Diagnostic Slide Session
96th Annual AANP

Case 7

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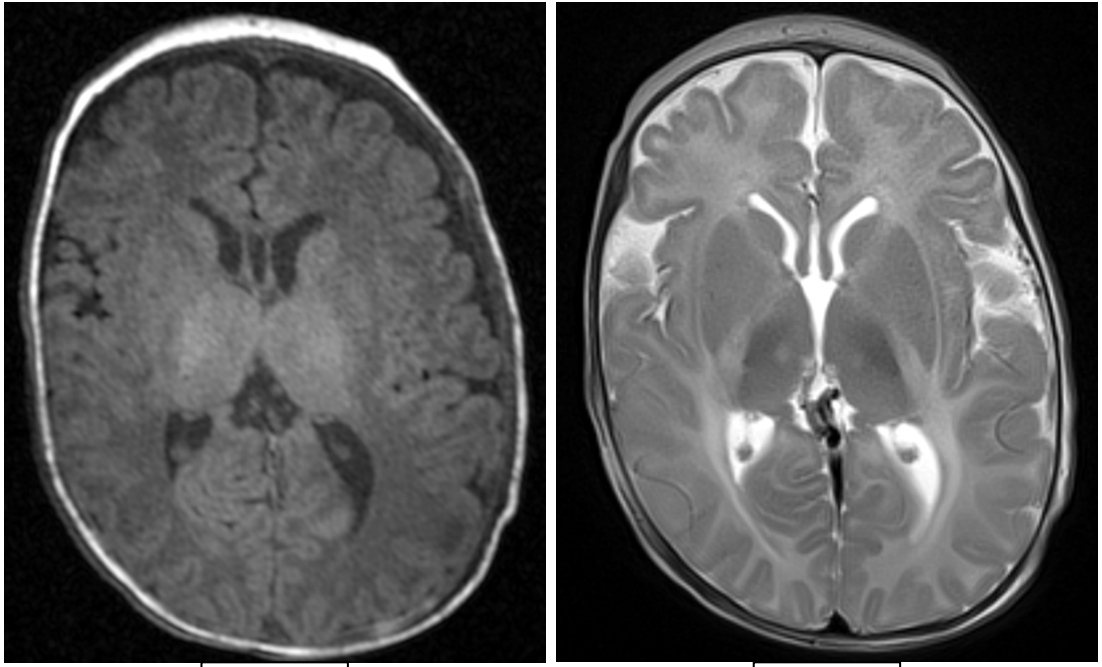
Clinical History

- 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

Imaging

- Mild edema and abnormal diffusion restriction throughout white matter tracts
  - Most notable in brainstem
  - Extending to upper cord
- Subacute infarct of periventricular white matter



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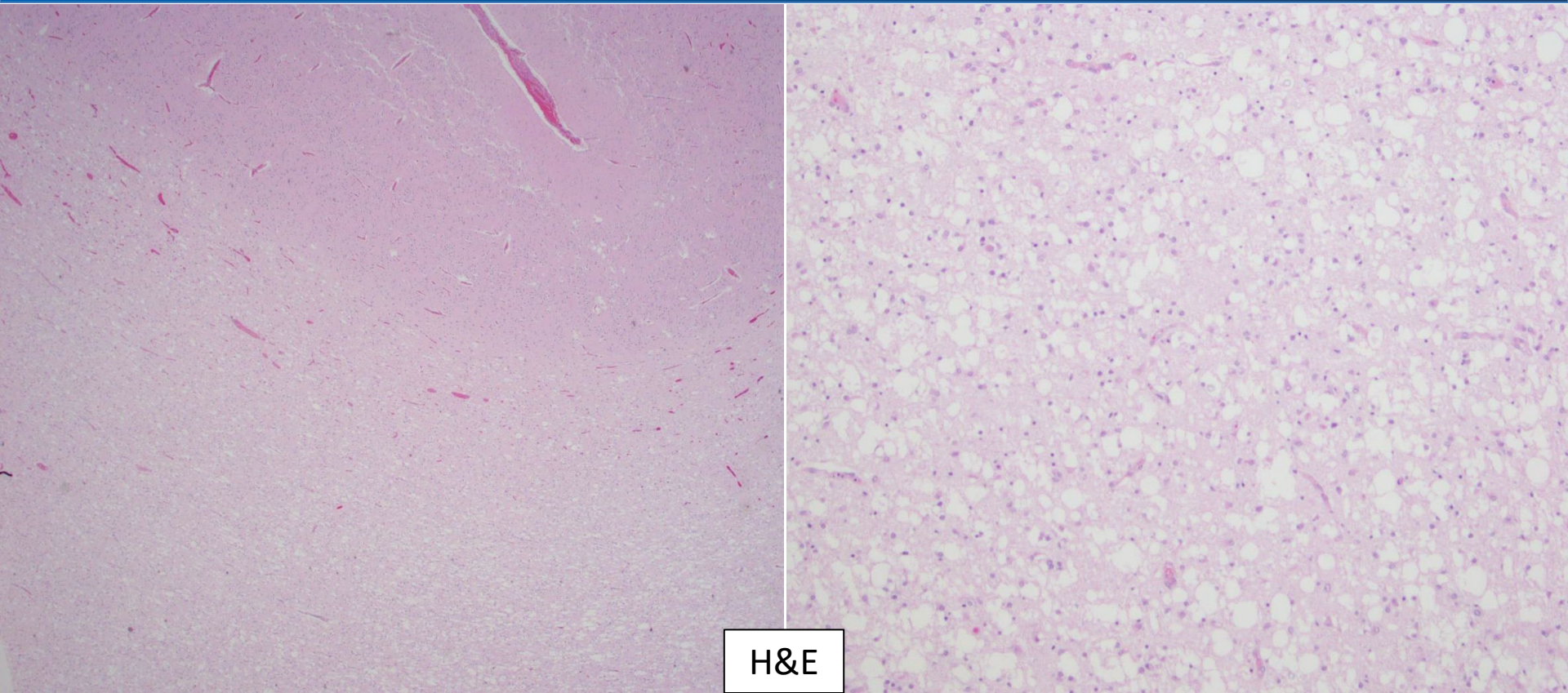
Subcortical White Matter



