2021 AANP Diagnostic Slide Session Case #2

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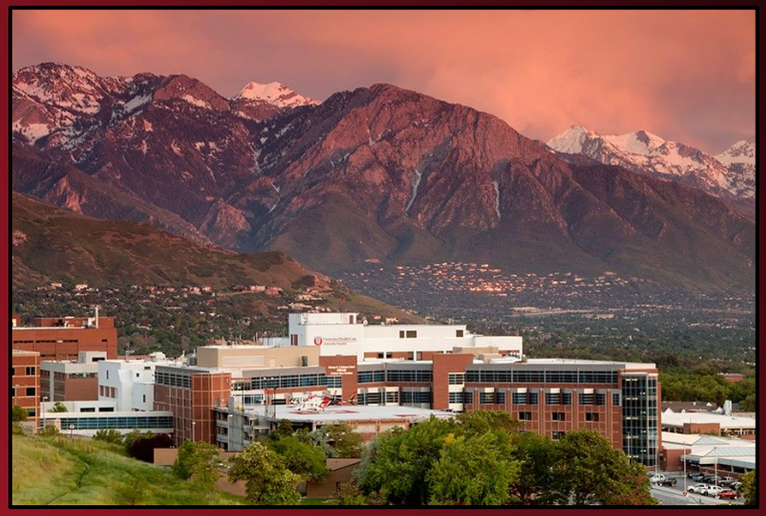


HEALTH
UNIVERSITY OF UTAH

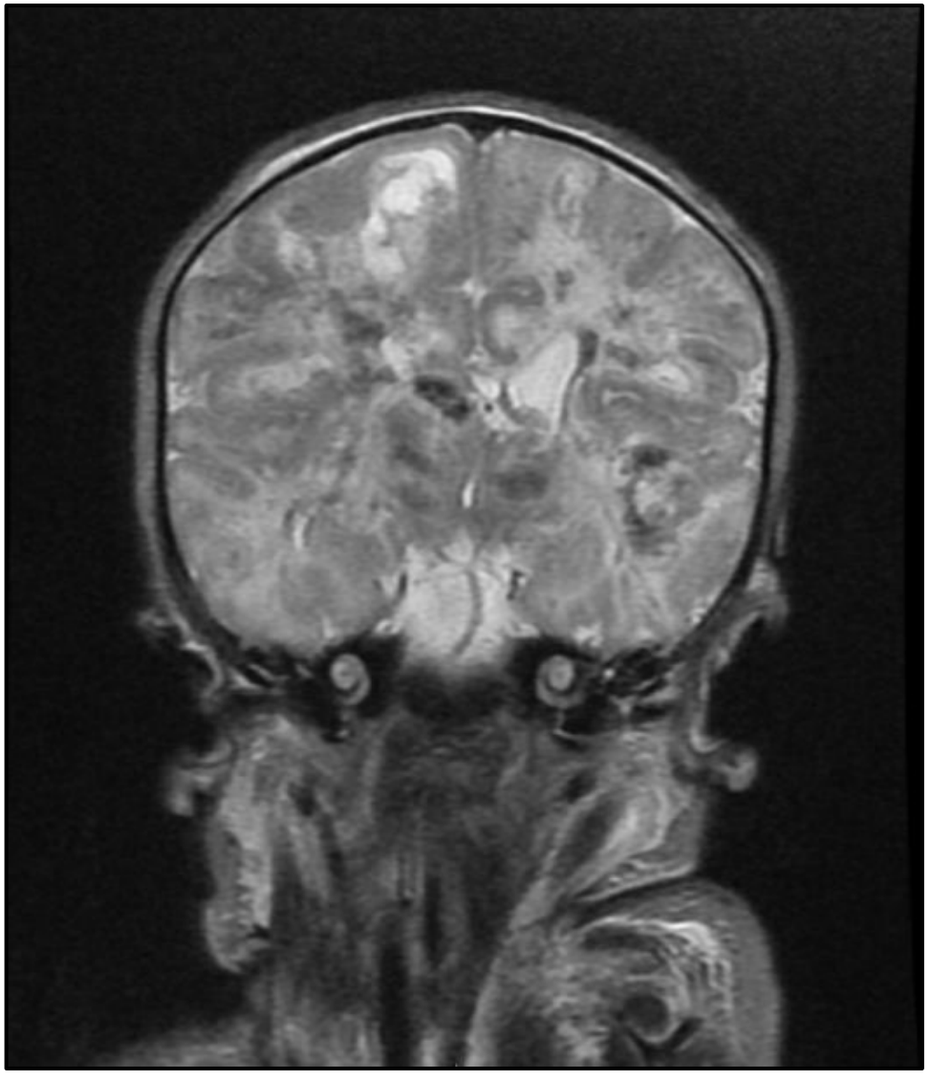
DISCLOSURE STATEMENT

- No financial relationships to disclose

CLINICAL HISTORY WITH NEUROIMAGING

Clinical History:

