Mitochondrial diseases in adults: how do we manage stroke-like episodes?

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Overview

• Mitochondria and mitochondrial disease

• What are stroke-like episodes?

• Recognition of stroke-like episodes

• Management of stroke-like episodes
Mitochondria and mitochondrial disease
mtDNA and mitochondrial diseases

>250 pathogenic mutations
Genetics of mitochondrial disease

37 genes

> 1000 genes
Genes of mitochondria-localised proteins linked to human disease

Genetic variability

- mtDNA
- mtDNA maintenance
- mtDNA transcription
- mtDNA translation
- Complex assembly and remaining 76 subunits
- 13 polypeptide subunits

Complex I: 7/44
Complex II: 0/4
Complex III: 1/11
Complex IV: 3/14
Complex V: 2/16
Clinical variability

- Respiratory Failure
- Optic Atrophy / Retinitis Pigmentosa / Cataracts
- Cardiomyopathy / Conduction Defects
- CVA / Seizures / Developmental Delay
- Liver / Renal Failure
- Deafness
- Short stature / Marrow Failure
- Peripheral Neuropathy
- Diabetes
- Hypothyroidism
- Myopathy
Clinical variability

Respiratory chain dysfunction

[Images of medical illustrations and genetic symbols]
How common is 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

Gorman et al 2015 Annals of Neurology
What are stroke-like episodes?
MELAS syndrome

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Strokelike Episodes: A Distinctive Clinical Syndrome

Steven G. Pavlakis, MD,‡ Peter C. Phillips, MD,‡ Salvatore DiMauro, MD,§ Darryl C. De Vivo, MD,‡ and Lewis P. Rowland, MD¶

We report on two patients who have a mitochondrial myopathy, encephalopathy, lactic acidosis, and recurrent cerebral insults that resemble strokes (MELAS). These two and nine other reported patients share the following features: ragged red fibers evident on muscle biopsy, normal early development, short stature, seizures, and homonymous hemianopia, or cortical blindness. Lactic acidemia is a common finding. We believe that MELAS represents a distinctive syndrome and that it can be differentiated from two other clinical disorders that also are associated with mitochondrial encephalopathy and cerebral disease: Kearns-Sayre syndrome and the myoclonic epilepsy with ragged red fiber syndrome. Existing information suggests that MELAS is transmitted by maternal inheritance. The ragged red fibers suggest an abnormality of the electron transport system, but the precise biochemical disorders in these three clinical syndromes remain to be elucidated.


A mutation in the tRNA\textsubscript{Leu(UUR)} gene associated with the MELAS subgroup of mitochondrial encephalomyopathies

Yu-ichi Goto*,†, Ikuya Nonaka* & Satoshi Hori†§

*Division of Ultrasonic Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Tokyo 187, Japan
†Department of Pediatrics, Hokkaido University School of Medicine, Sapporo 060, Japan
‡Department of Human Genetics, National Institute of Genetics, Mishima, Shizuoka 411, Japan

- 30+ different pathogenic mutations in mtDNA have been linked to MELAS
- MTTL-1 gene = 'hot spots' (n=6)
- m.3243A>G = 80% of cases
- Recessive mutations in POLG

Ischaemic stroke vs stroke-like episode

Katayoun Vahedi et al. Stroke. 2007;38:2506-2517

Stroke-like lesions

Severity

SLE

Ischaemic stroke

Time

mins
days
Seizures and stroke-like episodes
Seizures and stroke-like episodes

- Focal motor
- Focal sensory
- Focal dyscognitive
- Myoclonic
- Tonic clonic
- Bilateral convulsive
- Status epilepticus
- Stroke-like episode
Recognition of stroke-like episodes
STROKE - ACT F.A.S.T.

Act F.A.S.T. Home | Know the signs | Real stories | About stroke

- WHEN STROKE STRIKES, ACT F.A.S.T.
  - Face: Is their face fallen on one side? Can they smile?
  - Arms: Can they raise both arms and keep them there?
  - Speech: Is their speech slurred?
  - Time: Time to call 999 if you see any single one of these signs.
### SLE characteristics

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>92</td>
</tr>
<tr>
<td>Seizure</td>
<td>92</td>
</tr>
<tr>
<td>Mild pyramidal weakness</td>
<td>83</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>83</td>
</tr>
<tr>
<td>Visual field loss</td>
<td>74</td>
</tr>
<tr>
<td>Positive visual symptoms</td>
<td>69</td>
</tr>
<tr>
<td>EPC/GTCS</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## Visual disturbance

<table>
<thead>
<tr>
<th></th>
<th>Description of positive visual symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Visual hallucination (birds across sky)</td>
</tr>
<tr>
<td>4</td>
<td>Flashing light</td>
</tr>
<tr>
<td>5</td>
<td>Visual hallucination</td>
</tr>
<tr>
<td>7</td>
<td>Flashing light in the right visual field</td>
</tr>
<tr>
<td>8</td>
<td>Visual hallucination (seeing things even with eyes close)</td>
</tr>
<tr>
<td>9</td>
<td>Flashing light</td>
</tr>
<tr>
<td>10</td>
<td>Flashing light</td>
</tr>
<tr>
<td>11</td>
<td>Flashing light in the right visual field and visual hallucination</td>
</tr>
<tr>
<td>12</td>
<td>Intermittent kaleidoscopic vision in the left visual field</td>
</tr>
<tr>
<td>13</td>
<td>Coloured speckled appearance for 1 week</td>
</tr>
<tr>
<td>16</td>
<td>Visual hallucination</td>
</tr>
<tr>
<td>19</td>
<td>Colourful flashing light with pixel dots</td>
</tr>
<tr>
<td>21</td>
<td>Continuous flickering light for 3 months</td>
</tr>
<tr>
<td>24</td>
<td>Flashing light, visual hallucination (insects) in one eye initially then spread to contralateral eye</td>
</tr>
<tr>
<td>25</td>
<td>Visual hallucination</td>
</tr>
<tr>
<td>26</td>
<td>Flashing light for 4 days</td>
</tr>
<tr>
<td>29</td>
<td>Bright coloured icons in the right visual field</td>
</tr>
<tr>
<td>30</td>
<td>Flashing light</td>
</tr>
<tr>
<td>31</td>
<td>Visual hallucination (seeing worms creeping out from underneath his skin)</td>
</tr>
<tr>
<td>32</td>
<td>Bright coloured objects in the left visual field for 3 weeks</td>
</tr>
</tbody>
</table>
Management of stroke-like episodes
Management

1. Aggressive seizure treatment
2. Supportive care
3. (L-arginine)
1. **Susceptibility**
   - OXPHOS dysfunction
   - Vasculopathy

2. **Triggers**
   - Infection
   - Dehydration

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

4. **Irreversible phase**
   - Neuronal damage/death
   - Permanent neurological deficit

3. **Hyperexictability phase**
   - Spreading of the seizure
   - Focal neuro deficits
   - Reversible phase

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

- Identify trigger(s) and treat
- **Early and aggressive seizure management**
  - ?? L-arginine
Summary

• Mitochondria and mitochondrial disease

• What are stroke-like episodes?
  – Versus ‘typical’ strokes
  – Linked with seizures

• Recognition of stroke-like episodes:
  – Headache
  – Seizures
  – Visual disturbance
  – (Weakness)

• Management of stroke-like episodes:
  – Seizure control
  – Supportive therapy (hydration, antibiotics)
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