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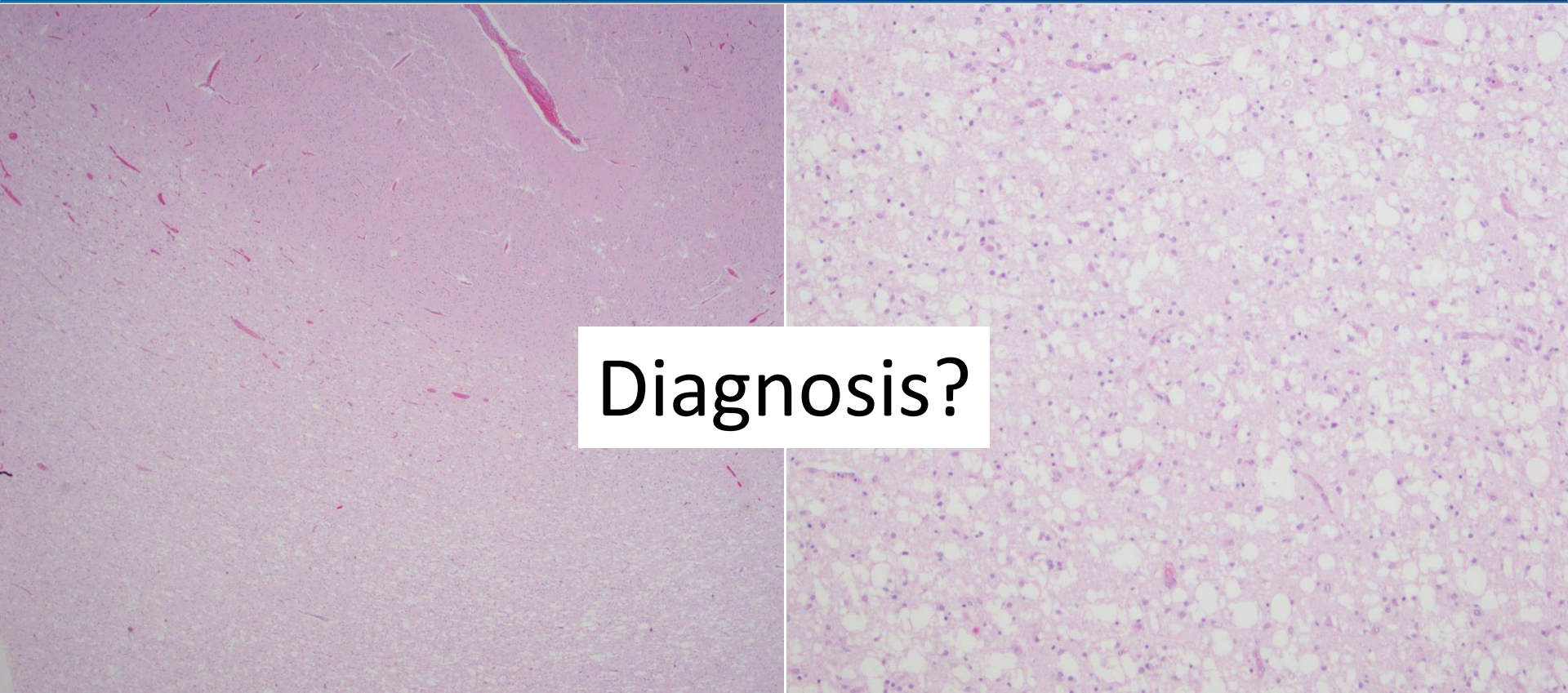
Subcortical White Matter



