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63rd Annual Diagnostic Slide Session

2022 - Case 2

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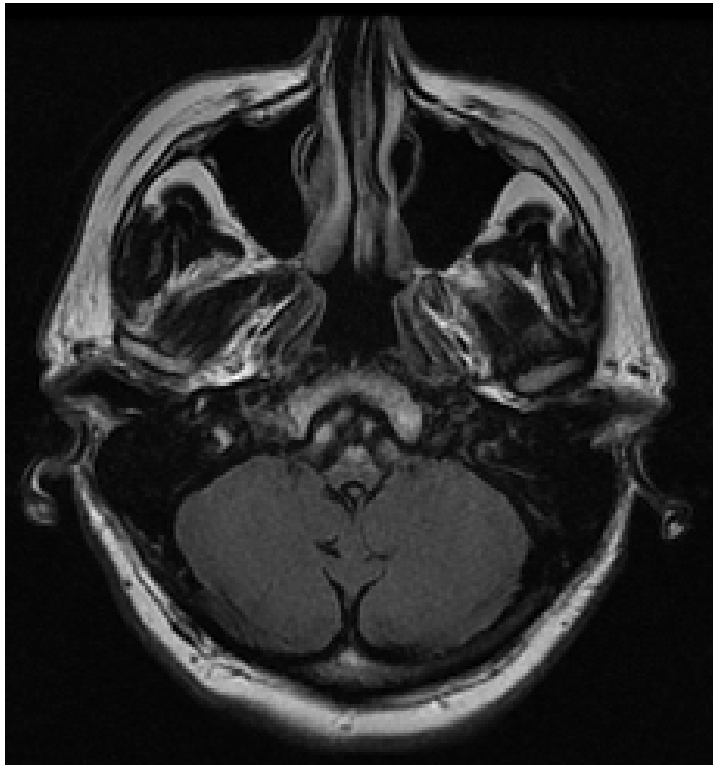
Disclosure

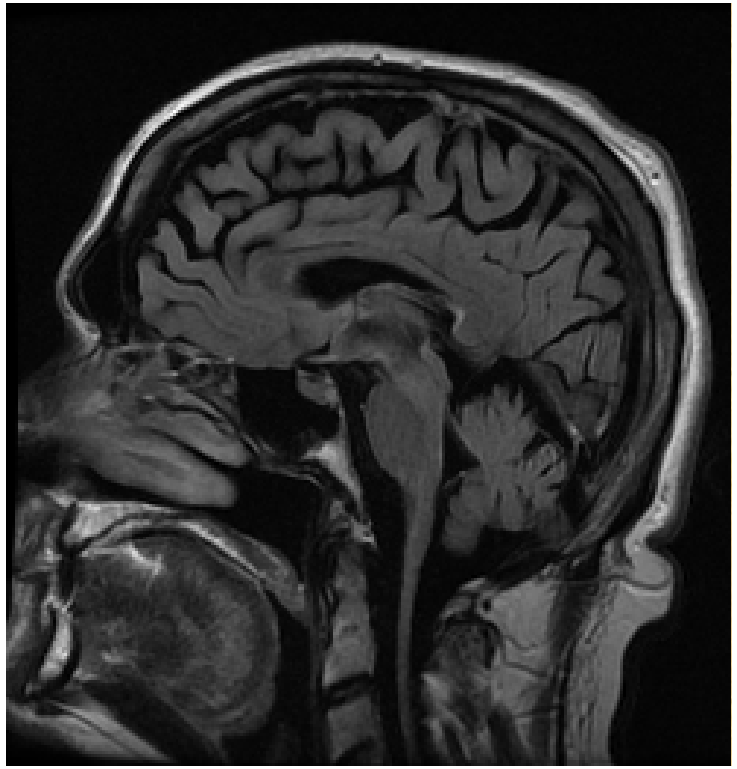
- No financial relationships to disclose

Clinical History

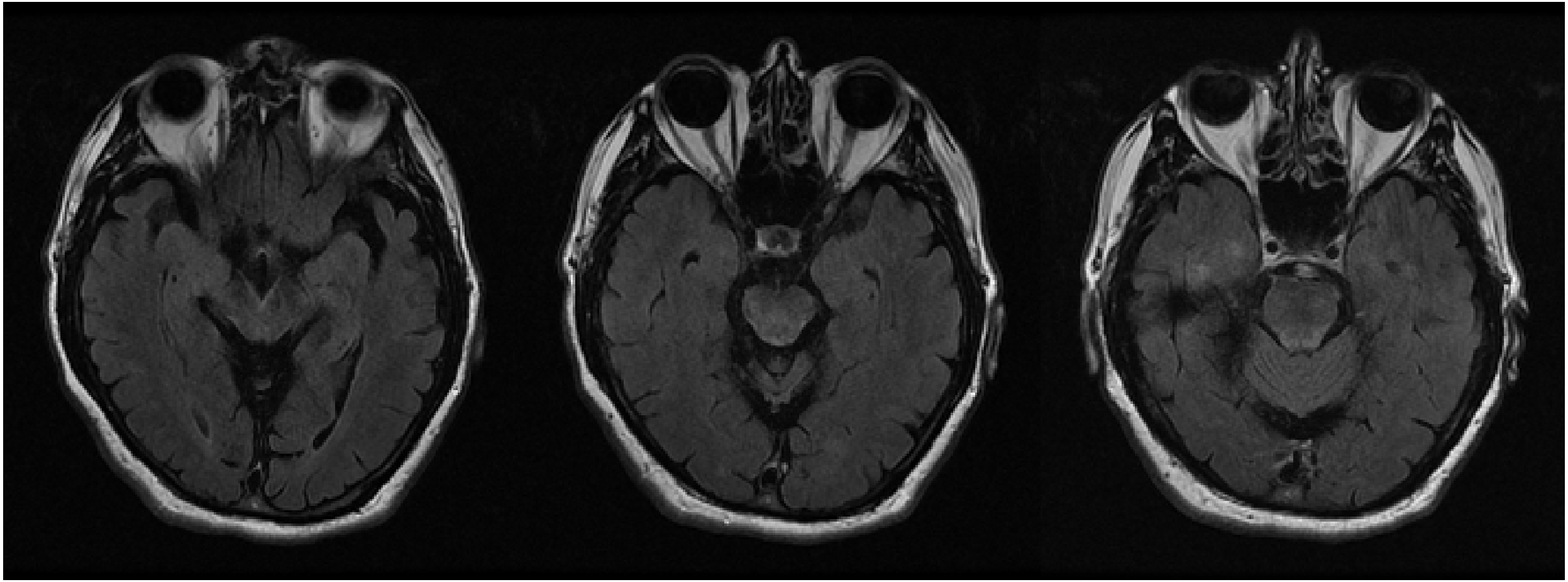
- 72-year-old man with progressive gait difficulties x 12 years
- Manifestation: ataxia, lower extremity weakness, orthostatic hypotension, neurogenic bladder, mild cognitive impairment
- (-) family history
- Brain MRI: brain atrophy, most pronounced in the medulla and upper cervical cord



