Primary Mitochondrial Disorders

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Overview (seek advice)

• Introduction to mitochondrial medicine

• Systems based approach:
  – Brain: Epilepsy/ Stroke-like episodes
  – GIT: Pseudo-obstruction
  – Cardiac: Sudden adult death syndrome (SADS)

• Guidelines
Mitochondria and Mitochondrial Disease
Mitochondrial Respiratory Chain

Nuclear DNA: 3,000,000,000 bp

mtDNA: 16,569 bp
Inheritance of Mitochondrial Disease

(Sporadic)

AR

AD

XR

Mat

UNAFFECTED
UNAFFECTED
UNAFFECTED
AFFECTED

UNAFFECTED
UNAFFECTED
UNAFFECTED
AFFECTED

UNAFFECTED
UNAFFECTED
UNAFFECTED
AFFECTED

UNAFFECTED
UNAFFECTED
UNAFFECTED
AFFECTED

55% Heteroplasmy

10% 25% 65% 80%
Geographical Distribution of All Cohort Patients (n=1218)

Newcastle 56%
London 32%
Oxford 6%
Others 6%

Figure. Patient recruitment

Last updated on 6/5/2015
# Prevalence of mitochondrial disease

Minimum point prevalence (mtDNA mutations): 1 in 5,000
Overt disease due to nDNA mutations: 2.9 per 100,000
Prevalence (total): 1 in 4,300

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Affected per 100,000 (CI)</th>
<th>‘At Risk’</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHON</td>
<td>3.7 (2.9-4.6)</td>
<td>4.4 (3.7-5.3)</td>
</tr>
<tr>
<td>m.3243A&gt;G</td>
<td>3.5 (2.7-4.4)</td>
<td>4.4 (3.7-5.3)</td>
</tr>
<tr>
<td>mtDNA deletion</td>
<td>1.5 (1.0-2.1)</td>
<td>0</td>
</tr>
<tr>
<td>m.8344A&gt;G</td>
<td>0.2 (0.1-0.5)</td>
<td>0.5 (0.2-0.8)</td>
</tr>
<tr>
<td>SPG7, ar</td>
<td>0.8 (0.5-1.3)</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td>PEO1, ad</td>
<td>0.7 (0.4-1.2)</td>
<td>2.3 (1.7-2.9)</td>
</tr>
<tr>
<td>OPA1, ad</td>
<td>0.4 (0.2-0.7)</td>
<td>0.7 (0.4-1.1)</td>
</tr>
<tr>
<td>POLG, ar</td>
<td>0.3 (0.1-0.6)</td>
<td>0.3 (0.1-0.6)</td>
</tr>
<tr>
<td>RRM2B, ad</td>
<td>0.2 (0.1-0.5)</td>
<td>0.7 (0.4-1.0)</td>
</tr>
<tr>
<td>nDNA (GD)*</td>
<td>0.2 (0.1-0.5)</td>
<td>0.3 (0.1-0.6)</td>
</tr>
</tbody>
</table>

*Genetically undetermined*
Figure. Genotypes in Newcastle patient cohort (n=689)

- m.3243A>G: 32%
- m.8993T>C/G: 2%
- Other mtDNA point mutations: 11%
- Single deletion: 15%
- Other nuclear genes: 5%
- Multiple deletions: 5%
- OPA1: 3%
- RRM2B: 3%
- POLG: 6%
- PEO1: 6%
- Other genetically undetermined: 6%
- Multiple deletions: 5%
- Other genetically undetermined: 6%

Last updated on 6/5/2015
Prevalence of clinical feature

Neurology
Ophthalmology
Gastrointestinal
Psychiatric
Cardiac
Endocrine
Prevalence of neurological features

Stroke-like episode
Extrapyramidal
Encephalopathy
Neuropathy
Epilepsy
Dysphagia
Cerebellar
Deafness
CPEO
Headache
Cognition
Myopathy

Neurological features

(%)

0 10 20 30 40 50 60 70 80
CLINICAL ACUMEN

MUSCLE BIOPSY

Cardiac muscle or liver

Histochemistry

Biochemistry

Cytochrome c oxidase (COX)-deficient fibres (uniform decrease or mosaic pattern)

