Diagnostic Slide Session
94th Annual AANP Meeting

Case 1

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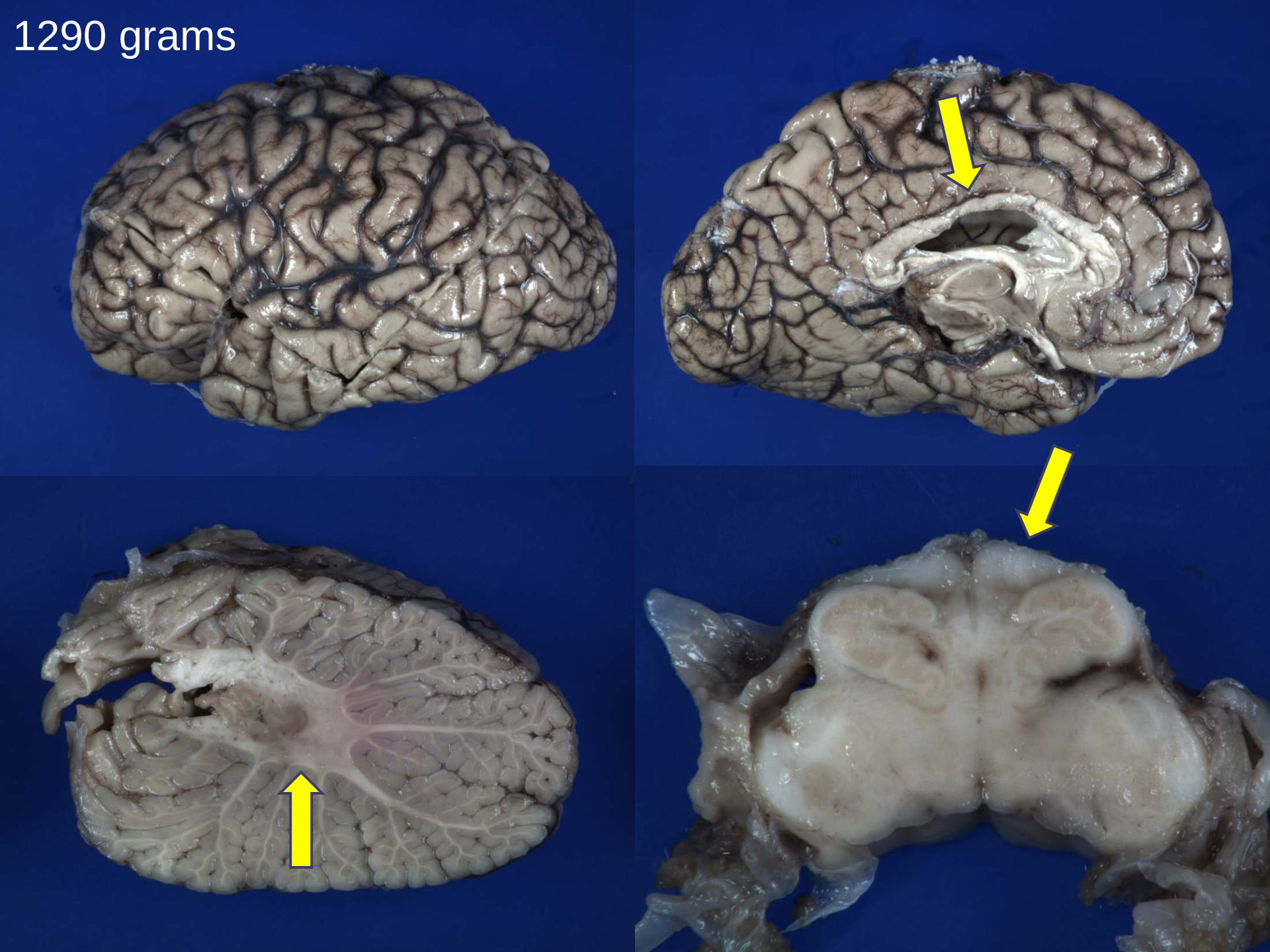
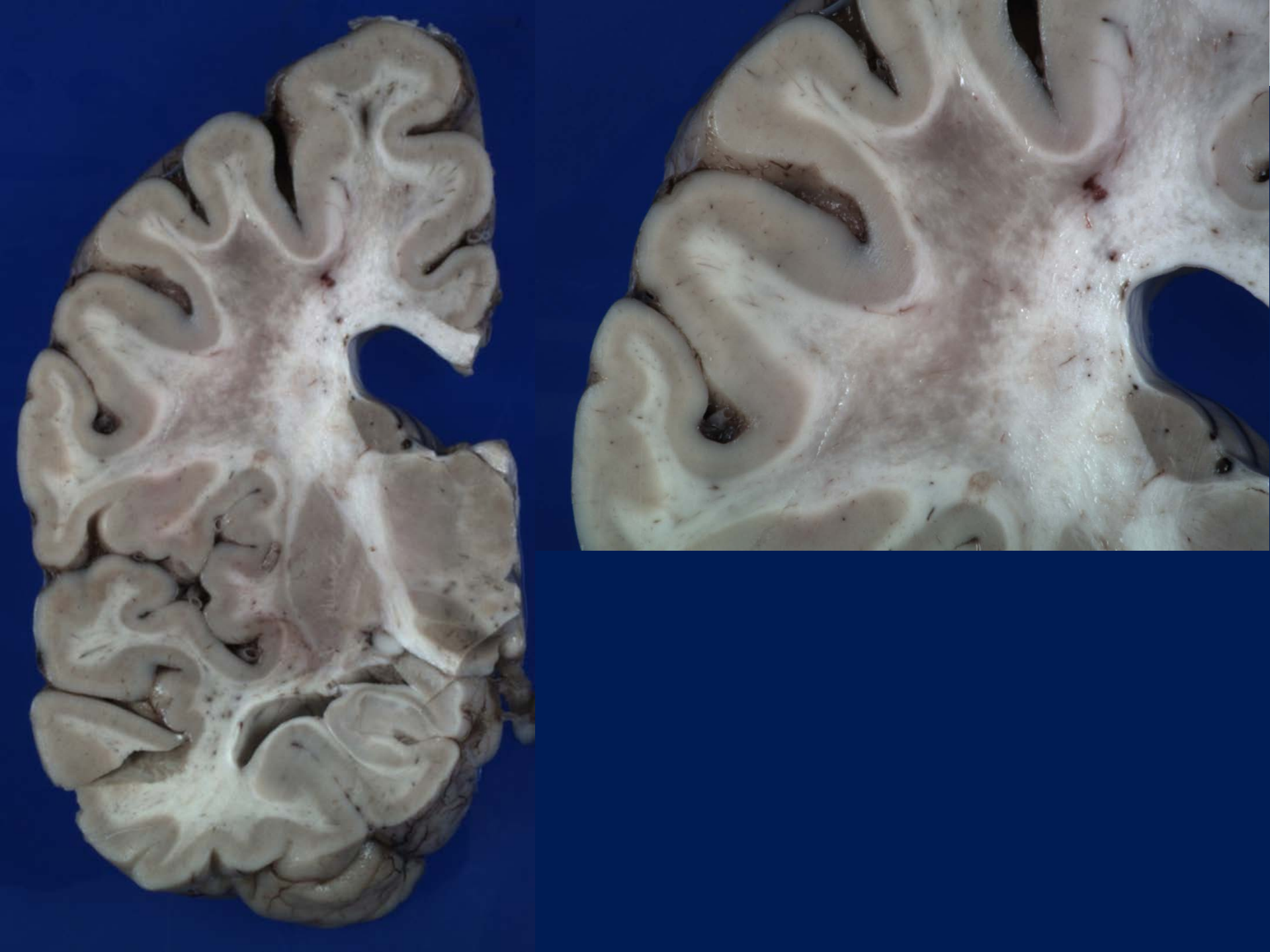
UPMC LIFE CHANGING MEDICINE