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Differential

- 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

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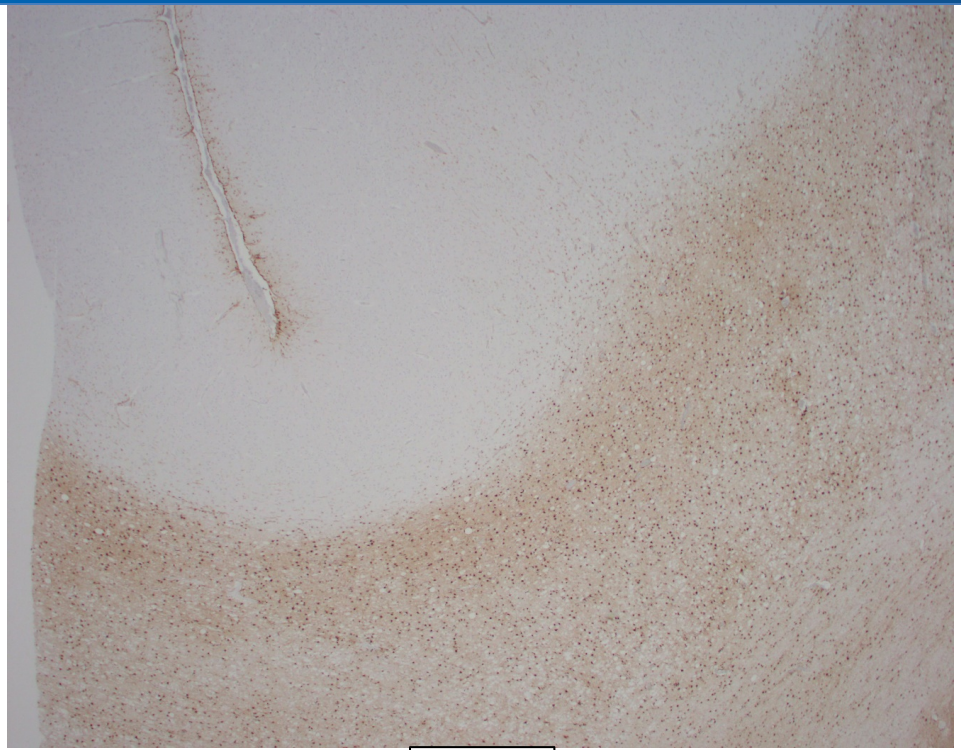
Subcortical White Matter



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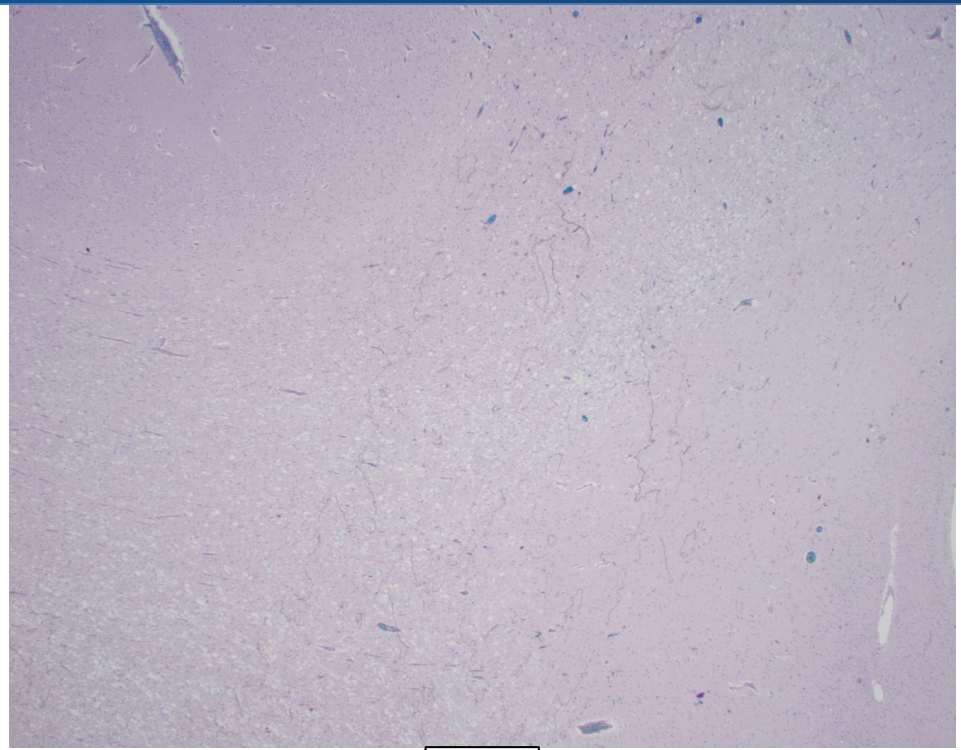