Measurement of respiratory chain complex activities and Ubiquinone (CoQ10)

Molecular Genetics

Characteristic clinical syndrome? (MELAS, MERRF, NARP, LHON, Pearson syndrome, Leigh Syndrome, Alpers syndrome)

Test common mtDNA or POLG mutations in blood

NO

YES

Negative result, further investigations required

Complex I deficiency – mtDNA and nuclear-encoded genes (structural and assembly factors)
Complex II deficiency – SDHA, SDHB, SDHC, SDHD analysis
Complex III deficiency – MTCYB (mtDNA), 10 nuclear structural genes, BCS1L
Complex IV deficiency – mtDNA, COX assembly factors (SURF1, SCO1, SCO2, COX10, COX15...)
Multiple complex deficiencies – mtDNA, nuclear mtDNA maintenance and translation genes
Ubiquinone deficiency - CABC1, COQ2, COQ9, PDSS1 gene analysis

POLG, PEO1, TK2, DGUOK, RRM2B, SUCLA2, MPV17 analysis

Multiple mtDNA deletion disorders POLG, POLG2, PEO1, SLC25A4, RRM2B analysis

mtDNA sequencing (novel or rare mtDNA mutations)

single fibre PCR and family studies

Real-time PCR (mtDNA depletion)

DNA rearrangements

PCR-RFLP (common mtDNA point mutations)

MT-CYB

SDHA, SDHB, SDHC, SDHD

BCS1L

SURF1, SCO1, SCO2, COX10, COX15...

CABC1, COQ2, COQ9, PDSS1
Same Genotype: Different Phenotype
Ophthalmoplegia
Short stature
Deafness
Myopathy
Cardiac conduction defect [pacemaker]
Diabetes
Adrenal failure
Died age 7

Ophthalmoplegia
Short stature
Deafness
Myopathy
Cardiac conduction defect
Died age 7

Ophthalmoplegia
Short stature
Deafness
Myopathy
Cardiac conduction defect
Aged 44

Ophthalmoplegia
Aged 68
Leber’s Hereditary Optic Neuropathy (LHON)

11778G>A, MTND4
Dystonia Phenotype

Dystonia and Complex I Deficiency: m.11778G>A
• Maternally Inherited Diabetes and Deafness
• Chronic Progressive External Ophthalmoplegia
• Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like episodes
• Over half of symptomatic patients do not have a ‘syndrome’

The UK MRC Mitochondrial Disease Patient Cohort Study: clinical phenotypes associated with the m.3243A>G mutation—implications for diagnosis and management

Victoria Nesbitt, Robert D S Pitceathly, Doug M Turnbull, et al.

J Neurol Neurosurg Psychiatry 2013 84: 936-938 originally published online January 25, 2013
doi: 10.1136/jnnp-2012-303528
m.3243A>G mutation in MTTL-1

- Neuropathy
- Stroke-like episode
- Cardiac
- CPEO
- Diabetes
- Exercise intolerance
- Myopathy
- Migraine
- Deafness
- GI
Mitochondrial Disease in Children: Complex I deficiency

93 patients with isolated complex I deficiency

mtDNA \((n=26)\)
- LIMD: 7.5%
- Leigh/Leigh-like: 7.5%
- MELAS: 27%
- Myopathy: 46%
- Encephalopathy: 12%

nuclear \((n=36)\)
- LIMD: 3%
- Leigh/Leigh-like: 14%
- MELAS: 50%
- Myopathy: 50%
- Encephalopathy: 33%
Complex I deficiency: Age at onset of symptoms

![Graph showing the age of onset of symptoms for mtDNA and Nuclear with Log Rank Test p<0.005.]