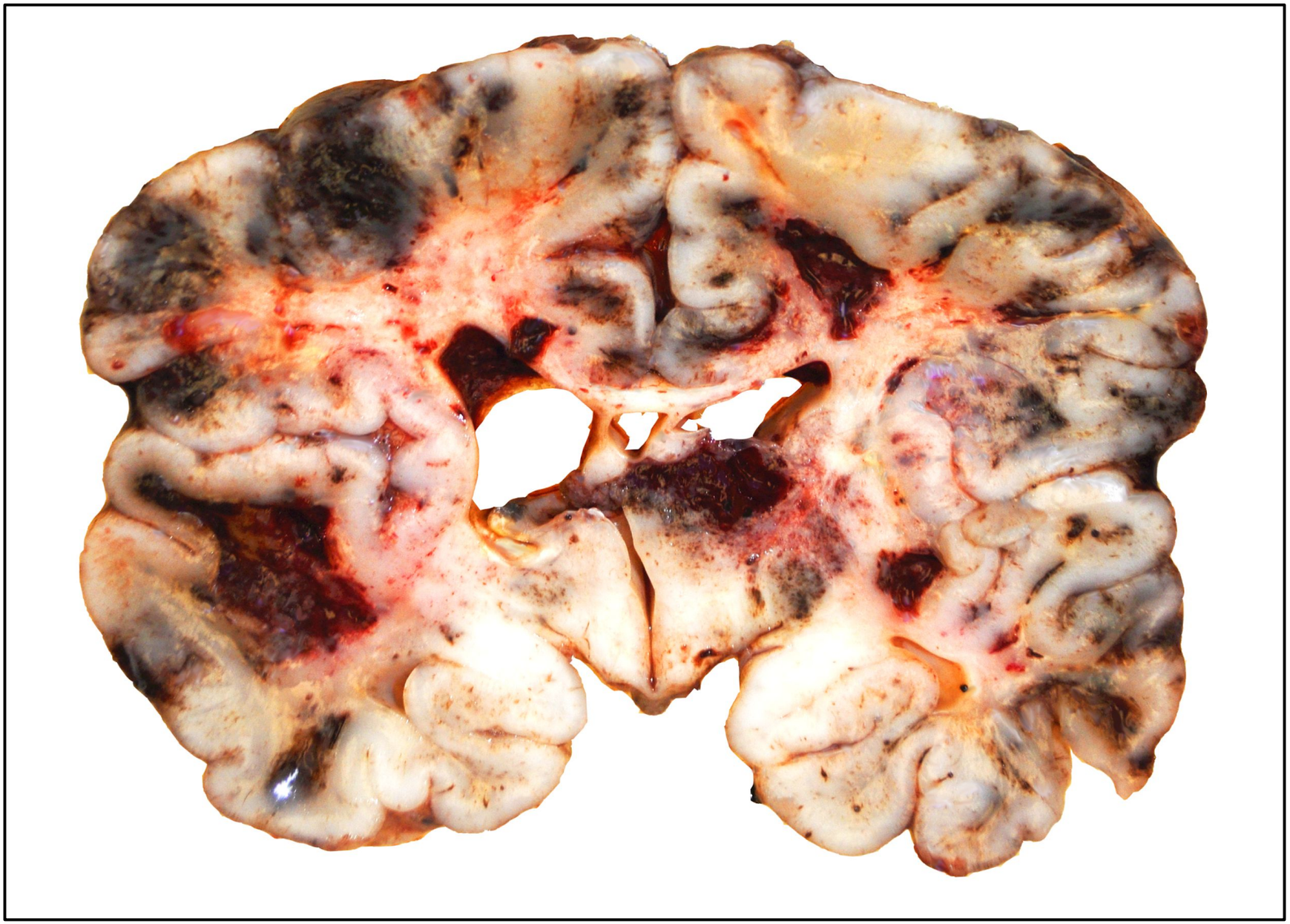
- Female neonate delivered at 39 weeks gestation via emergency Cesarean section due to non-reassuring fetal heart tones
- Routine prenatal care testing for 35-year-old G2P1 mother was unremarkable
- At birth, the infant's respiratory effort was absent, and was subsequently intubated
- Infectious work-up and newborn screening tests were all negative
- Infant died on day 3 of life shortly after being transitioned to comfort care
- Permission for unrestricted autopsy was obtained from the parents