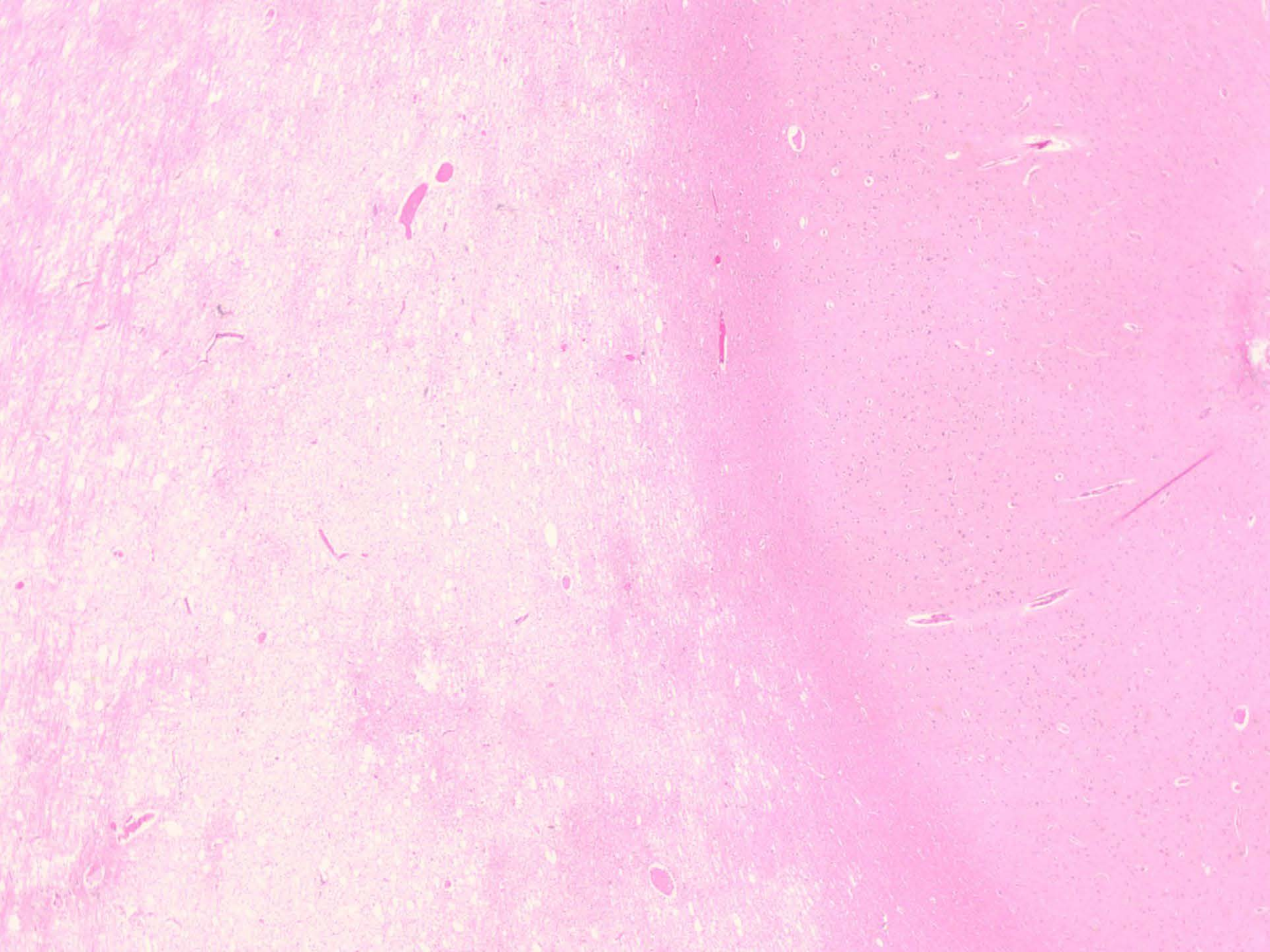
No disclosures or conflicts of interest

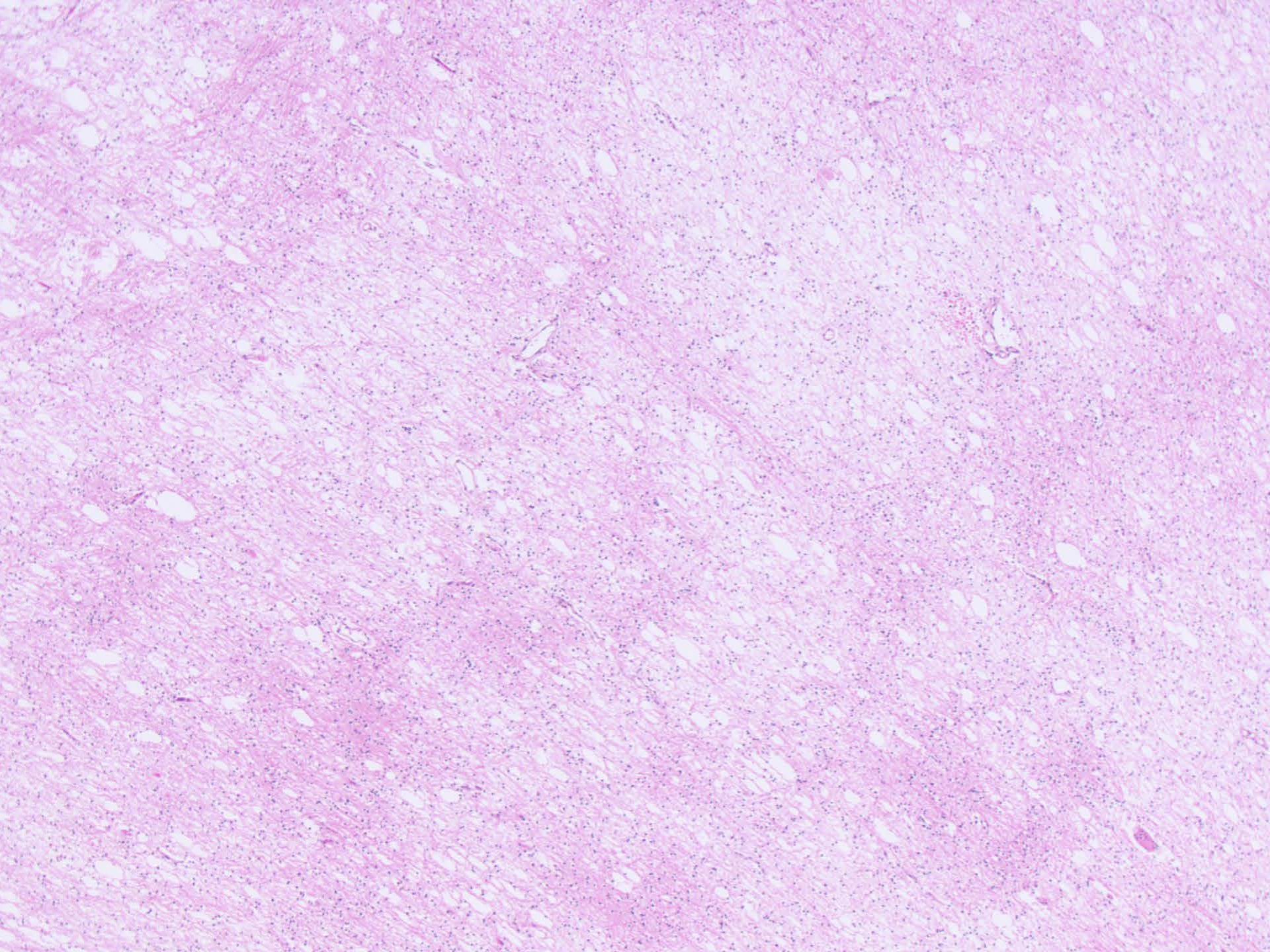
Clinical History

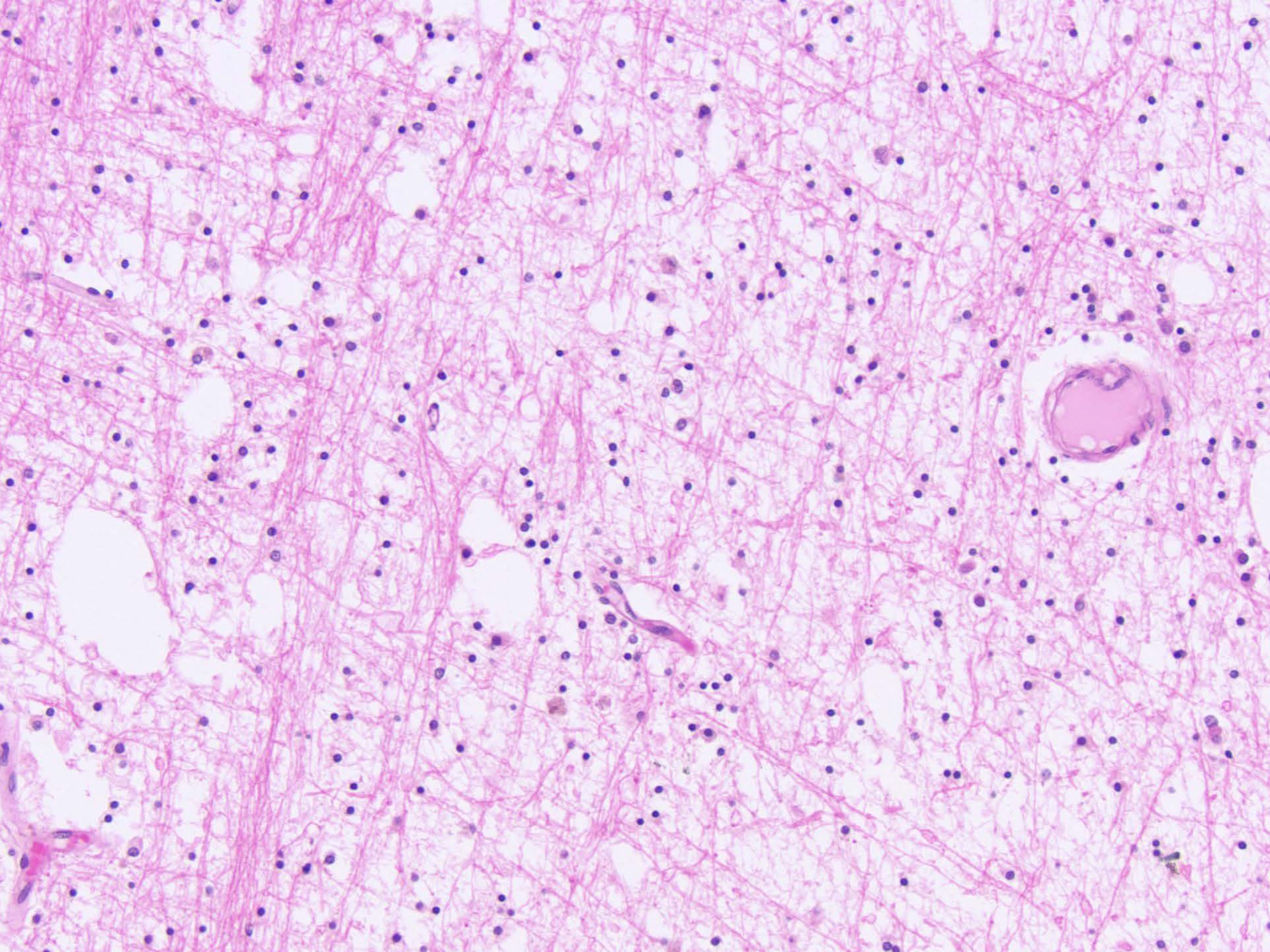
- Female patient with no significant PMH
- Initially presented with **syncopal episodes at age 49**
- CT scan: “white matter abnormalities”
- Subsequently developed gait abnormalities but remained cognitively intact
- Late 50s: could no longer walk, urinary incontinence
- Final months: short-term memory lapses
- **Died at age 61**
- Family history: father, 2/3 siblings and 1 cousin with similar disease process