(left) T2 FLAIR axial



(right) T2 FLAIR sagittal



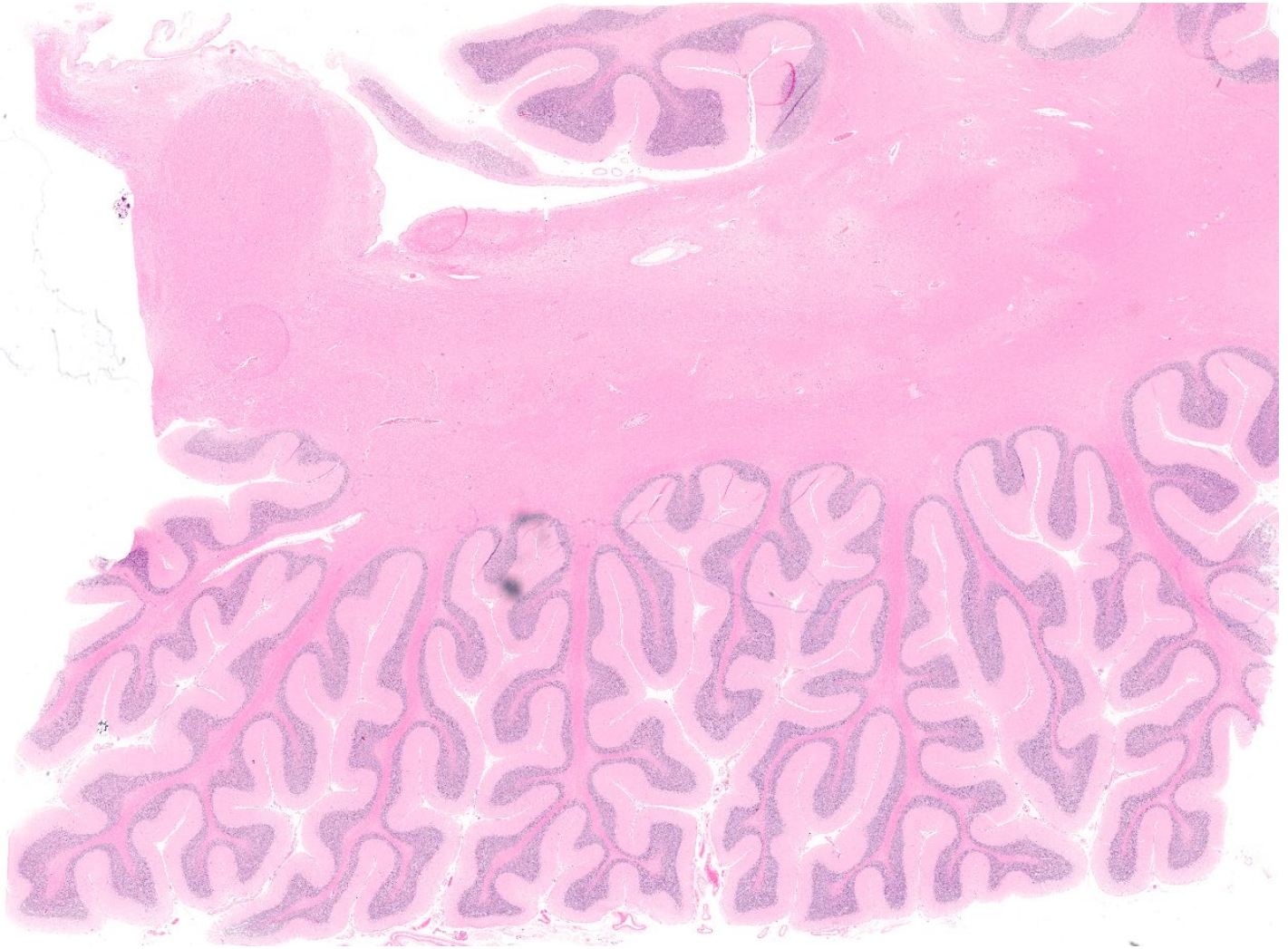
Clinical impression: multiple system atrophy, cerebellar type