Brain MRI:

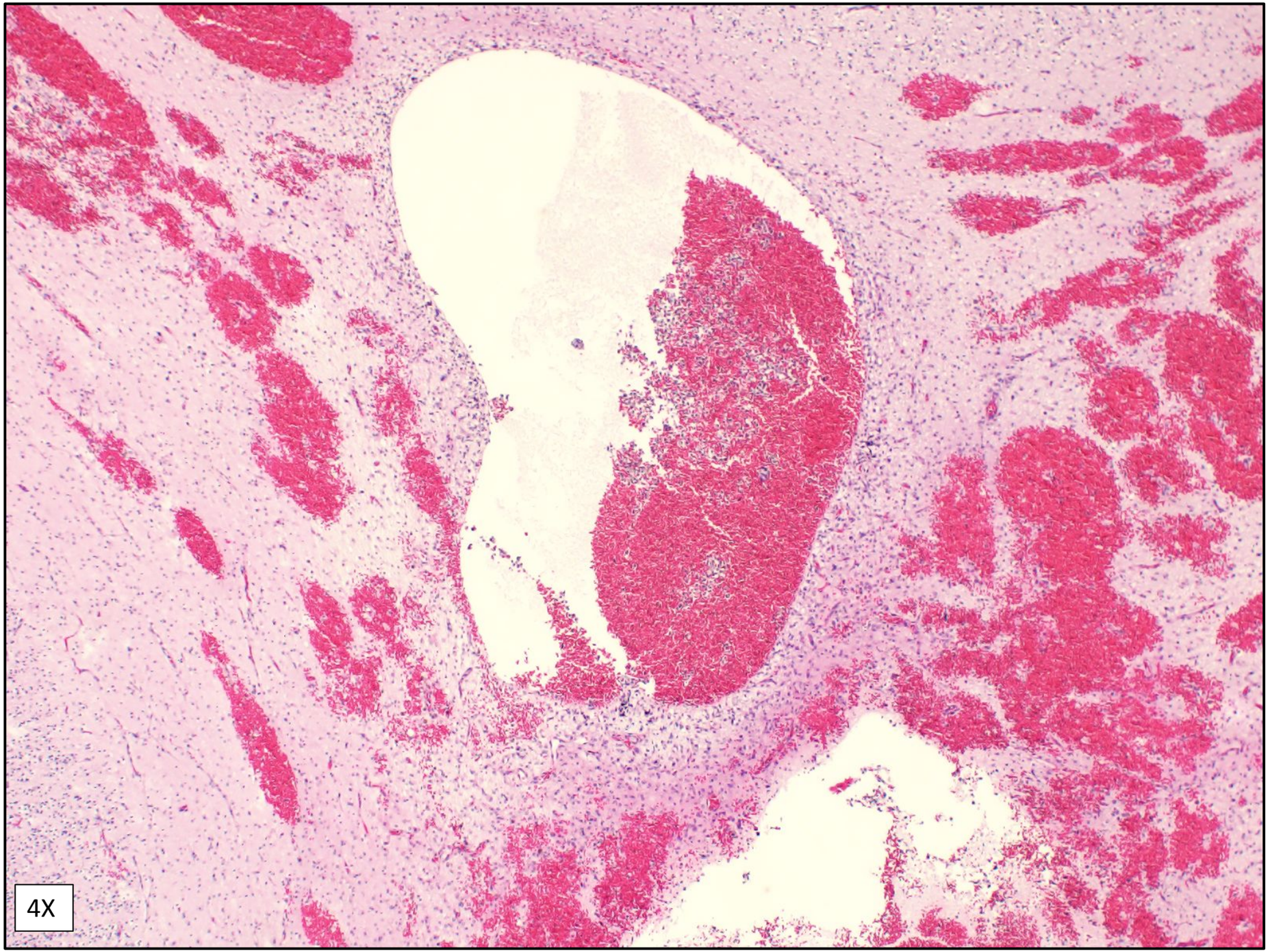
- Extensive areas of signal abnormality, T1 type hyperintensity, and cystic lesions