1290 grams





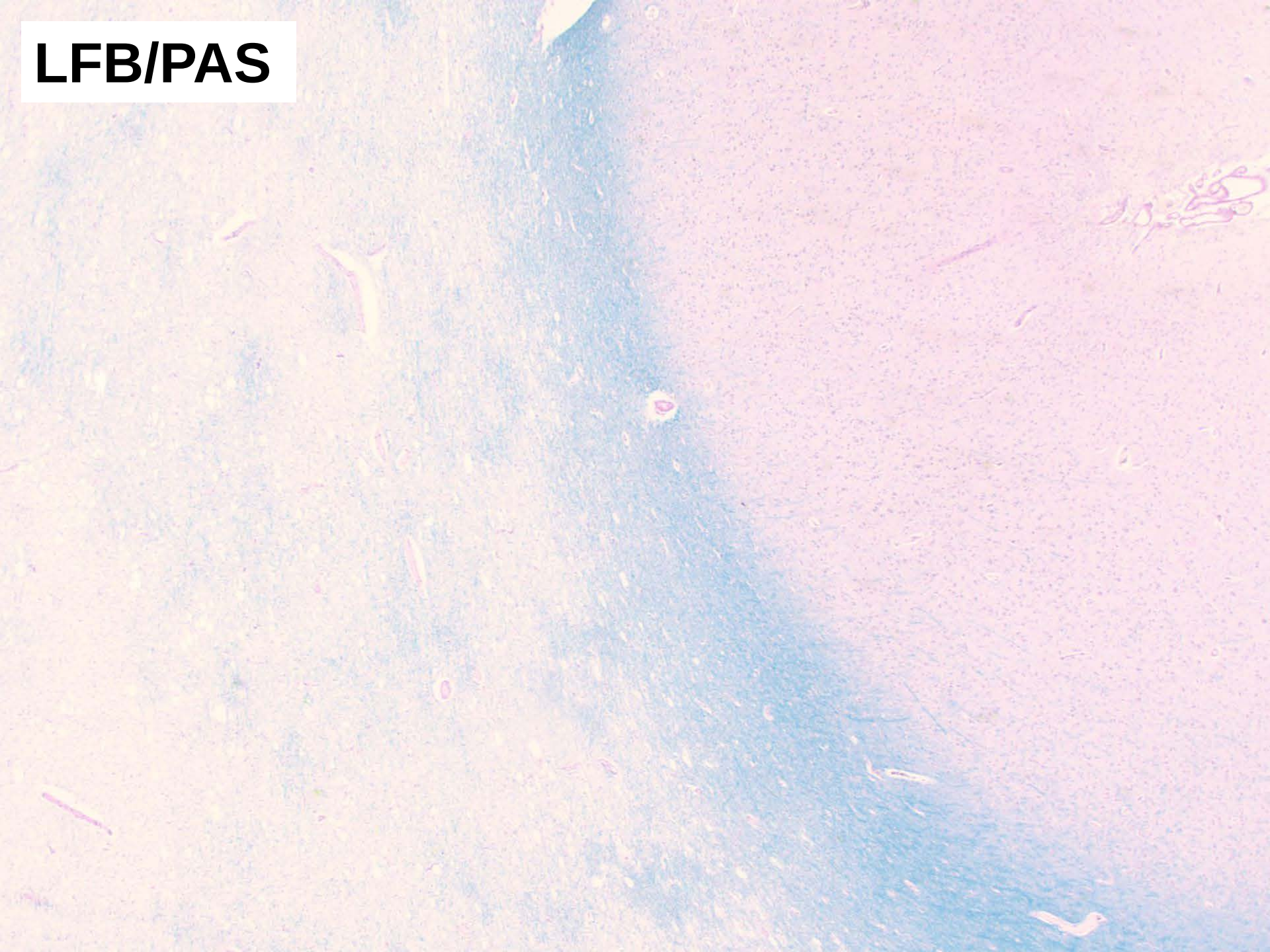


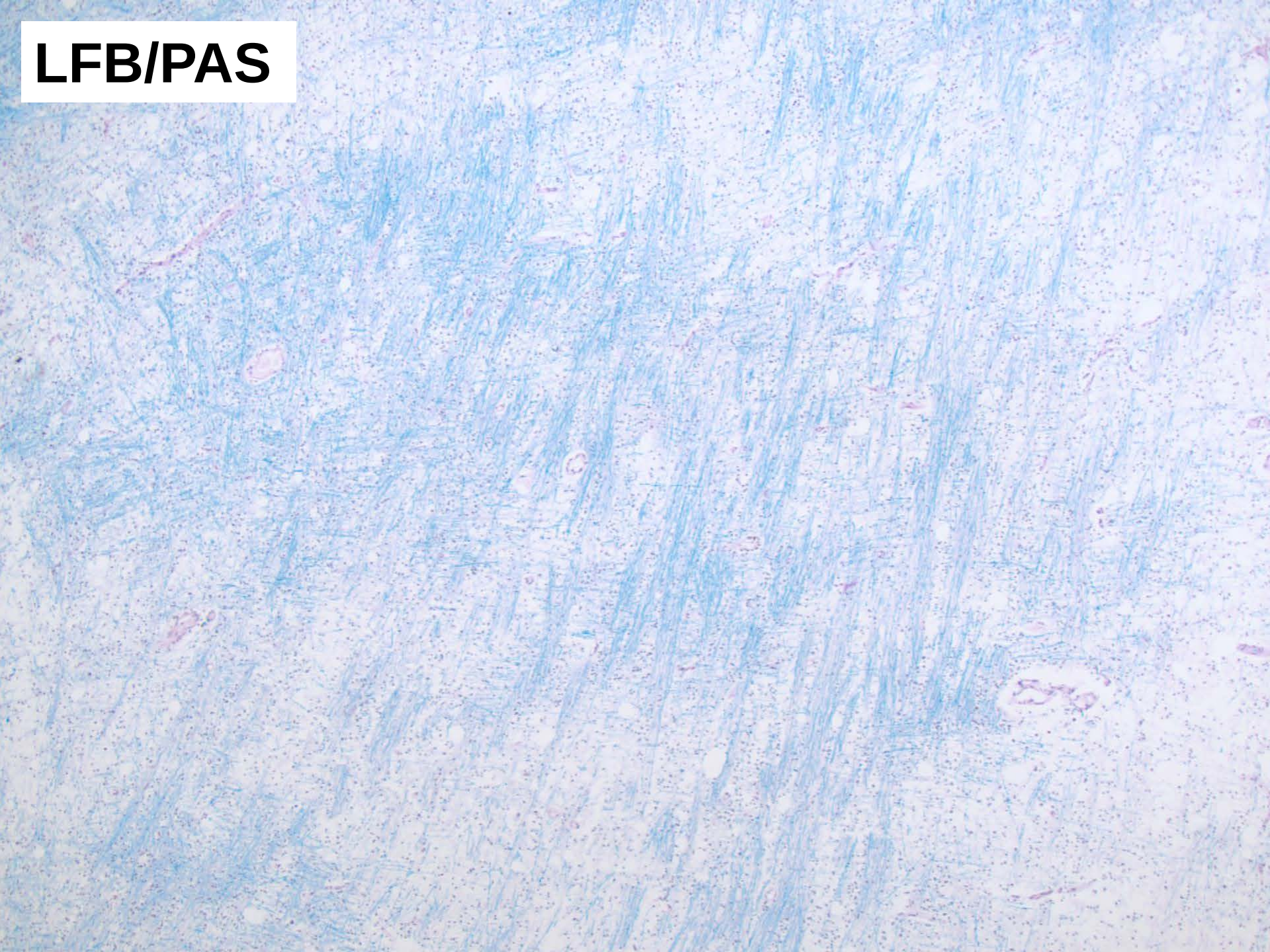