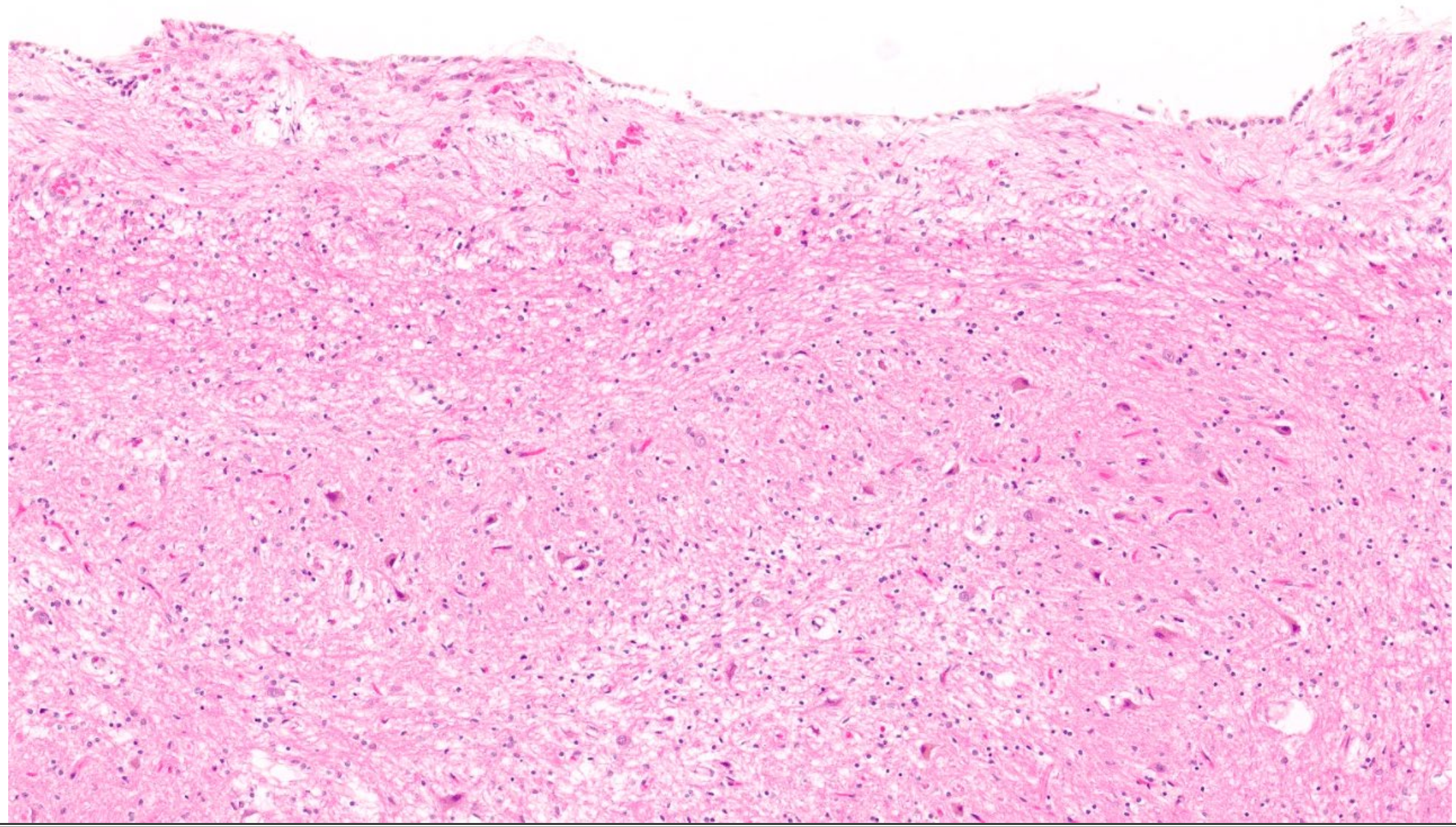
Autopsy Findings

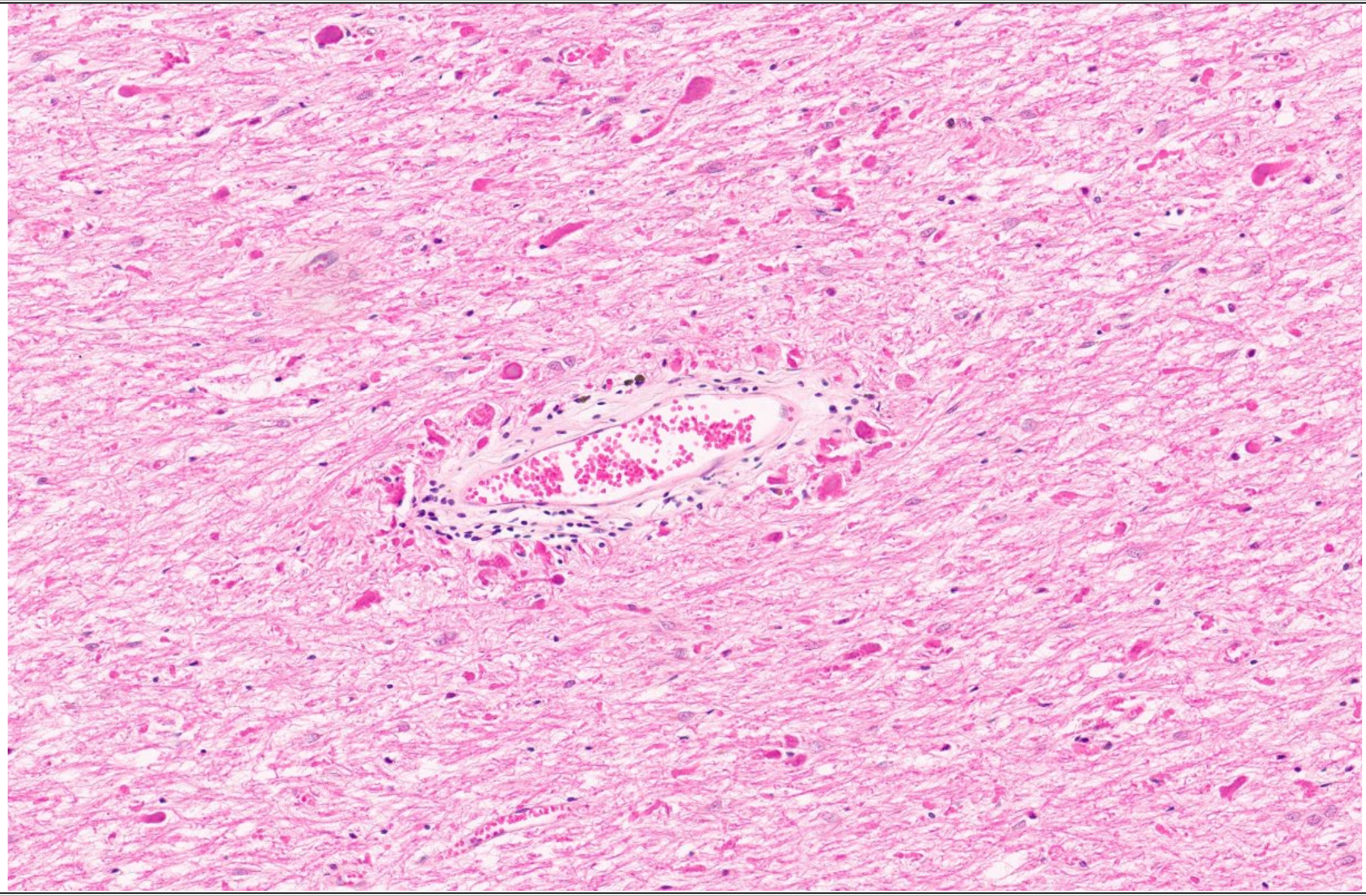
Gross Examination

- Brain weight: 1150 grams
- Mild atrophy of bilateral frontal, temporal and parietal lobes
- Disproportionate atrophy of the medulla oblongata
- (-) basal ganglia, hippocampus, substantia nigra