LFB

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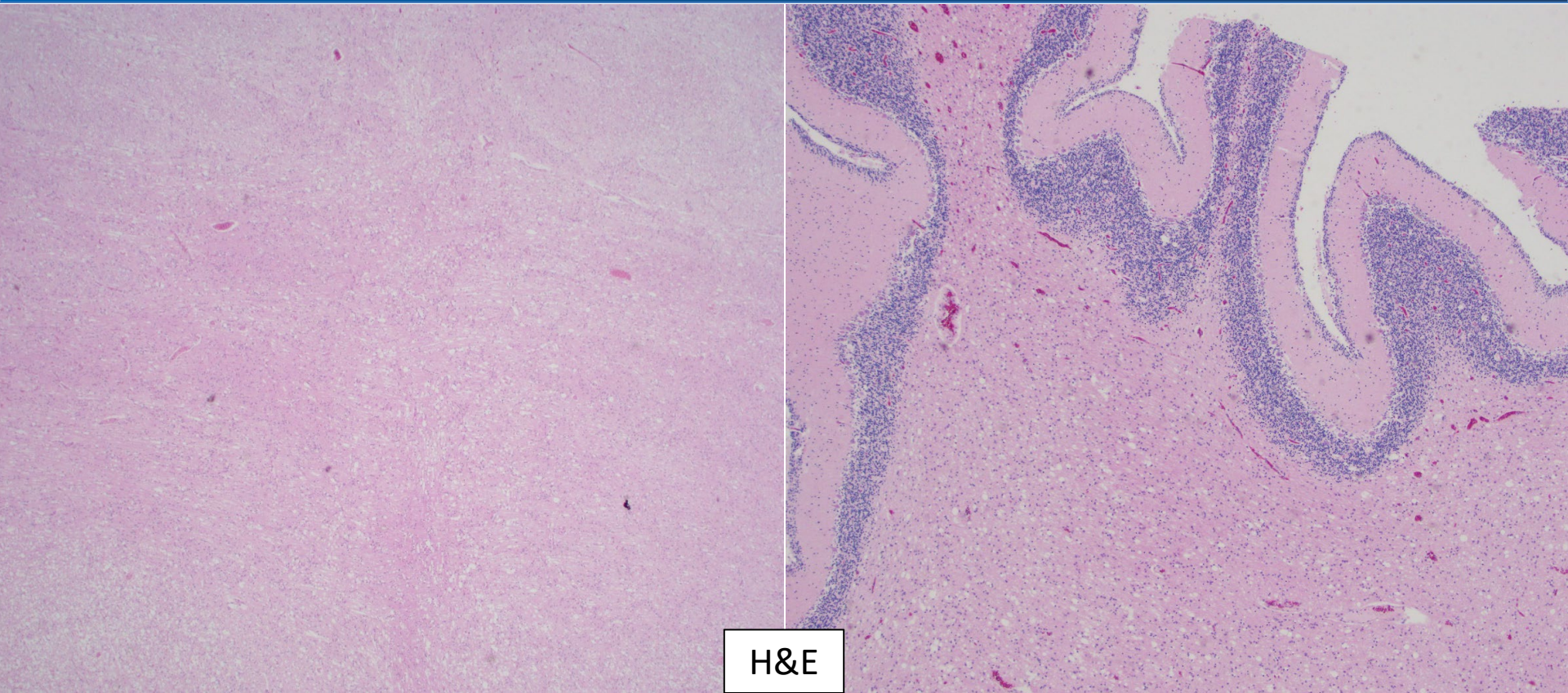
Pons & Cerebellum



