg temp lobe/psychosis Lactic acidosis accepted but not part of definition. Normal lactate (esp in POLG) should not reassure

Q14 How do you diagnose a stroke-like episode in your current clinical practice?

Other (please specify):
 We do clinical/MR/EEG as all can contribute - however EEG often misses seizures and MR can be normal if attack caught early/treated acutely and MR delayed

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes? Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label)	Agree
Comment:	Key points are evolving encephalopathy +/- focal features, and presence of clinical or EEG features of focal status. MR helps confirm a serious SLE but inclusion in definition should not delay diagnosis and Mx

Q16 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	Strongly agree
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Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label)	Strongly agree
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Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label)	Strongly agree
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Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Strongly agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Comment: Wouldn't focus on apraxia - just common focal signs - hemianopia, dysphasia, apraxia ie cortical features - most commonly posterior

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Strongly agree
Urea and creatinine (kidney function)	Strongly agree
Liver function test (LFT)	Strongly agree
Serum lactate (without tourniquet applied)	Agree
C-reactive protein (CRP)	Strongly agree
Creatine kinase (CK)	Agree
Random glucose	Strongly agree
HbA1c	Agree
Coagulation screen	Disagree
Urinalysis and urine culture	Strongly agree
Blood culture	Disagree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Agree
Arterial blood gas (ABG)	Disagree
Other (please specify):	BC if septic. ABG if hyperventilation/concerns over resp/CO2. Not routinely. AED levels OK but should not delay AED loads/increases if SLE suspected

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Strongly agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Strongly agree
Electrocardiogram (ECG)	Agree
Lumbar puncture	Strongly disagree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Agree**

Comment: So long as available everywhere - should NOT cause a delay.

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T2,
FLAIR,
DWI ,
ADC

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Agree
Chest radiograph	Disagree
Abdominal X-ray	Disagree
Electrocardiogram (ECG)	Disagree
Lumbar puncture	Disagree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Neither disagree nor agree
Other (please specify):	'disagree' assumes no specific concerns (eg bloated abdo/SOB) Major concern is ongoing seizures - clinical and EEG main pointers. MR less of a role. Can help when 'functional' is in differential (eg POLG) as helps provide objective evidence

Q27 What access to EEG monitoring do you have in the acute setting?

Standard EEG recording (~30 mins) ,
Ambulatory EEG monitoring ,
Continuous single channel EEG monitoring ,
Videotelemetry

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	Strongly agree
Other (please specify):	Ideally guided by experienced specialists

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

Intravenous anti-epileptic drug ,
Other (please specify):
no objection to IV L-arginine but ltd evidence and rarely available - should NOT delay available Rx such as AEDs and fluids

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	2
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	1
Phenobarbitone (15mg/kg)	4
Lacosamide (200-400mg)	3
Other	5

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

Intravenous anti-epileptic drug ,

Other (please specify):

unless improving - if so could observe/optimize oral AEDs

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)

Strongly agree

Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)

Agree

Comment:

Seems logical but evidence that AEDs prevent recurrence ltd - may be just as effective to Rx acute episodes and limit background AEDs

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label)

Agree

Other (please specify):

IV AEDS preferable in this situation! Some AEDs/important meds may need NGT and feeding needs to be addressed (may not need NGT for feeding if on IVI and settles quickly)

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)

Strongly agree

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label)

Agree

Comment:

should not replace assessment but may allow Rx earlier

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label)

Strongly agree

Comment:

Valproate should be avoided. Unless decisions re NOT escalating care have been made with patient/family/specialists beforehand

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus**
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Focal status epilepticus with retained consciousness >60 minutes failing to respond to IV AEDs**
- Occipital status epilepticus (and at risk of developing cortical blindness) which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**
- Other (please specify):
Balance of risks needs to be considered in each case - will not be appropriate for ALL cases

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	1
Propofol	4
Midazolam	2
Ketamine	3
Other	5

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Agree**
 Comment: ltd evidence and most patients will probably tolerate this. Best avoid if other options

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Agree**
 Comment: Exception: Not all cases have EEG correlate - less vital in these cases