- **mtDNA**
  - Median: 7.5 months
  - Range: 0 - 180 months

- **Nuclear**
  - Median: 3.0 months
  - Range: 0 - 60 months

Log Rank Test

p<0.005
Complex I deficiency: Patient survival

- mtDNA
  - Median 84m
  - Range 1 - 432m

- Nuclear
  - Median 34m
  - Range 0 - 276m

Log Rank Test
Not significant
Same Phenotype: Different Genotype
Leigh Syndrome

- Progressive neurodegenerative disorder
- Onset in early childhood
- Developmental regression
- Can have long ‘plateau’ phases
- Brainstem & basal ganglia dysfunction
- Hypopnoea → Apnoea
- Recurrent admissions to PICU
- Death from respiratory failure
- mtDNA and nDNA mutations
Symmetrical changes in basal ganglia and brainstem on MRI

Leigh Syndrome
**RARS2** Mutation: Pontocerebellar Hypoplasia*

*Image from Edvardson et al. AJHG 2007; 81: 857-862

**DARS2** Mutation: LBSL Leukoencephalopathy
Brainstem and Spinal cord involvement with elevated Lactate

**AARS2** Mutation: Mitochondrial cardiomyopathy

**HARS2** – Ovarian dysgenesis and SNHL

**YARS2** – Myopathy Lactic Acidosis and Sideroblastic Anaemia (MLASA)

**SARS2** – Hyperuricaemia, pulmonary hypertension, renal failure and alkalosis (HUPRA syndrome)

**FARS2** – Alpers and Infantile Spasms
Systems based approach: case reports
Epilepsy and SLE (MELAS)
m.3243A>G \textit{MTTL1}

Poor weight gain  Short stature
Evolution of stroke-like lesion

7 days  14 days  32 days  183 days  Time
Only 10% of Newcastle Cohort recruits with the m.3243A>G have had stroke-like episodes
So, What Is New About This?

- Mean age of 1\textsuperscript{st} SLE = 34 (SD 13, range 12.5 to 56.5)

- No difference in mean and median age between male and female (p value= 0.217)

- 31% (n=11) had their 1\textsuperscript{st} SLE > 40 years

- However, more women with 1\textsuperscript{st} SLE presented >50 years than previously reported?
What is the frequency of stroke-like episode as a first clinical manifestation?

Other: Exercise intolerance (n=2), myopathy (n=1), cardiomyopathy (n=1), cyclical vomiting (n=1), recurrent miscarriages (n=1), failure to thrive (n=1), rhabdomyolysis (n=1), recurrent ecclampsia (n=1)
Figure. Clinical features of stroke like episode

Figure. Imaging changes associated with 1st stroke-like episode
Mechanism of Stroke-like Episode

- **Cytopathy**
  (underlying OXPHOS dysfunction)

- **Neuronal hyperexcitability**
  (role of seizure and ‘spreading’ of SLL)

- **Angiopathy**
  (deficiency of arginine and NO)

Koga et al. 2010

Courtesy of Nichola Lax
**Stroke-like episode & Management**

**Triggers**
- eg. infection, dehydration

**Prodromal phase**
- Headache, N/V
- Visual symptoms
- Occipital seizure

**Hyperexcitability phase**
- Spreading of the seizure
- Focal neurological deficits
- Reversible phase

**Irreversible phase**
- Neuronal damage & death
- Permanent neurological deficit

**Susceptibility**
- OXPHOS dysfunction
- Vasculopathy

**Current situation:**
- Delay in recognition
- Delay +/- insufficient anti-seizure treatment

**Recommendations:**
- Identify trigger(s) and treat
- Early and aggressive seizure Mx
  - ?? L-arginine
Natural history of MELAS

Prodrome: headache, nausea/ vomiting, visual symptoms (+ve & -ve phenomenon)

Subacute & progressive presentation: focal seizure (occipital/motor), encephalopathy, focal deficit (hemianopia & others)

Concomitant systemic features: lactic acidosis, bowel dysmotility

Prognosis: Mostly good with prompt Mx. Cumulative effect → cognitive impairment
A Teenager With Refractory Seizure

- Previously well
- Headache plus visual symptoms
- Focal & generalised seizure
- Migratory, multiple ictal foci on EEG
- Concomitant liver dysfunction
- EPC on clinic review
- No family history
4 weeks of headache and visual symptoms