AUTOPSY FINDINGS



- Brain weight 299.67 g (expected 355+/-49 g for 39 weeks gestational age)
- Diffuse hemorrhagic lesions of chronological heterogeneity and cystic lesions

MICROSCOPIC FINDINGS



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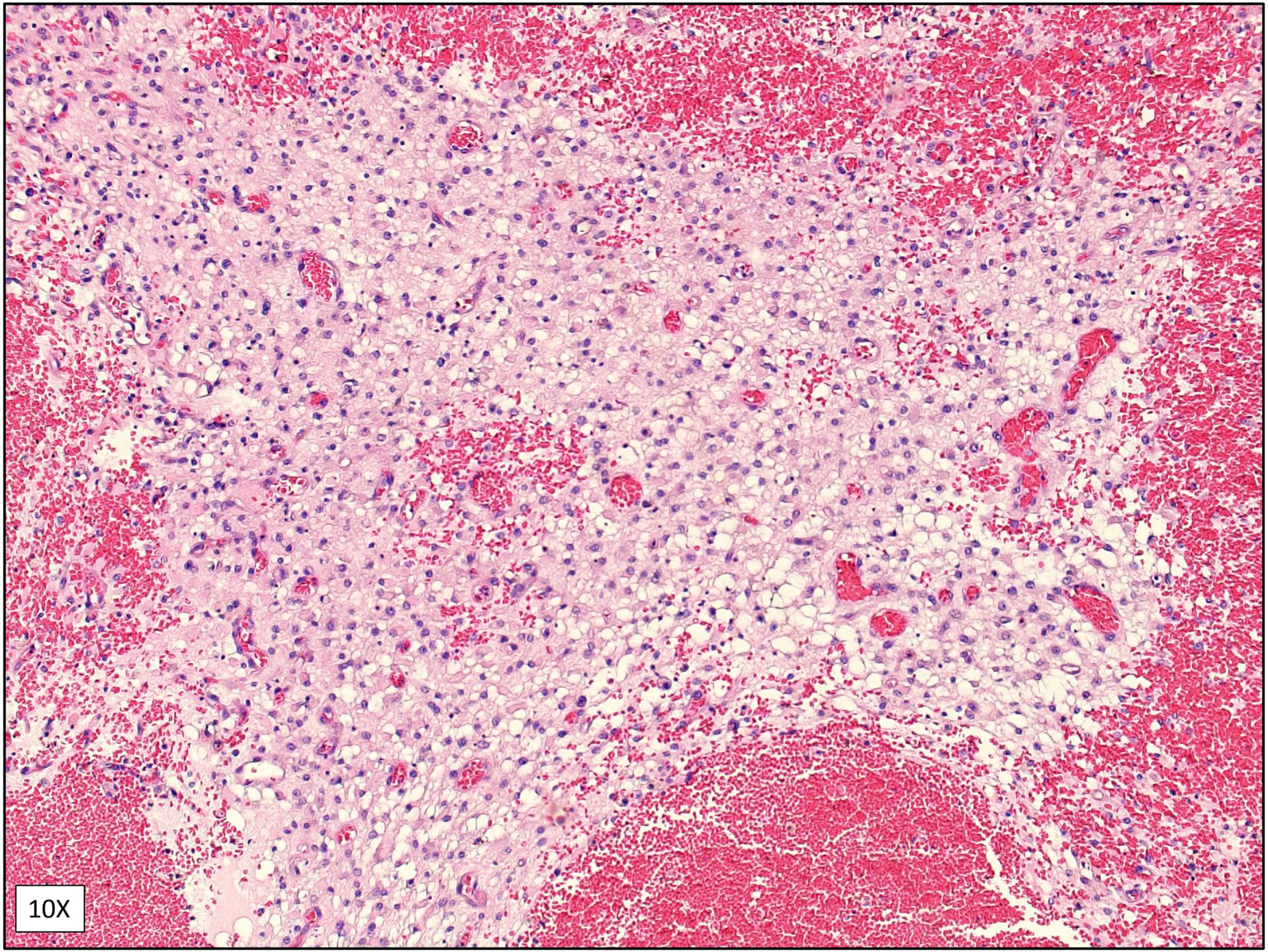