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

- Ketogenic diet or similar diet**
- Intravenous methylprednisolone,**
- Neurostimulation (e.g. vagal nerve stimulator, transcranial magnetic stimulation, transcranial direct current stimulation)**
- Intravenous magnesium,**
- Ketamine,**
- Hypothermia,**
- Folinic acid,**
- Other (please specify):
L-arginine IV - no effect (n=1)

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label)

Strongly agree

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label)

Agree

Comment:

rare

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label)

Neither disagree nor agree

Comment:

Not so well defined and open to misinterpretation in DGH for example
Agitation with encephalopathy and focal features - OK agitation but alert/not confused - SLE unlikely

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

Benzodiazepine,

Haloperidol,

Quetiapine,

Olanzapine,

Risperidone,

Other (please specify):

Often behaviour demands control to allow Rx. Can withdraw later

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label)

Agree

Comment:

but just ECG usually

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)

Neither disagree nor agree

Comment:

Rx is of underlying disease and not sure they add much

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)

Strongly agree

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label)

Strongly agree

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label)

Strongly agree

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Strongly agree**

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Agree**

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label) **Agree**

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label) **Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label) **Agree**

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Agree**

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Agree**

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Neither disagree nor agree**

Comment: problem is often hard to predict that unless had similar episodes before

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Strongly agree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Agree**

Comments: with specialist input

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label) **Agree**

Comment: but also no evidence of harm. Better studies needed

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Strongly agree**

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label) **Strongly agree**

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label) **Strongly agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Agree**

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Agree**

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital? **Within 72 hours**

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Blood,**
Urine,
Other (please specify):
for 3243. blood for POLG. Muscle gold standard

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **Yes**

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Disagree**
 Comments: depends on timescale of both mtDNA sequencing specific but quick Bx may confirm mito disease beyond doubt and allow Rx plan

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**
 Comment: see above

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Disagree**
 Comment: much less than vascular stroke - political!

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education** ,
- Cognitive impairment,**
- Social isolation** ,
- Financial hardship,**
- Dependence for activities of daily living** ,
- Caregiver burden of other family members** ,
- Depression,**
- Other**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label) **Agree**
 Comments: Considered. No evidence but weighed up vs catastrophic consequences. Note many AEDS used for pain and migraine with no concerns.

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)

Comments:

Strongly agree

No evidence but weighed up vs catastrophic consequences. Even more so than 3243. Note many AEDS used for pain and migraine with no concerns. Women at higher risk If I had AR POLG I would want an AED. Not one with cerebellar toxicity though - ? keppra

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

For men

Keppra

For women of childbearing age

Keppra

For children

?Keppra - don't do paed

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop.

Lack of evidence and natural Hx

??trials of prophylactic AEDS in POLG

#10

COMPLETE

Collector: Web Link 1 (Web Link)
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Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	National Referring Centre for Mitochondrial Disease
Q2 What is your current job title?	Clinical academics
Q3 Which of the following group of patients do you see in your routine clinical practice?	Adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	>15
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	<p>Patients are directly admitted under your care in a university/teaching hospital</p> <p>,</p> <p>Hub and spoke model (providing advice via telephone, video-link and/or email)</p> <p>,</p> <p>Patients are transferred from a satellite (or district) hospital to the hospital where you base but not necessarily directly under your care</p>
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	<p>Taught that way by your mentor(s) ,</p> <p>Personal experience,</p> <p>Published literature</p>
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting.	
(no label)	Strongly disagree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Agree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Neither Agree nor Disagree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Neither Agree nor Disagree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Part-time (50%)

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label) **Strongly agree**

Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms **Strongly agree**

Headache **Strongly agree**

Nausea and vomiting **Strongly agree**

Altered conscious level/ encephalopathy **Strongly agree**

Focal motor seizures (including epilepsy partialis continua) **Strongly agree**

Generalised seizures **Strongly agree**

Non-convulsive status epilepticus **Strongly agree**

Elementary visual hallucination e.g. coloured flashing light **Strongly agree**

Formed, complex visual hallucination **Strongly agree**

Visual field defect **Strongly agree**

Focal motor weakness **Agree**

Focal sensory symptoms **Strongly agree**

Dysphasia **Agree**

Apraxia **Strongly agree**

Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance) **Strongly agree**

Lactic acidosis **Strongly agree**

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head plus EEG**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes? Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Strongly agree**

Q16 Stroke-like episodes should be suspected irrespective of patient's age, although it is more common under age of 40.