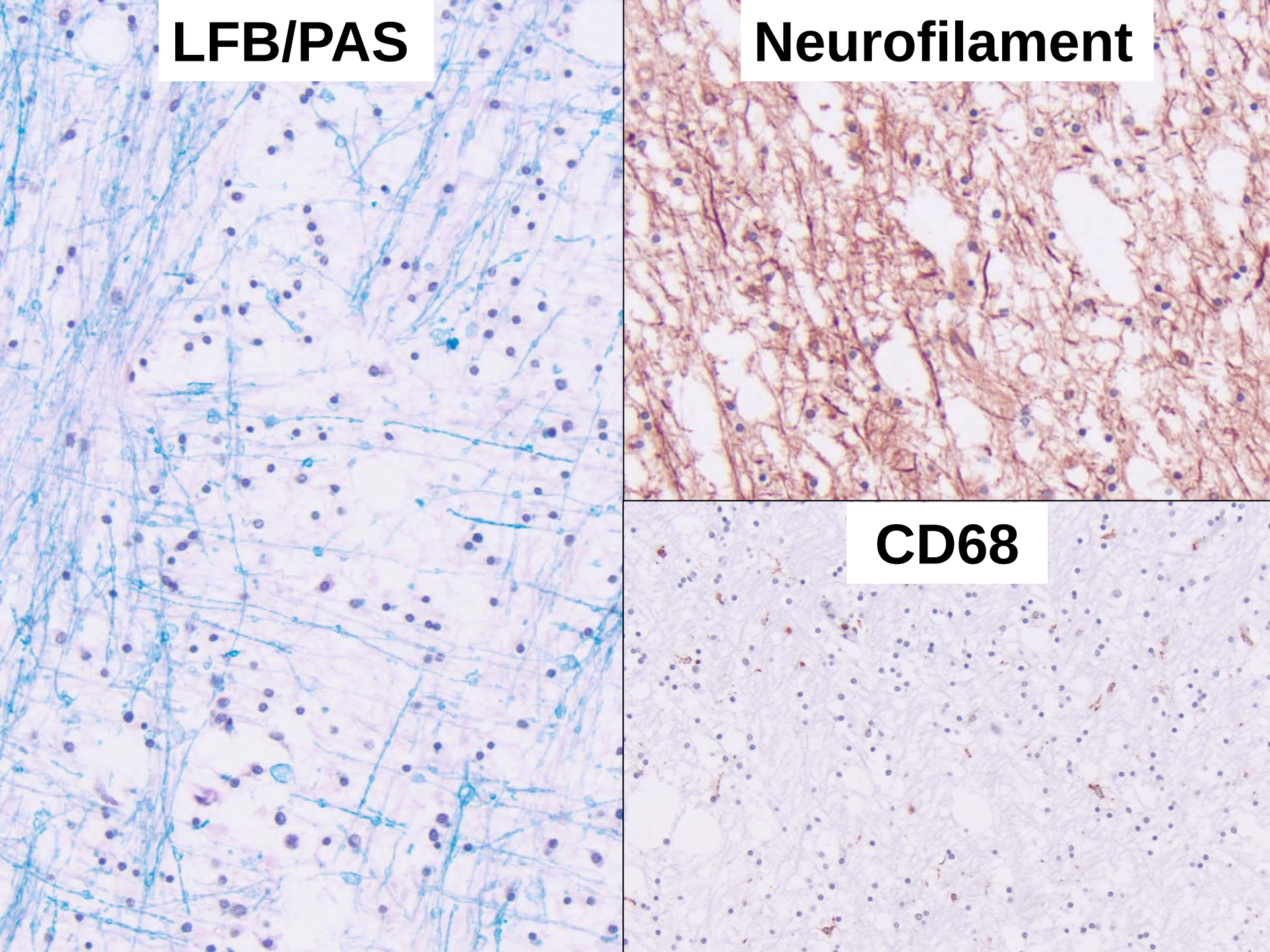
Differential Diagnosis?