+10 days

+25 days
Diagnostic process

Catheter cerebral angiogram

Invasive brain biopsy

Negative m.32423A>G

Homozygous p.A467T in POLG gene
**POLG related seizure**

based on literature review (76 studies, 403 patients)

Factors influencing the disease onset:
1. Male has an earlier onset
2. Combination of the pathogenic variants

Figure. Imaging findings associated with POLG-related seizure (n=120)

- Cerebellar WM
- Atrophy
- Basal ganglia
- Thalamus
- Occipital lobe
- SLL
Epilepsy and SLE (MELAS): m.3243A>G and POLG

Similarities
• Occipital seizure is very common
• Predilection for occipital and parietal lobe involvement; ‘spreading’
• Cellular energy failure

Differences
• Onset >40 yo is rare in POLG
• (?) Temporal lobe involvement more common in m.3243A>G
• Seizure control is more attainable in m.3243A>G
• POLG-related seizure has a more relentless, progressive course
• Hepatic involvement in POLG (with or without valproate)
POLG Disease

- **POLG** – Mitochondrial polymerase
  - A467T, W748S, G848S

- Alpers Huttenlocher Syndrome
  - Children 1-3yrs with normal prior development
  - Explosive onset of seizures
  - Occipito-parietal cerebral atrophy
  - Hepatic failure (Valproate?)
  - *FARS2, MPV17, DGUOK, RRM2B*

- Adolescent-onset Refractory Epilepsy
  - Predominantly focal refractory epilepsy
  - Progressive encephalopathy

Courtesy of Dr A M Devlin
**Diagnostic Work Up & Supportive Care**

- Admit to hospital
- Assess ABCDE, glucometer
- Establish IV access
- Urgent blood: FBC, glucose, electrolytes, HCO₃⁻, lactate, LFT, therapeutic AED levels +/- ABG
- Contributing factor:
  - Infection/dehydration
  - Stroke-like episode
  - Bowel pseudo-obstruction
  - AED adherence
- Tests indicated:
  - Septic screen
  - EEG
  - MRI head

**EARLY LIAISON WITH NEWCASTLE MITOCHONDRIAL DISEASE TEAM**

**OFFICE HOUR:** 0191 282 0340  
**OUT OF HOUR:** Contact RVI switchboard 0191 233 6161

**Other supportive care**

- Strict fluid balance¹ (+/- urinary catheter)
- Nutritional state assessment (avoid fasting)
- Bowel care (+/- AXR)

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**Acute Management of Status Epilepticus in Adult Patients with Mitochondrial Disease**

- **Status epilepticus** (including generalised, focal convulsive and non-convulsive)

  - IV lorazepam up to 0.1mg/kg OR
  - Buccal midazolam 5-10mg OR
  - IV diazepam 5-10mg OR
  - Rectal diazepam 10-20mg

  - IF phenytoin up to 20mg/kg at < 50mg/minute OR
  - IV levetiracetam 30mg/kg over 10 mins OR
  - IV phenobarbital up to 20mg/kg at < 100mg/minute

**AVOID SODIUM VALPROATE**

- Optimize maintenance AED (for phenytoin, aim therapeutic level 20mg/L)
- Add clobazam 10-30mg daily

**AVOID PROPOFOL (if possible)²**

- Further doses of IV phenytoin 5-10mg/kg up to total 30mg/kg at <50mg/minute
- Give 2nd IV AED (LEV or PBT)

**Seizure aborted**

- **Consider general anaesthesia**
  - IV midazolam 0.1-0.2mg/kg bolus then at 0.05-0.5mg/kg/hour OR
  - IV thiopentone 3-5mg/kg bolus then 3-5mg/kg/hour OR
  - IV ketamine 1-3mg/kg bolus then up to 5mg/kg/hour

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¹Prevalence of cardiomyopathy in m.3243A>G mutation is up to 56%.

²Respiratory chain deficiency in mitochondrial disease may predispose some patients at higher risk of developing propofol infusion syndrome especially when prolonged infusion is required for seizure control.