(no label) **Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Strongly agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Agree
Urea and creatinine (kidney function)	Strongly agree
Liver function test (LFT)	Strongly agree
Serum lactate (without tourniquet applied)	Agree
C-reactive protein (CRP)	Agree
Creatine kinase (CK)	Neither disagree nor agree
Random glucose	Strongly agree
HbA1c	Disagree
Coagulation screen	Agree
Urinalysis and urine culture	Agree
Blood culture	Neither disagree nor agree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Agree
Arterial blood gas (ABG)	Strongly agree
Other (please specify):	AED level of on treatment

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Strongly agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Agree
Electrocardiogram (ECG)	Agree
Lumbar puncture	Agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Strongly agree**
 Comment: Yes

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

- T1,
- T2,
- FLAIR,
- DWI ,
- ADC,
- DTI,
- T2 gradient echo ,
- Other (please specify):
- Volumes

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph	Agree
Abdominal X-ray	Agree
Electrocardiogram (ECG)	Disagree
Lumbar puncture	Disagree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q27 What access to EEG monitoring do you have in the acute setting?

- Standard EEG recording (~30 mins)** ,
- Ambulatory EEG monitoring** ,
- Continuous single channel EEG monitoring** ,
- Videotelemetry**

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	Strongly agree
------------	-----------------------

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

- Oral anti-epileptic drug** ,
- Intravenous anti-epileptic drug**

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	3
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	1
Phenobarbitone (15mg/kg)	2
Lacosamide (200-400mg)	4
Other	5

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

- Oral anti-epileptic drug**

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label) **Strongly agree**

Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label) **Strongly agree**

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label) **Agree**

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Strongly agree**

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Strongly agree**

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Strongly agree**

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus**
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	2
Propofol	5
Midazolam	1
Ketamine	3
Other	4

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Neither disagree nor agree**

Comment: Depends on age potentially

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Strongly agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Neurostimulation (e.g. vagal nerve stimulator, transcranial magnetic stimulation, transcranial direct current stimulation),
 ,
 Intravenous magnesium,
 Folinic acid

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label)

Neither disagree nor agree

Comment:

Duration directed by response- would suggest 'at least'

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label)

Strongly agree

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label)

Agree

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

Benzodiazepine,
 Haloperidol,
 Quetiapine,
 Olanzapine,
 Risperidone

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label)

Strongly disagree

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)

Agree

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)

Strongly agree

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidaemia in patients with mitochondrial disease.

(no label)

Neither disagree nor agree

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label)

Strongly agree

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? Yes

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Agree**

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label) **Strongly agree**

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label) **Agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label) **Strongly agree**

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Strongly agree**

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Strongly agree**

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Strongly disagree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label)

Strongly agree

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label)

Strongly agree

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label)

Strongly agree

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label)

Agree

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label)

Strongly agree

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label)

Strongly agree

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label)

Strongly agree

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label)

Strongly agree

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)

Strongly agree

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital?

72 hours to one week

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?

**Blood,
Urine,
Buccal,
Muscle**

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?

Yes

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Agree**
 Comments: Pending turn around time

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Disagree**

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education** ,
- Cognitive impairment,**
- Social isolation** ,
- Financial hardship,**
- Dependence for activities of daily living** ,
- Caregiver burden of other family members** ,
- Depression**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label) **Neither disagree nor agree**

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Neither disagree nor agree**

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED? **Respondent skipped this question**

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop.