Microscopic Examination

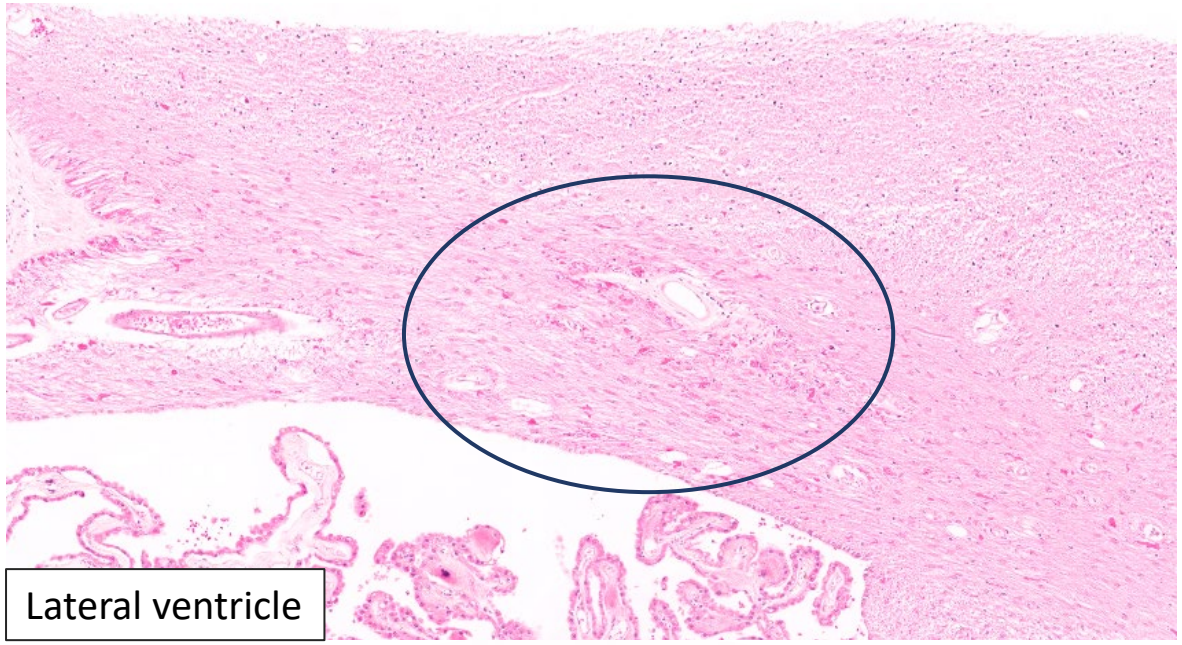




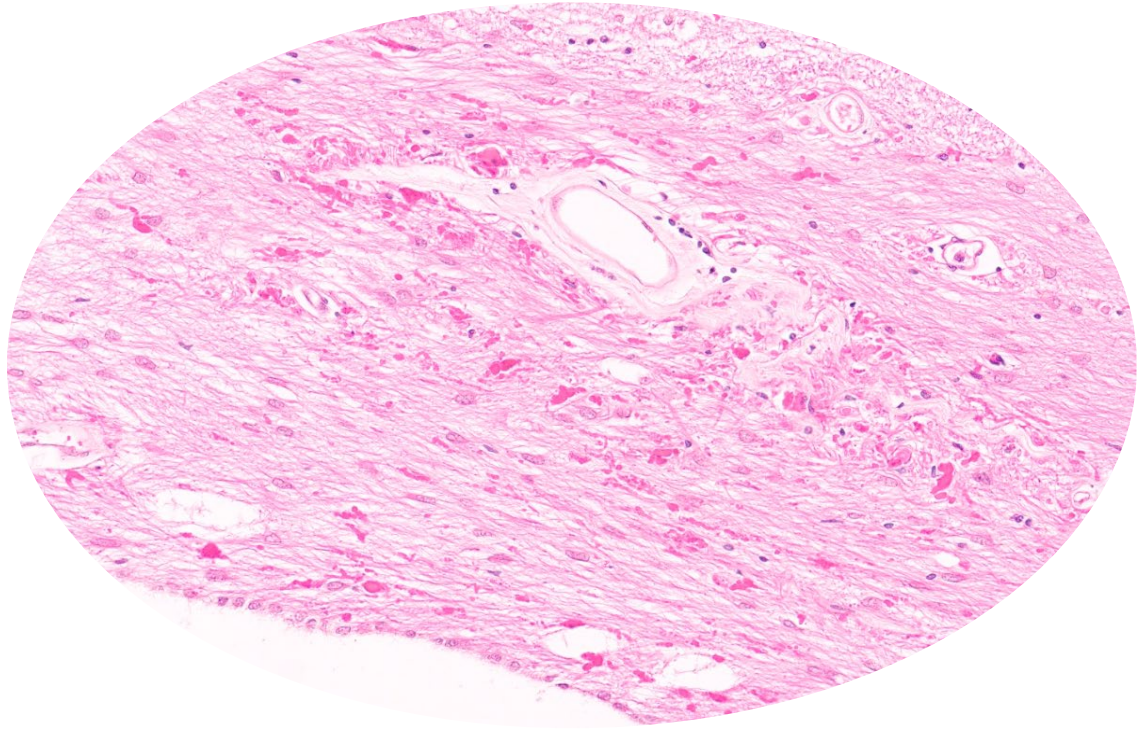