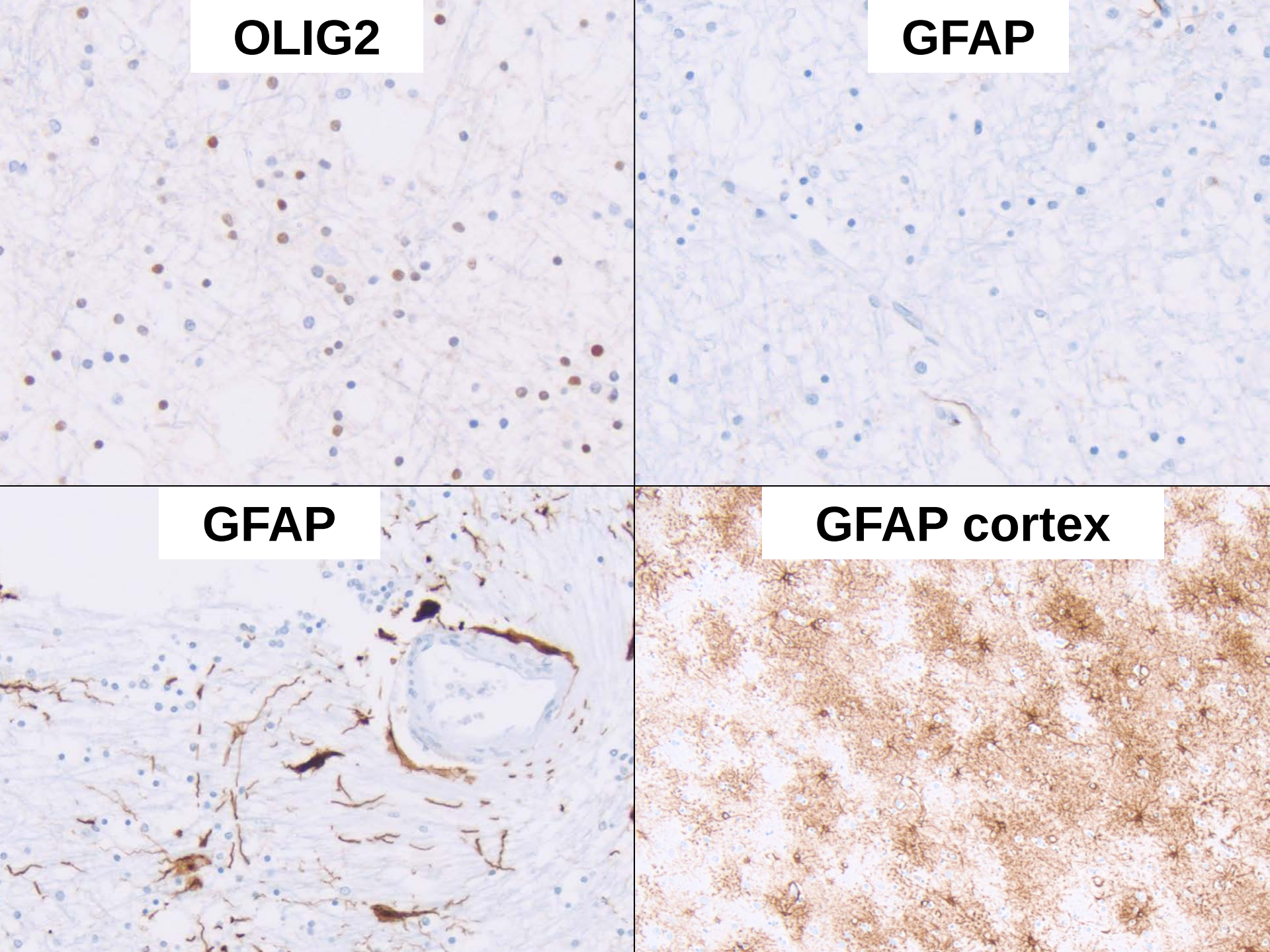
Differential diagnosis of adult-onset leukodystrophies

- Multiple sclerosis
- Adult-onset Krabbe disease
- Adult-onset Alexander disease
- Autosomal dominant leukodystrophy (ADLD)
- Adult-onset leukodystrophy with axonal spheroids (ALAS)
- Orthochromatic leukodystrophy (OLD)
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Metachromatic leukodystrophy
- Adrenoleukodystrophy/adrenomyeloneuropathy
- Pelizaeus-Merzbacher disease
- Leukoencephalopathy with vanishing white matter


LFB/PAS


LFB/PAS


LFB/PAS
Neurofilament
CD68


OLIG2
GFAP
GFAP
GFAP cortex

Autopsy findings are characteristic of her known genetic alteration:

Lamin B1 (*LMNB1*) gene duplication on chromosome 5q

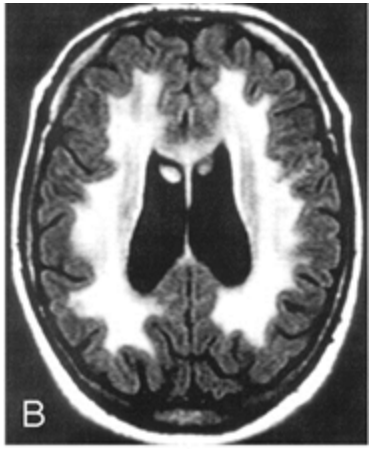
Adult-Onset Autosomal Dominant Leukodystrophy

