Diagnostic Slide Session
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Case 7

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3 month old male, born at 35 weeks, presents to pediatric emergency department with weakness and respiratory distress

- Hypotonia, lethargy, hypothermia on physical exam
- CSF, blood, and sputum cultures negative
- Progressive lactic acidosis
- Deceased two weeks after presentation
• Mild edema and abnormal diffusion restriction throughout white matter tracts
  – Most notable in brainstem
  – Extending to upper cord
• Subacute infarct of periventricular white matter
Subcortical White Matter

H&E
Subcortical White Matter

Diagnosis?
• Nonspecific Vacuolation
  – Diffuse White Matter Injury/Periventricular Leukomalacia

• Spongiform White Matter Changes
  – Mitochondrial diseases
  – Canavan Disease
  – Galactosemia
  – Toxins
  – Vanishing White Matter Disease
  – Pelizaeus-Merzbacher Disease
Liver Pathology in Mitochondrial Complex I Deficiency From Bi-Allelic Mutations in NDUFS2: A Report of Findings at Autopsy

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Affiliations  + expand
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Molecular Findings

- GeneDx Mitochondrial Genome Sequence Analysis
  - Negative for mitochondrial DNA alterations
Molecular Findings

- *GeneDx Lactic Acidosis/Pyruvate Metabolism Nuclear Gene Panel*
- Bi-allelic *NDUFS2* mutations
  - C.552delC (S413P) – Pathogenic variant
  - C.1237 C>T (M185WfsX3) – Likely pathogenic variant
- Heterozygous variants of unknown significance
  - *NDUFV1*
    - C.800 G>A (R267K)
  - *COQ7*
    - C.104 G>A (R35H)
NDUFS2 encodes the NDUFS2 subunit of complex I (NADH ubiquinone oxidoreductase) of the mitochondrial respiratory chain.

NDUFS2 mutations have been associated with:
- LHON-like optic neuropathy (Gerber et al 2017)
- Encephalomyopathy and cardiomyopathy (Loeffen et al 2001)

Other complex I mutations:
- Cavitating leukoencephalopathy (Ferreira et al 2011, Kashani et al 2014, Ren et al 2017)
- Rapidly progressive leukoencephalopathy (Baertling et al 2014)
- Leukoencephalopathy with vanishing white matter (Pagnez-Mammeri et al 2010)
Mitochondrial Encephalo(myo)pathies

- Leigh syndrome*
- Kearns-Sayer syndrome
- Infantile-onset spinocerebellar ataxia
- Alpers syndrome
- And many more
• Multiple focal lesions with necrosis or spongiform vacuolation
  – Often symmetric, with involvement of:
    • Basal ganglia
    • Thalamus
    • Midbrain
    • Brainstem
    • Cerebellar nuclei
    • Spinal cord
  – Spares the cortex
  – Neuropil destruction followed by gliosis
• Is this a case of Leigh syndrome?
Why the variability with mitochondrial disorders?

- Heteroplasmy
  - Only relevant in discussing disorders linked to mitochondrial DNA
- Synergy between heterozygous bi-allelic mutations
- May depend on timing and severity of an inciting event

- There is much left to be learned...
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