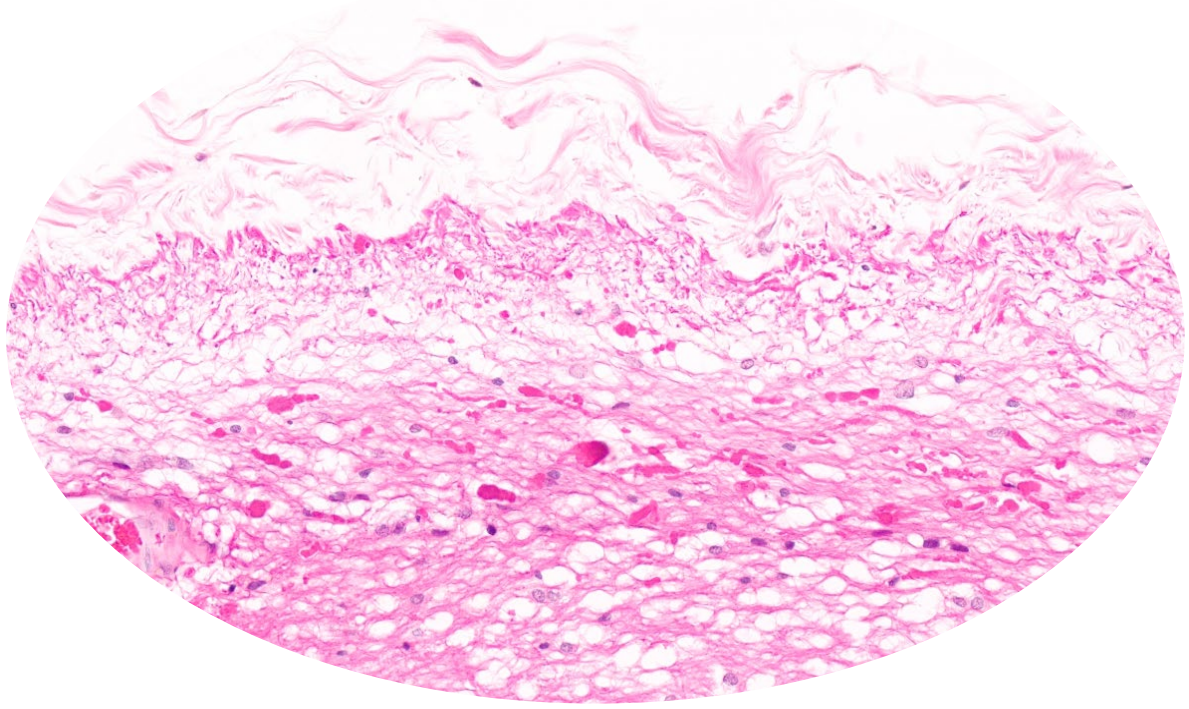
Discussion

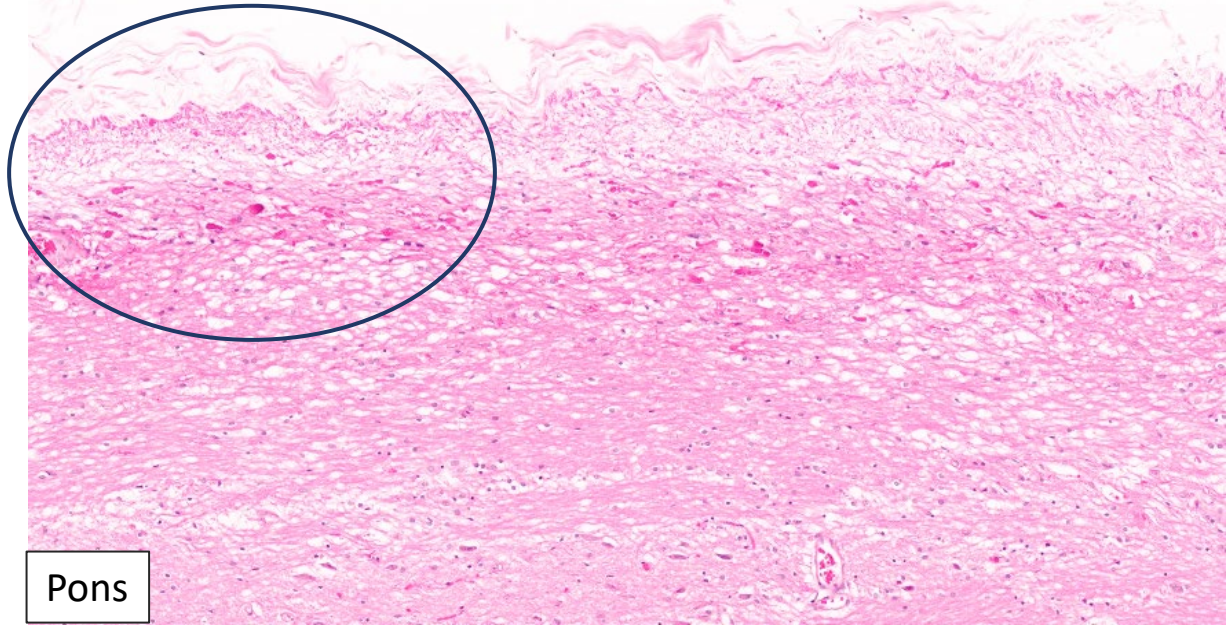
- Differential diagnosis?
- Further workup?