Other experimental treatments
 Any evidence of patient preferences

#11

COMPLETE

Collector: Web Link 1 (Web Link)
Started: Sunday, February 25, 2018 11:47:13 AM
Last Modified: Sunday, February 25, 2018 12:33:32 PM
Time Spent: 00:46:19
IP Address: 31.53.117.148

Page 2: SECTION A: Demographic Data

Q1 Which of the following best describes your clinical practice in mitochondrial disease?	National Referring Centre for Mitochondrial Disease
Q2 What is your current job title?	Clinical academics
Q3 Which of the following group of patients do you see in your routine clinical practice?	Both paediatrics and adults
Q4 How many patients with stroke-like episodes have you directly involved in acute care to date?	1-5
Q5 What is the care model within your health care system for patients presenting with stroke-like episodes? (tick as many as applicable)	Patients are transferred from a satellite (or district) hospital to the hospital where you base but not necessarily directly under your care
Q6 What is your source of information for the management of stroke-like episodes? (more than one option is permitted)	Personal experience, Published literature
Q7 All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting. (no label)	Strongly agree
Q8 In general, patients and their carers are well-informed about recognising stroke-like episodes	Strongly Disagree
Q9 In general, my community colleagues (general practitioners/primary care physicians) are well-informed about stroke-like episodes in mitochondrial disease.	Strongly Disagree
Q10 In general, my neurology colleagues from different hospitals are well informed about stroke-like episodes in mitochondrial disease.	Strongly Disagree
Q11 How active are you in clinical research of mitochondrial disorders? (based on your job plan)	Full-time

Page 3: SECTION B: Defining Stroke-like Episodes

Q12 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management. (no label)	Strongly agree
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Q13 Which of the following are accepted features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	Strongly agree
Headache	Strongly agree
Nausea and vomiting	Strongly agree
Altered conscious level/ encephalopathy	Strongly agree
Focal motor seizures (including epilepsy partialis continua)	Strongly agree
Generalised seizures	Agree
Non-convulsive status epilepticus	Agree
Elementary visual hallucination e.g. coloured flashing light	Agree
Formed, complex visual hallucination	Agree
Visual field defect	Strongly agree
Focal motor weakness	Agree
Focal sensory symptoms	Agree
Dysphasia	Agree
Apraxia	Agree
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	Agree
Lactic acidosis	Agree

Q14 How do you diagnose a stroke-like episode in your current clinical practice? **Clinical assessment plus MRI head plus EEG**

Q15 Do you agree with the following statement provides a better definition of stroke-like episodes?Subacute onset, evolving neurological symptoms (headache, nausea, vomiting, focal seizures with or without bilateral convulsion, confusion/drowsiness, neuropsychiatric symptoms, focal neurological deficit) with supporting evidence of corresponding stroke-like lesion detected on MRI head and/or abnormal EEG appearance (focal or generalized slowing, focal or generalised ictal discharge can be seen).

(no label) **Strongly agree**

Q16 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label) **Agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q17 All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Strongly agree**

Q18 Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.

(no label) **Neither disagree nor agree**

Page 5: Section D: Clinical Assessment

Q19 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label) **Agree**

Q20 A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).

(no label) **Strongly agree**

Q21 A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.

(no label) **Strongly agree**

Page 6: Section E: Investigations

Q22 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes

Full blood count	Strongly agree
Urea and creatinine (kidney function)	Strongly agree
Liver function test (LFT)	Strongly agree
Serum lactate (without tourniquet applied)	Strongly agree
C-reactive protein (CRP)	Strongly agree
Creatine kinase (CK)	Strongly agree
Random glucose	Strongly agree
HbA1c	Strongly agree
Coagulation screen	Strongly agree
Urinalysis and urine culture	Strongly agree
Blood culture	Neither disagree nor agree
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone)	Strongly agree
Arterial blood gas (ABG)	Strongly agree

Q23 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph (if aspiration pneumonia suspected)	Strongly agree
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	Strongly agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q24 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label) **Agree**

Q25 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion? (more than one option is permitted)

T1,
T2,
FLAIR,
DWI

Q26 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	Strongly agree
Chest radiograph	Strongly agree
Abdominal X-ray	Strongly agree
Electrocardiogram (ECG)	Strongly agree
Lumbar puncture	Strongly agree
Electroencephalogram (EEG)	Strongly agree
MRI head (unless there is contraindication, then CT head)	Strongly agree

Q27 What access to EEG monitoring do you have in the acute setting?