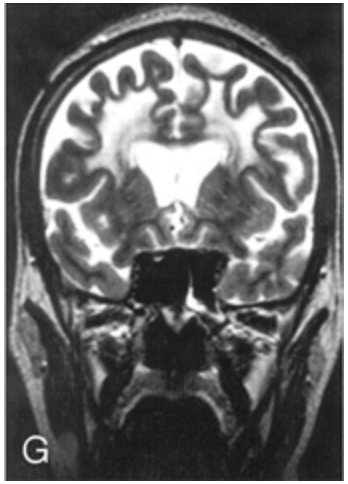
Adult-Onset Autosomal Dominant Leukodystrophy (ADLD)

- Rare, slowly progressive and fatal demyelinating disorder
- Onset in 4th to 5th decade
- AD inheritance pattern
- Clinical course:
  - Autonomic dysfunction (early)
  - Pyramidal signs (late)
  - Cerebellar signs (late)

Diagnosis/Testing

- Characteristic clinical and MRI findings
- *LMNB1* duplication (most commonly)
- Deletion upstream of *LMNB1* promoter (rarer)





Adapted from Melberg et al. AJNR 2006; 27: 904-911

Histologic findings in ADLD

"Tigroid" appearance of white matter throughout the CNS, especially the corticospinal tract, with:

- Vacuolization of neuropil
- Loss of myelin
- Relative preservation of axons
- Preservation of oligodendrocytes
- **Absence of reactive astrocytes/gliosis**

LMNB1 encodes one of the nuclear lamins

- Intermediate filament proteins located in the nuclear membrane
- Structural role
- Roles in transcription, DNA replication/repair and epigenetic regulation

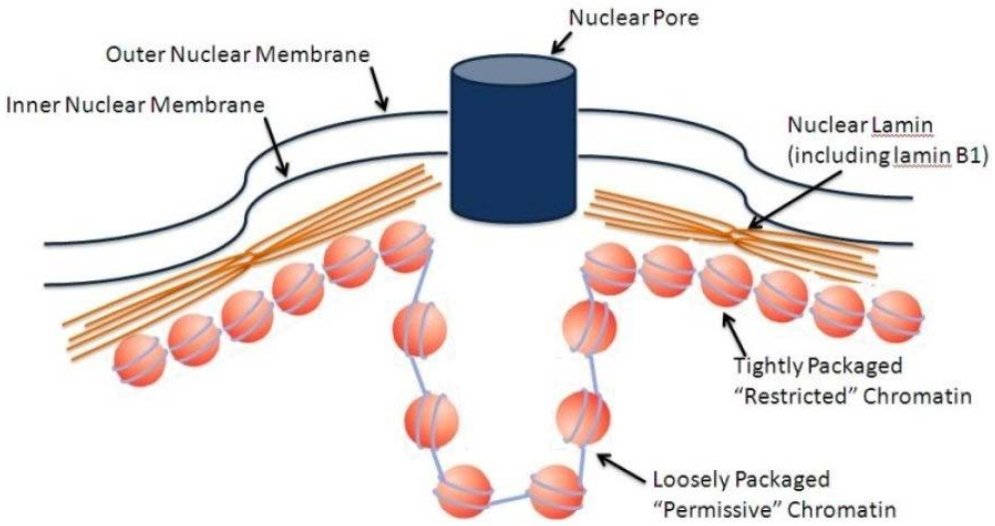
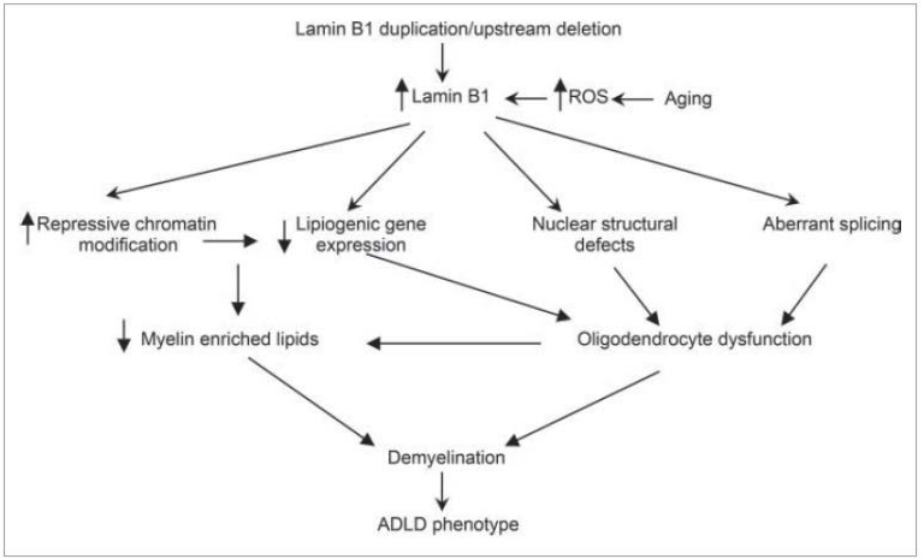


Image courtesy of Perelman School of Medicine at the University of Pennsylvania

LMNB1 duplication results in increased lamin B1 protein expression

- Pathogenesis of ADLD is unclear
  - Differential sensitivity of oligodendrocytes and astrocytes to increased lamin B1?



Padiath *Nucleus* 2016 7:6 (547-553)

- Evidence from transgenic mouse models: lamin B1 overexpression downregulates expression of lipid synthesis genes and myelin enriched lipids

- Lipid dysregulation leading to demyelination?

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