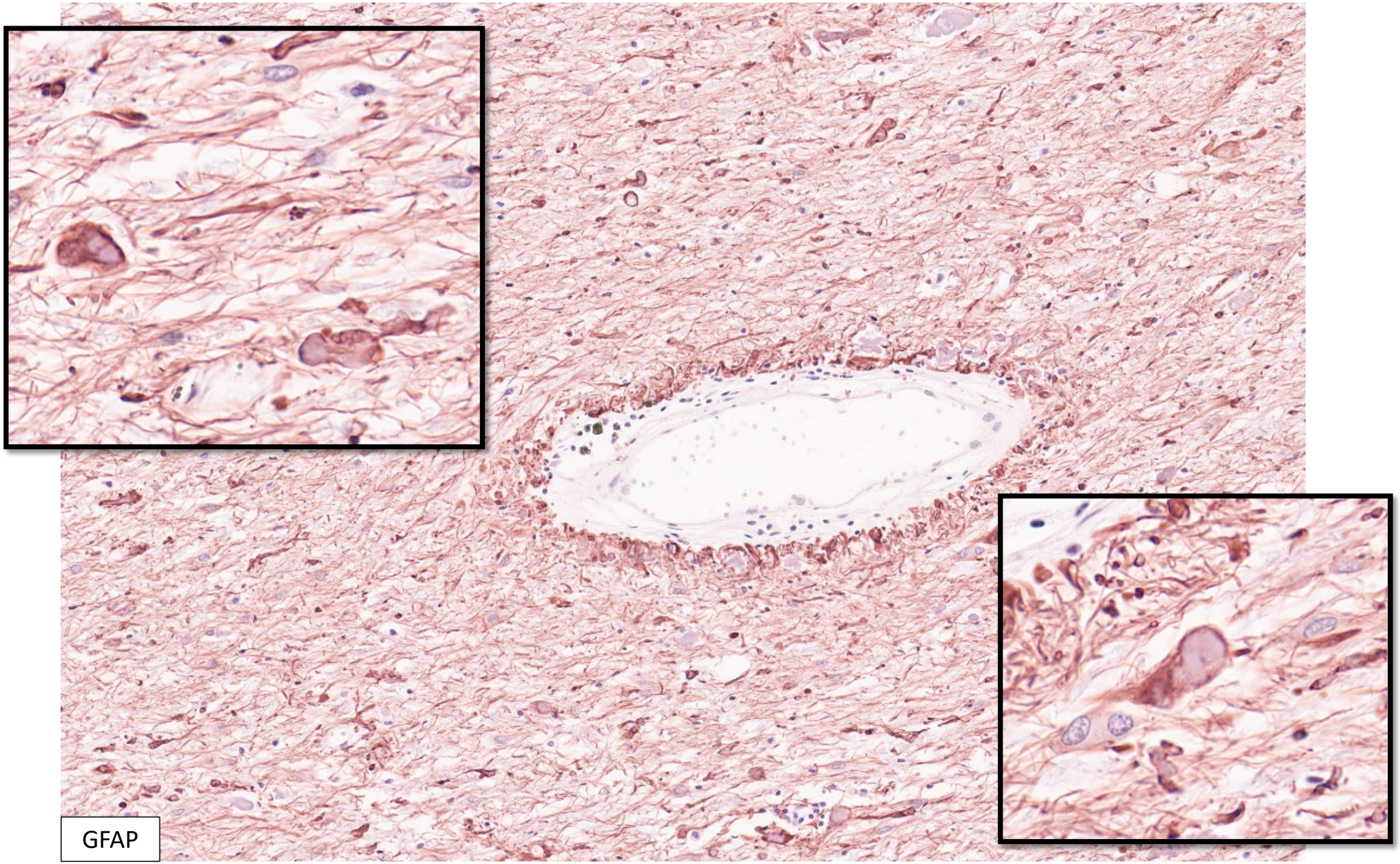
Lateral ventricle

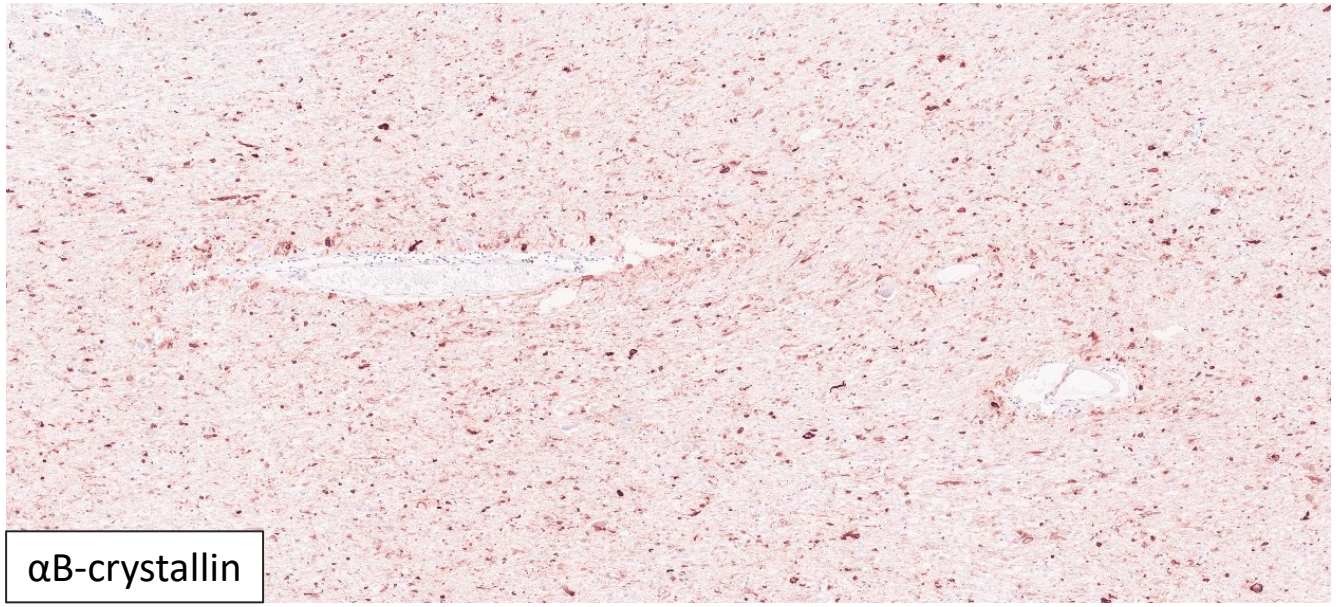




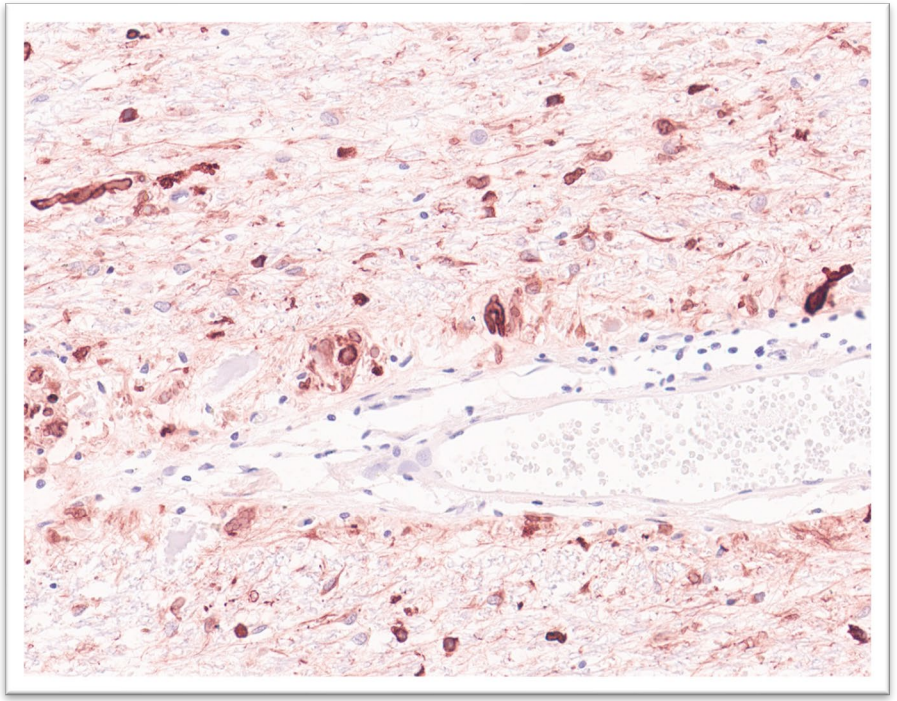


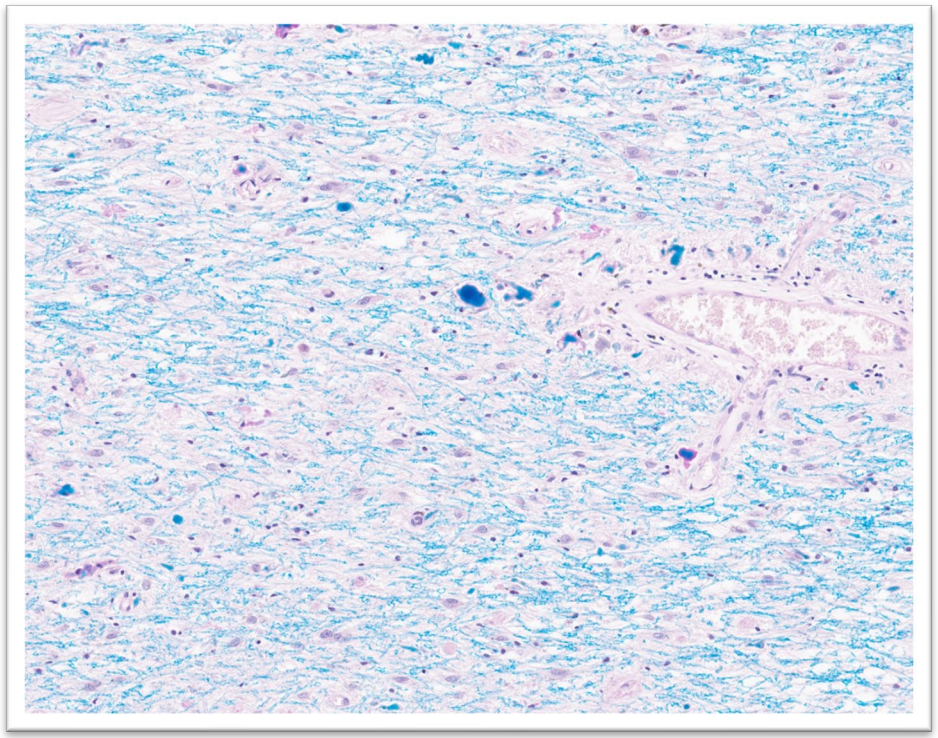
Pons

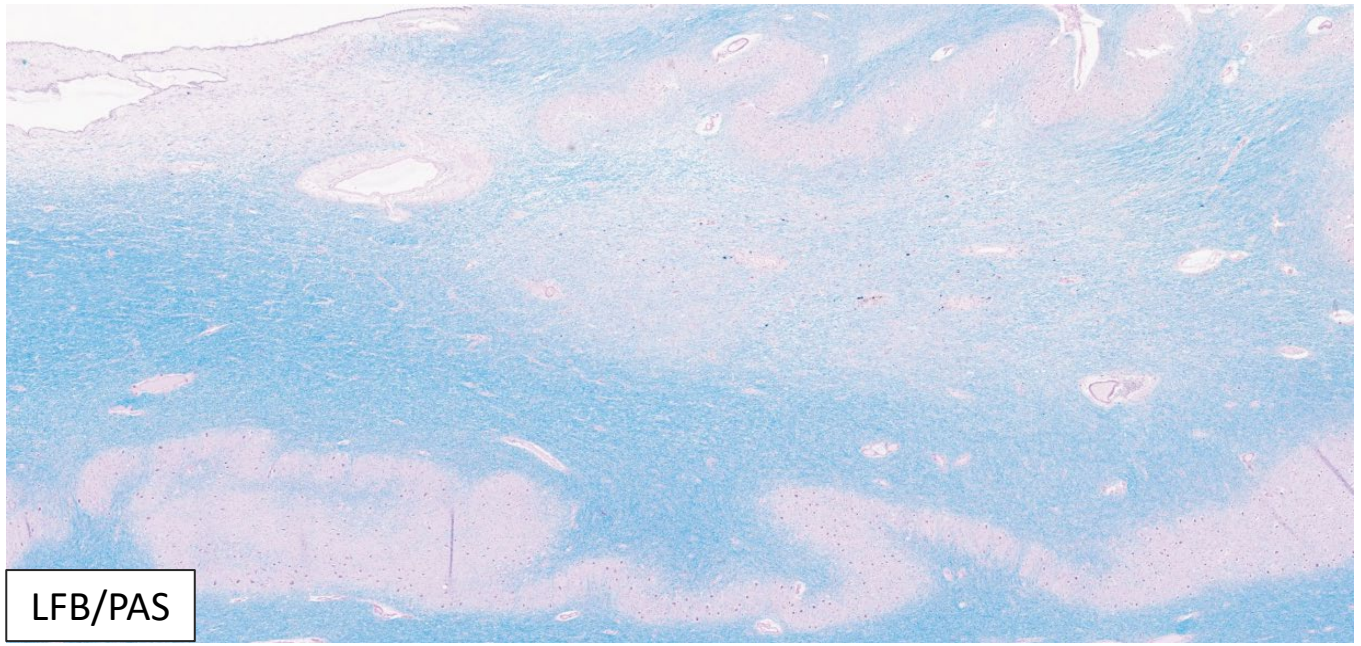

GFAP



αB-crystallin







LFB/PAS

Other Pathologic Findings

- Primary Age-Related Tauopathy (PART), BRAAK STAGE 1/6
- Limbic-Predominant, Age-Related TDP43 Encephalopathy (LATE), STAGE 2/3
- Atherosclerosis, Mild
- Remote microinfarct, subiculum

Pertinent Negatives

- No Lewy body pathology or other synucleinopathy
- No amyloid deposition
- No evidence of neoplastic process

Whole Genome Sequencing

GFAP

- c.469G>A (p.D157N)
- c.1371-177A>G

Benign/Likely Benign

Other genetic variants

Gene	Exon/Intron	Nucleotide Change	Zygosity	Variant Classification
AMACR	exon	c.154T>C (p.S52P)	heterozygous	LP
KIF1A	exon	c.2766G>C (p.Q922H)	heterozygous	VUS
POU4F1	exon	c.365C>T (p.S122L)	heterozygous	VUS
PLEC	intron	c.2059-44C>T	heterozygous	VUS
PLEC	intron	c.194-2263C>T	heterozygous	VUS
GAN	intron	c.167+458C>T	heterozygous	VUS
GAN	intron	c.633+336C>G	heterozygous	VUS

GFAP binding partners

FINAL NEUROPATHOLOGIC DIAGNOSIS:

LEUKOENCEPHALOPATHY WITH ROSENTHAL FIBERS, MOST CONSISTENT WITH ADULT-ONSET ALEXANDER DISEASE

Alexander Disease

- A rare autosomal dominant leukodystrophy, most common in infants and very young children
- Adult subtype:
  - Mostly sporadic, with predilection for infratentorial involvement
  - Presentations: bulbar symptoms (e.g. dysphagia, dysphonia, palatal myoclonus), ataxia, spastic paraparesis, dysautonomia (e.g. orthostatic hypotension, urinary retention)
  - Favorable prognosis (median survival of 25 years)
- Juvenile subtype: intermediate between infantile and adult forms
- Histopathological hallmark: aggregation of Rosenthal fibers, particularly in subpial, subependymal and perivascular

Pathogenic variant of GFAP in approximately 95% of cases

- gain-of-function point mutations in vast majority
- rare in-frame insertions/deletions, truncation and frameshift mutations, splicing alterations