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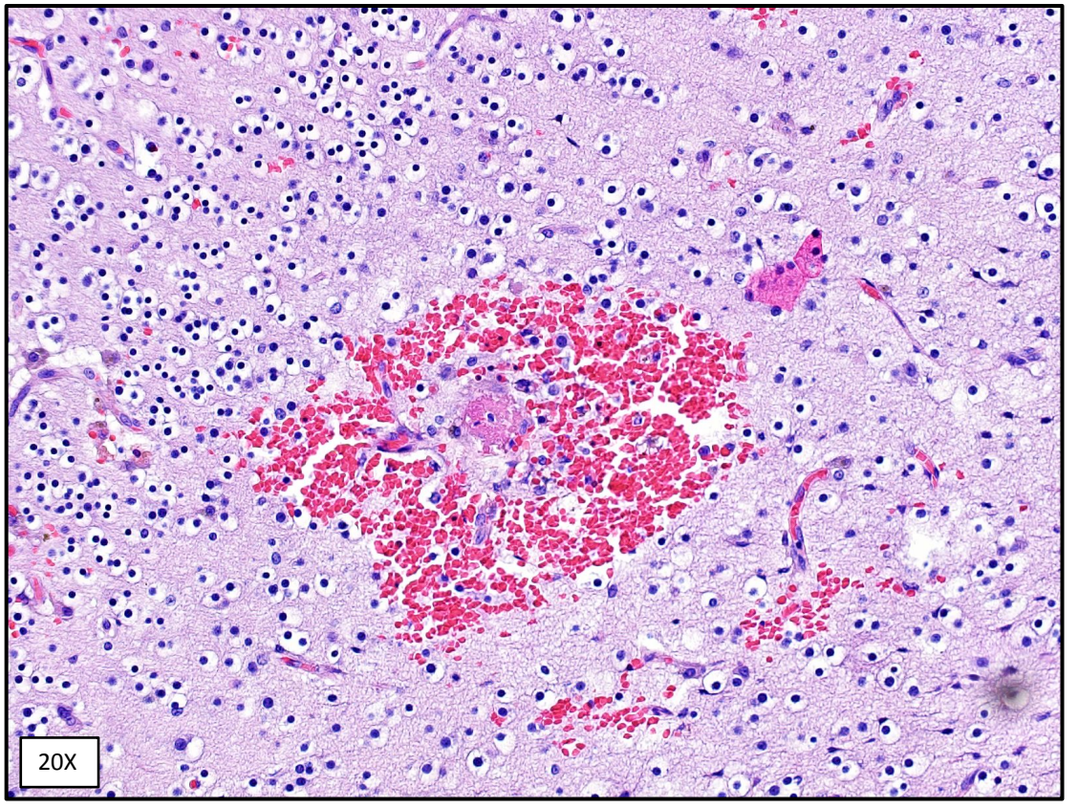