Standard EEG recording (~30 mins)
Ambulatory EEG monitoring

Page 7: Section F: Treatment for Seizures

Q28 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label) **Agree**

Q29 At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)

Oral anti-epileptic drug
Intravenous anti-epileptic drug

Q30 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	1
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	4
Phenobarbitone (15mg/kg)	3
Lacosamide (200-400mg)	2
Other	5

Q31 At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit for example hemianopia but no clear seizure activity evident, how would you manage this? (more than one option is permitted)

Oral anti-epileptic drug

Q32 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label) **Strongly agree**

Q33 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label) **Strongly agree**

Q34 Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.

(no label) **Agree**

Q35 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label) **Agree**

Q36 In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.

(no label) **Agree**

Q37 If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010).

(no label) **Strongly agree**

Q38 Indications for intensive care unit admission (more than one option is permitted):

- Convulsive (generalised) status epilepticus**
- Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Focal status epilepticus with retained consciousness >60 minutes failing to respond to IV AEDs**
- Occipital status epilepticus (and at risk of developing cortical blindness) which fail to respond to IV AEDs (and titration of usual maintenance AEDs)**
- Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q39 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	1
Propofol	5
Midazolam	2
Ketamine	3
Other	4

Q40 There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.

(no label) **Strongly agree**

Q41 Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.

(no label) **Agree**

Q42 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Ketogenic diet or similar diet

Q43 Burst suppression is the commonly used EEG target of GA agents and should be maintained for a period of 24-48 hours.

(no label) **Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q44 Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.

(no label) **Agree**

Q45 It is important to consider non-convulsive status epilepticus is the underlying cause of new-onset neuropsychiatric symptoms and treat aggressively with AED as outlined in the previous section.

(no label) **Agree**

Q46 Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)

Benzodiazepine

Q47 Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).

(no label) **Agree**

Q48 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Agree**

Page 9: Section H: General Medical Treatment

Q49 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q50 The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.

(no label) **Agree**

Q51 Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

(no label) **Agree**

Q52 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q53 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Agree**

Q54 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q55 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q56 Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).

(no label) **Agree**

Q57 Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.

(no label) **Agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q58 Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.

(no label) **Agree**

Q59 Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric tube.

(no label) **Agree**

Q60 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Agree**

Q61 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Agree**

Q62 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Agree**

Q63 Intestinal pseudo-obstruction should not be managed with surgery.

(no label) **Agree**

Q64 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q65 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q66 Do you routinely use oral L-arginine as a prophylactic agent for stroke-like episodes? **No**

Q67 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Neither disagree nor agree**

Q68 Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.

(no label) **Neither disagree nor agree**

Q69 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Agree**

Q70 High dose replacement of ubiquinone (5-50 mg/kg) may be beneficial for patients who have seizures and stroke-like episodes secondary to the primary ubiquinone deficiency.

(no label) **Agree**

Q71 Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.

(no label) **Agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q72 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Neither disagree nor agree**

Q73 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Agree**

Q74 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Agree**

Q75 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q76 How long does it take for the genetic analysis and report of m.3243A>G and POLG mutations in your hospital? **Greater than two weeks**

Q77 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Blood,
Urine,
Buccal,
Fibroblast,
Muscle**

Q78 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **Yes**

Q79 Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and POLG).

(no label) **Agree**

Q80 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**

Q81 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Q82 Although it is rare, if primary ubiquinone deficiency is suspected (e.g. presence of steroid resistant nephrotic syndrome, prominent cerebellar ataxia), multi-gene panel or whole exome sequencing may be a preferred method for the further genetic workup.

(no label) **Agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q83 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Neither disagree nor agree**

Q84 In general, what are the difficulties patients with stroke-like episodes face after leaving the acute hospital?

- Unemployment/ Drop out of education ,
- Cognitive impairment,
- Social isolation ,
- Financial hardship,
- Dependence for activities of daily living ,
- Caregiver burden of other family members ,
- Depression

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q85 The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.

(no label) **Agree**

Q86 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Agree**

Q87 If your answer is either 'Agree' or 'Strongly agree' for questions 86 and 87, what would be your preferred choice of AED?

- For men **Levetiracetam**
- For women of childbearing age **Levetiracetam+Folic acid**
- For children **ketogenic diet?**

Page 16: SECTION O: Your Comments

Q88 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful for further discussion at the mitochondrial workshop.

Respondent skipped this question