³Timing for GA varies between generalised and focal status. If patients known to have POLG1 mutations, consider GA early irrespective of seizure type.
GIT and pseudo-obstruction
Evolution of pseudo-obstruction

Figure. Abdominal radiograph (a) and (b) on admission (c) 5 days later (d) 10 days later (e) 20 days later
Cardiac and SADS
mtDNA

- m.1624C>T  MTTV
- m.3243A>G  MTTL1
- m.3260A>G  MTTL1
- m.3303C>T  MTTL1
- m.4269A>G  MTTI
- m.4295A>G  MTTI
- m.4300A>G  MTTI
- m.4317A>G  MTTI
- m.4320C>T  MTTI
- m.8296A>G  MTTK
- m.8344A>G  MTTK
- m.8348A>G  MTTK
- m.8529G>A  MTATP8
- m.9997T>C  MTTG
- m.12192G>A  MTTH (Dilated)
- m.12297T>C  MTTL2 (Dilated)
- m.13513G>A  MTND5
- m.15243G>A  MTCYB
- m.15498G>A  MTCYB
- Large single deletion (KSS)

Cardiac Phenotype

nDNA

- SCO2
- COX15
- NDUFA2
- NDUFS2
- NDUFV2
- SLC25A3
- SLC25A4
- ATPAF2
- TAZ1 (G4.5)
- FRDA (Frataxin)
- TK2
- AGK
- AARS2
30 year old
Worked full time
Regular in gym
Night out with friends
Found dead next morning
33 year old teacher
Worked full time
Regular in gym
Night out dancing with friends
Found dead next morning
m.3243A>G
71% in urine, 30% in blood

No history of seizures or faints
ECG, 24-hour Holter monitoring and echocardiogram had all been unremarkable
m.3243A>G

68% in urine and 30% in blood

No history of epilepsy or faints

Mild left ventricular hypertrophy detected on the routine echocardiogram, normal ECG
Why do young adults die suddenly?

1 per 100,000 deaths

• Cardiac deaths
• Epilepsy
Left ventricle

Deficient

Normal
Left ventricle
m.3243A>G
Left ventricle (91%)
Right ventricle (95%)
Muscle (85%)
Brain (90%)
m.3243A>G
Left ventricle (76%),
Right ventricle (78%)
Muscle (90%)
Brain (85%)
What should we do?
At a glance Guidelines
At a glance Guidelines

• For full guideline visit:
  
1. Pre-operative preparation
   – Seek specialist advice
   – Bloods (liver, renal, lactate)
   – Cardiac: ECG, echo
   – Respiratory (FVC (erect and supine))
   – Bowel care (consider PFA/AXR)- risk of constipation, pseudoileus
At a glance Guidelines

2. Pre-operatively Management
   - Seek specialist advice
   - Minimise fasting
   - Administer important meds (cardiac, AEDS)
   - AVOID VALPROATE (C/I)
   - Diabetes care (managed in the usual way (metformin))
• 3. Anaesthesia
  – Good evidence is lacking for benefit or harm specific to any anaesthetic agent
  – Muscle relaxants are best avoided in those with significant respiratory muscle weakness unless absolutely necessary
  – Diabetes care (managed in the usual way (metformin avoided)
  – No credible evidence for an increased risk of malignant hyperthermia syndrome.
3. Anaesthesia

- Propofol appears safe for induction.
- Prolonged use for maintenance of anaesthesia may risk exacerbation of lactic acidosis.
- Intravenous fluids: lactate buffers (eg Ringer’s Solution) should be avoided.
- Overall risk appears proportionate to severity of comorbidities (esp cardiorespiratory disease)
4. Post-operative Management:

- See Pre-operative Care: minimise fasting, administer drugs, usual post-op diabetic care.

- Bowel Care: constipation or paralytic ileus is common in the post-operative period (esp m.3243A>G or MNGIE). Patients often fail to report this. Comparison to pre-op AXR/PFA may be helpful.

- Discussion with a mitochondrial specialist advised if fails to respond to treatment.
Mitochondrial disease Summary

• Discussion with a mitochondrial specialist advised early

• Provision of 24 hour advice (Mito card)

• http://www.newcastle-mitochondria.com/
“...can give rise to any symptom, in any organ or tissue, at any age, and with any mode of inheritance...”