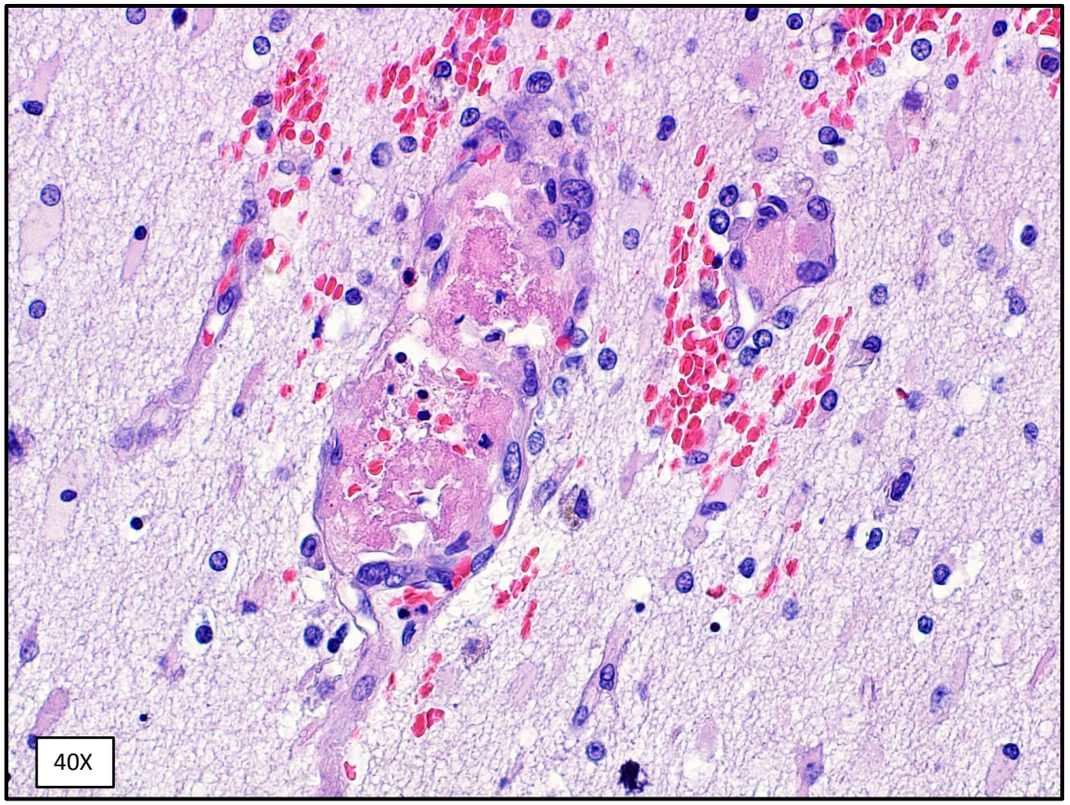
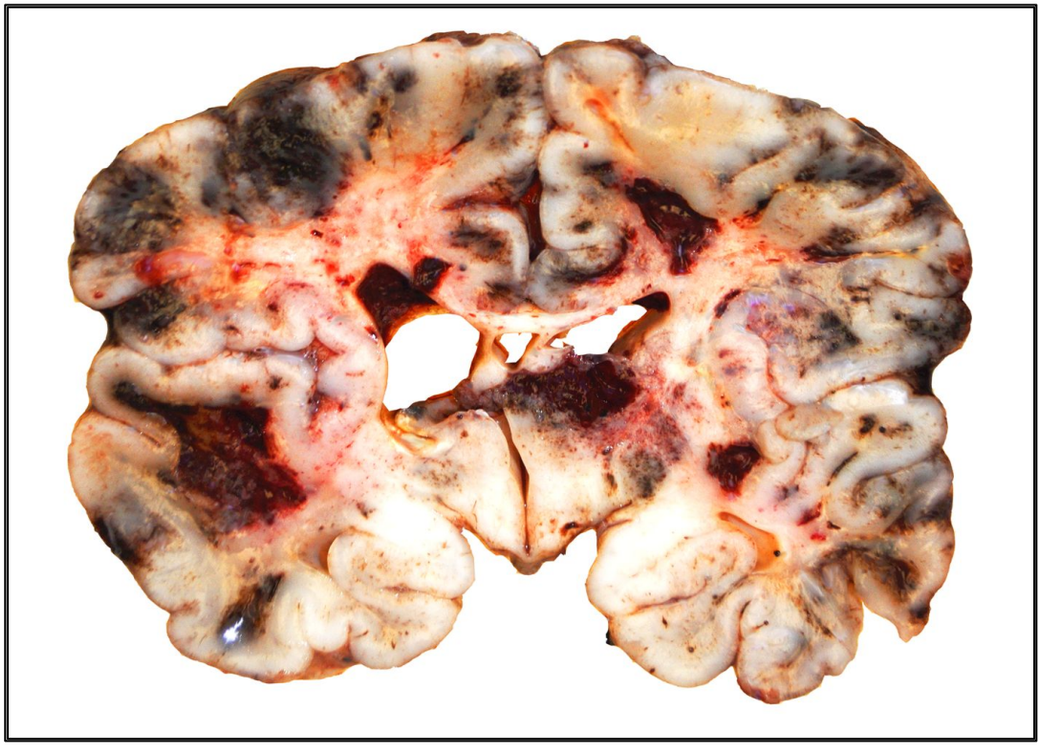
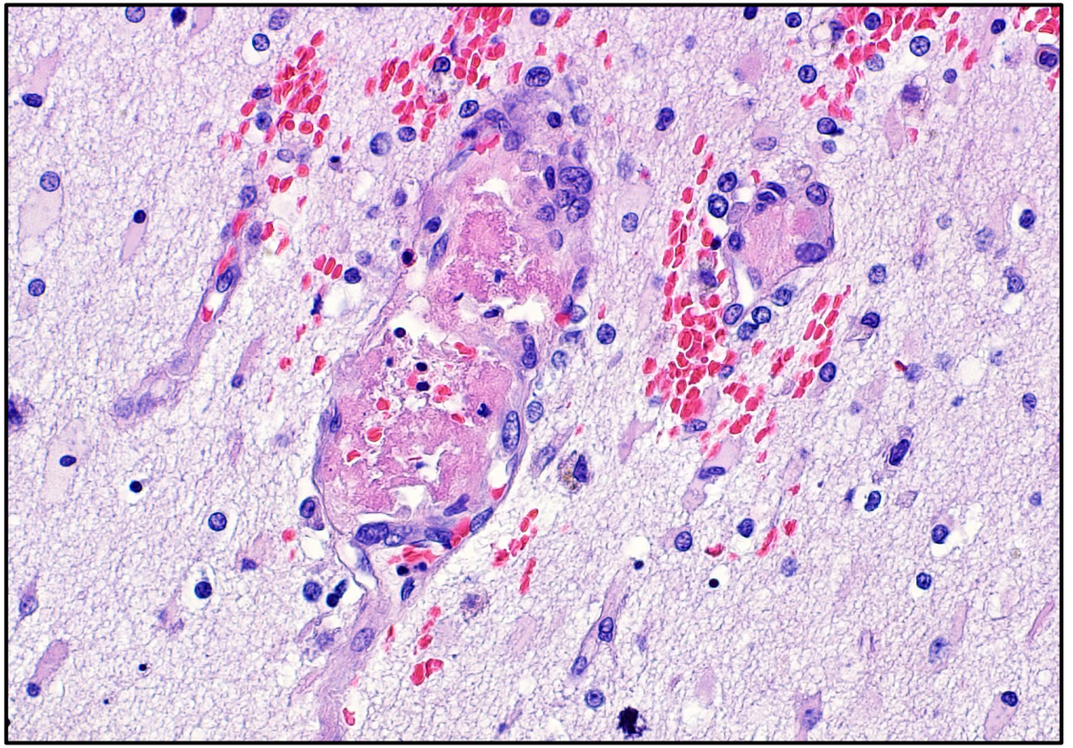




