LASOP Resident/Fellow Symposium 2013

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History

- 9 mo old with shock and shallow fast breathing
- Born at 35 weeks due to oligohydramnios
- G6P6A0
- Normal growth and development till 5-6 months
- Decreased activity and crying
Milestones

• Unable to sit
• Unable to roll from side to side
• No eye contact or tracking
• No vocalizations
Physical Examination

- Hypotonia and hyper-reflexia
- Disconjugate gaze with poor response to visual stimuli
- Kussmaul respirations
- Tachycardia and delayed capillary refill
Labs

- pH: 7.48 (7.35-7.45)
- $\text{paCO}_2$: 15 mmHg (35-45)
- $\text{HCO}_3^{-}$: 10 mEq/L (22-26)
- Lactate: 6.5 mmol/L (0.5-2.2)
Increased CSF spaces
Autopsy Findings

• Organomegaly:
  - Heart: 50 grams (37 grams)
  - Lungs: right: 88 grams; left: 75 grams (right – 53 grams; left – 47 grams)
  - Liver: 297 grams (260 grams)
Midbrain
Midbrain
Putamen – 10x
http://www.stonybrookmedicalcenter.org/sbumcfiles/images/220-001.jpg
Thalamus, Mammillary body
Muscle Biopsy

• No identifiable histochemical abnormality.

• Most muscle fibers are 10 – 15 um diameter, infrequently up to 20 um
Summary

• Three affected in one generation

• Lactic acidosis – anaerobic respiration

• Brain affected
**Cultured Fibroblast Assay**

![Image of results from blue native page and in-gel activity staining]

<table>
<thead>
<tr>
<th>Complex</th>
<th>Evaluation following in-gel activity staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal activity</td>
</tr>
<tr>
<td>II</td>
<td>Normal activity</td>
</tr>
<tr>
<td>IV</td>
<td>Normal activity</td>
</tr>
<tr>
<td>V</td>
<td>Normal activity but the presence of bands of incomplete assembly of complex V</td>
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</tbody>
</table>

**Interpretation**

Presence of incompletely assembled subunits of complex V. This can indicate a defect in the assembly of complex V, in a mitochondrial DNA encoded subunit of complex V (e.g. mtDNA 8393 mutation, most likely), or could indicate a defect in the mitochondrial transcription or translation (see Electrophoresis 2009;30:3565-72). Given the high activity of complex 1, the latter (defects in transcription/translation are not likely).
Diagnosis?
Criteria for Leigh Syndrome

- Progressive neurological disease with motor and intellectual delay
- Signs and symptoms of brainstem and/or basal ganglia disease
- Raised lactate levels in blood and/or CSF
- And one or more of the following
  - Characteristic features of Leigh syndrome on neuroimaging
  - Typical neuropathological changes at postmortem, or
  - Typical neuropathology in a similarly affected sibling

Dennis Leigh, 1951

Vascular proliferation in the anterior nucleus of the thalamus. Perdrau's silver stain x 90.

Leigh Syndrome

• Most common disorder of the respiratory chain in infancy and childhood
• Frequency of 1:40,000 live births
• Variants
  – Late adult – onset
  – French – Canadian variant
  – Faroe Islands variant

Leigh Syndrome

- Neurological manifestations
- Non neurological manifestations
- Laboratory findings
- Radiological features
Genetic Origin & Functional Interaction of the OXPHOS Complexes

Figure 2 from Werner JH Koopman et al. *The EMBO Journal* online publication 13 November 2012 doi:10.1038/emboj.2012.300

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Other Mutations

• Mutations in proteins involved in mitochondrial translation

• Mutations in proteins involved in mtDNA maintenance: SURF1

• Coenzyme-Q Deficiency

• Pyruvate Dehydrogenase Complex Deficiency

Management

• High doses of thiamine, coenzyme-Q, or L-carnitine

Differential Diagnosis

• Wernicke’s encephalopathy
• Methyl alcohol poisoning
• Other mitochondrial disorders
• Infarct
References

References, cont.


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