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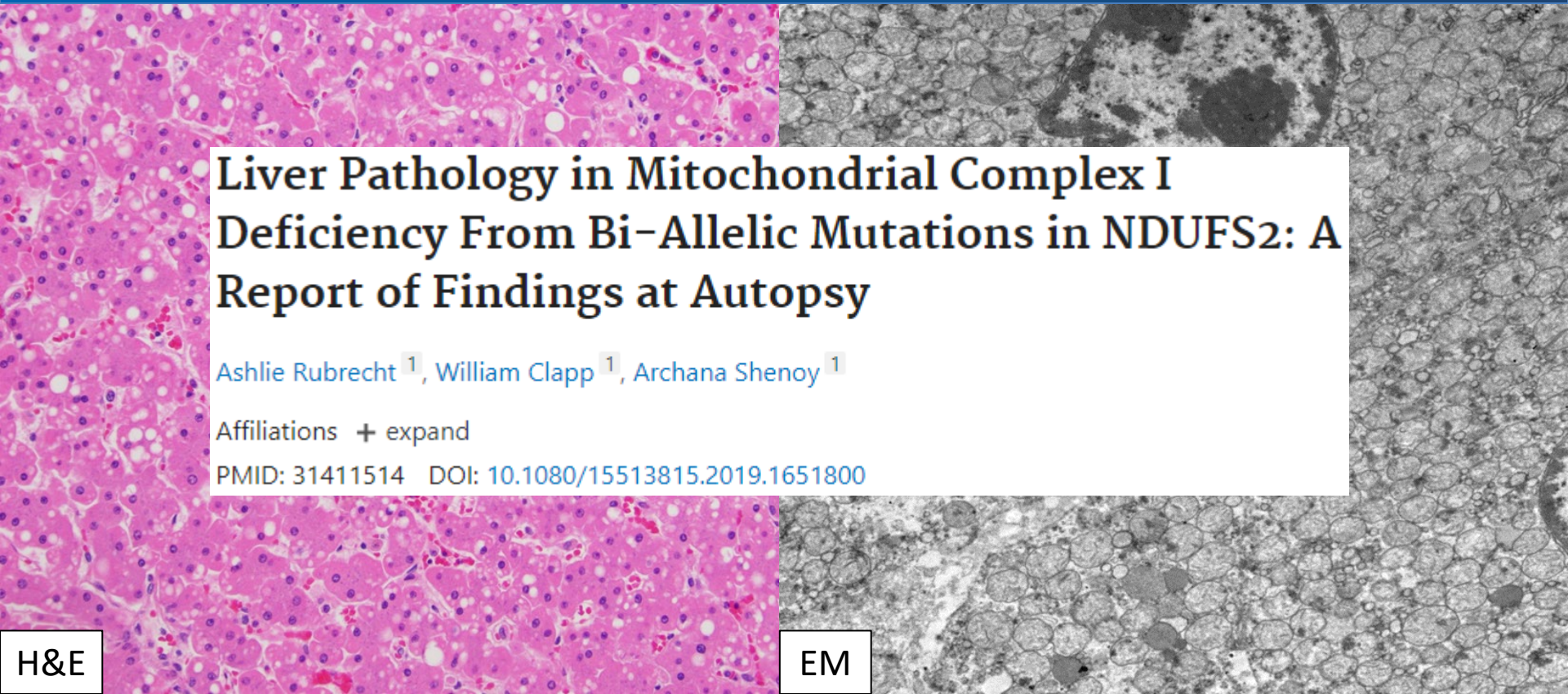
Autopsy Findings - Liver



Liver Pathology in Mitochondrial Complex I Deficiency From Bi-Allelic Mutations in NDUFS2: A Report of Findings at Autopsy

Ashlie Rubrecht [1], William Clapp [1], Archana Shenoy [1]

Affiliations + expand

PMID: 31411514 DOI: 10.1080/15513815.2019.1651800

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EM

Molecular Findings

- *GeneDx* Mitochondrial Genome Sequence Analysis
  - Negative for mitochondrial DNA alterations

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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)

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Background – *NDUFS2*

- *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)
  - Leigh syndrome (Marin *et al* 2013, Ngu *et al* 2012, Tuppen *et al* 2010)
- 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 (Pagniez-Mammeri *et al* 2010)

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Mitochondrial Encephalo(myo)pathies

- Leigh syndrome*
- Kearns-Sayer syndrome
- Infantile-onset spinocerebellar ataxia
- Alpers syndrome
- And many more

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Leigh Syndrome

- 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?

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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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