DIFFERENTIAL DIAGNOSIS & DISCUSSION?

(Audience Discussion)





DIFFERENTIAL DIAGNOSIS (CONTINUED)

- Congenital Vascular Malformations
- Congenital Coagulopathies
- Infection
- Connective Tissue Disorders
- Cancer

ADDITIONAL FINDINGS

- Genetic testing and results

Gene/Test	Technical Result	Variant Type	Clinical Relevance
COL4A1	c.2870G>A; p.Gly957Glu	Heterozygous Missense	Pathogenic

Athena Insight pathogenicity assessment

COL4A1 c.2870 G>A is a missense variant classified as pathogenic based on the following information:

Variant: COL4A1 c.2870 G>A (p.Gly957Glu)

- This variant has not been reported in large, multi-ethnic general populations.
- The current individual with this variant presents with clinical features associated with this gene.
- Majority of the pathogenic variants in this gene involve the substitution of a glycine residue in the triple-helix domain, resulting in disruption of protein function (PMID: 29632050, 21421911, 19344236).
- To the best of our knowledge, this variant has not been reported previously.
- Computational tools yielded predictions that this variant may interfere with normal RNA splicing.

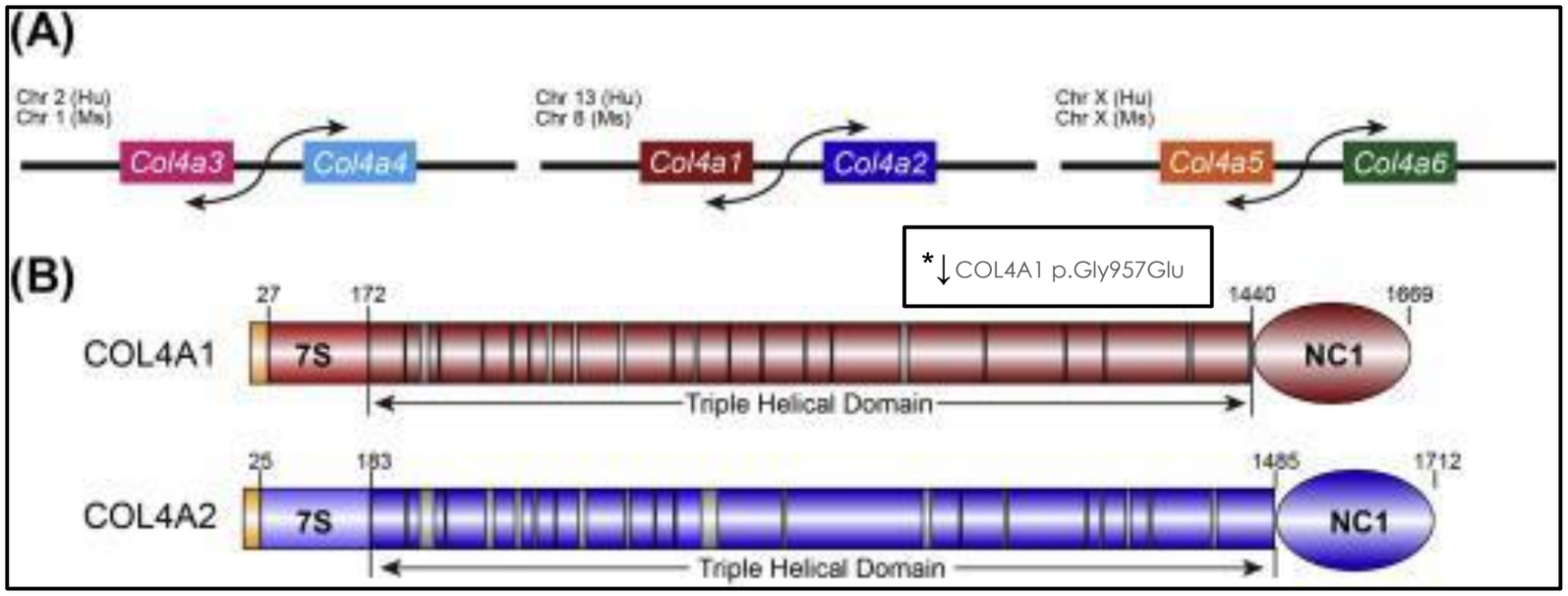
References:
Genome Aggregation Database (gnomAD), Cambridge, MA (URL: http://gnomad.broadinstitute.org)

athena insight

NEUROPATHOLOGICAL DIAGNOSIS:

Microangiopathic Leukoencephalopathy Associated With COL4A1 Mutation

COL4A1 MUTATION



- Type IV collagens comprise a major component to all basement membranes throughout the body
- COL4A1 gene is associated with autosomal dominant cerebral small vessel disease
- Almost all COL4A1 mutations reported have been missense mutations involving highly conserved glycine residues in a triple helical domain of the gene
- Clinical onset and symptoms widely vary among patients
  - 4 main phenotypes

(Mao, et al; 2015)

COL4A1 MUTATION PHENOTYPES

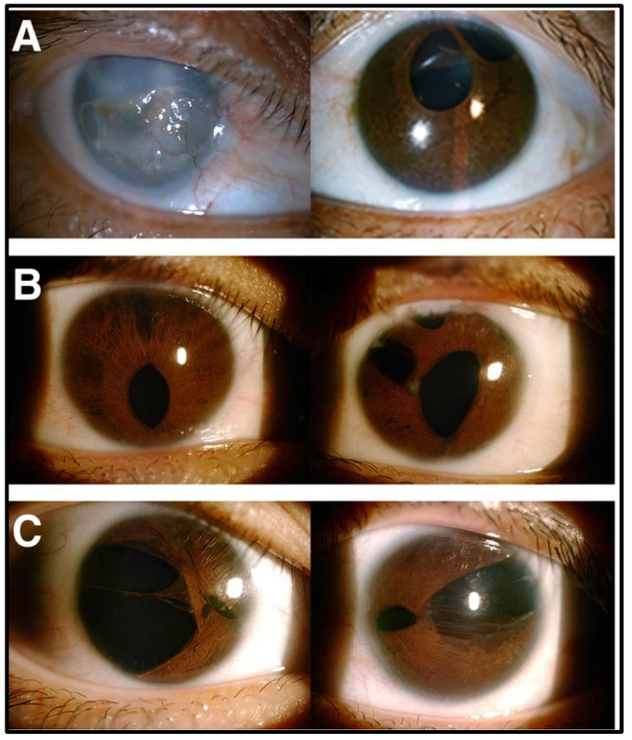
1. Perinatal hemorrhage with proencephalopathy in survivors

2. Hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL)

Retinal Arteriolar Tortuosity

(Villanueva, 2020)

3. Small vascular disease with Axenfeld-Rieger anomaly (anterior segment dysgenesis of the eye)



Axenfeld-Rieger Anomaly

(Zhang et al, 2019)

4. Hereditary angiopathy with nephropathy, aneurysms (typically of the internal carotid artery), and muscle cramps (HANAC)

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