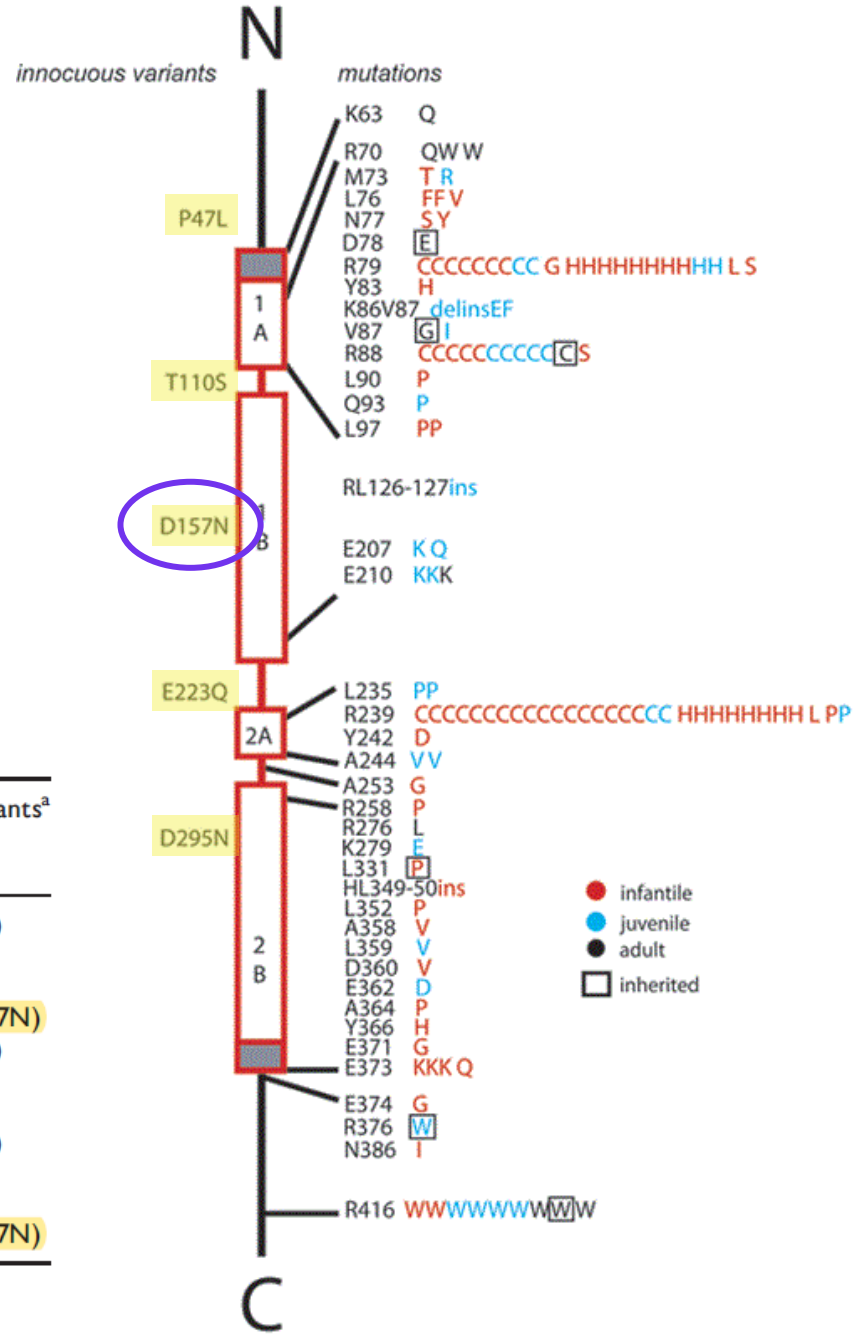
doi:10.1093/brain/awn178 *Brain* (2008), **131**, 2321–2331

Adult-onset Alexander disease: a series of eleven unrelated cases with review of the literature

Davide Pareyson,[1] Roberto Fancellu,[1] Caterina Mariotti,[1] Silvia Romano,[2] Andrea Salmaggi,[3] Francesco Carella,[4] Floriano Girotti,[5] Grazietta Gattellaro,[6] Maria Rita Carriero,[7] Laura Farina,[6] Isabella Ceccherini[8] and Mario Savoiardo[6]

Table 3 Missense variants of the *GFAP* gene in the present AOAD series

Patient	Missense mutations				Additional coding variants[a]
	Exon	Nucleotide change	Aminoacid substitution	Reference	
1	6	c.1076T>C	p.L359P	Romano *et al.*, 2007[b]; Caroli *et al.*, 2007[b]	Ex1: c.14IG>A (p.P47P)
2	8	c.1178G>T	p.S393I	Salmaggi *et al.*, 2007[b]	
3	8	c.1246C>T	p.R416W	Waisman Center and Caroli *et al.*, 2007[b]	
4	1	c.209G>A	p.R70Q	Caroli *et al.*, 2007[b] and Sechi *et al.*, 2008[b]	Ex2: c.469G>A (p.D157N)
5	3	c.613G>A	p.E205K	This study	Ex1: c.14IG>A (p.P47P)
6	1	c.208C>T	p.R70W	Waisman Center and Caroli *et al.*, 2007[b]	
7	6	c.994G>A	p.E332K[c]	Balbi *et al.*, 2008	
8	3	c.613G>A	p.E205K	This study	Ex1: c.14IG>A (p.P47P)
9	8	c.1193C>A	p.S398Y	This study	
10	1	c.382G>A	p.D128N	This study	
11	–	–	–		Ex2: c.469G>A (p.D157N)



ORIGINAL ARTICLES

Glial Fibrillary Acidic Protein Mutations in Infantile, Juvenile, and Adult Forms of Alexander Disease

Rong Li, MD,[1] Anne B. Johnson, MD,[2] Gajja Salomons, PhD,[3] James E. Goldman, MD, PhD,[4] Sakkubai Naidu, MD,[5] Roy Quinlan, PhD,[6] Bruce Cree, MD, PhD, MCR,[7] Stephanie Z. Ruyle, MD,[8] Brenda Banwell, MD,[9] Marc D'Hooghe, MD,[10] Joseph R. Siebert, PhD,[11,12] Cristin M. Rolf, MD,[13,14] Helen Cox, MB, ChB,[15] Alyssa Reddy, MD,[16] Luis González Gutiérrez-Solana, MD,[17] Amanda Collins, FRCP,[18] Roy O. Weller, MD, PhD,[19] Albee Messing, VMD, PhD,[20] Marjo S. van der Knaap, MD,[3] and Michael Brenner, PhD[1]

Ann Neurol 2005;57:310–326

Table 4. GFAP Polymorphisms Detected

Polymorphism[a]	Frequency[b]	Present (patient no.)	Absent (patient no.)
Exon 1			
c140C > T (P47L)	1/76 (1.3%)	20	1–19, 22, 26–29, 31–40, 42–44
c141G>A (P47P)	2/76 (2.6%)	19, 29	1–18, 20, 22, 26–28, 31–40, 42–44
c343G>A (V115I)	1/176 (0.6%)	42	1–20, 22, 26–29, 31–40, 43, 44 and 50 controls
Exon 2			
c469G>A (D157N)	6/150 (4.0%)	35, 5 controls	2, 9, 11, 16–20, 22, 26–29, 31–33, 36–40, 42–44 and 45 controls

What about the binding partners of GFAP?

- **plectin (PLEC)**
- **gigaxonin (GAN)**

} Intronic VUS in our patient

- alpha B-crystallin (CRYAB)
- heat shock protein 27 (HSP27)

letter

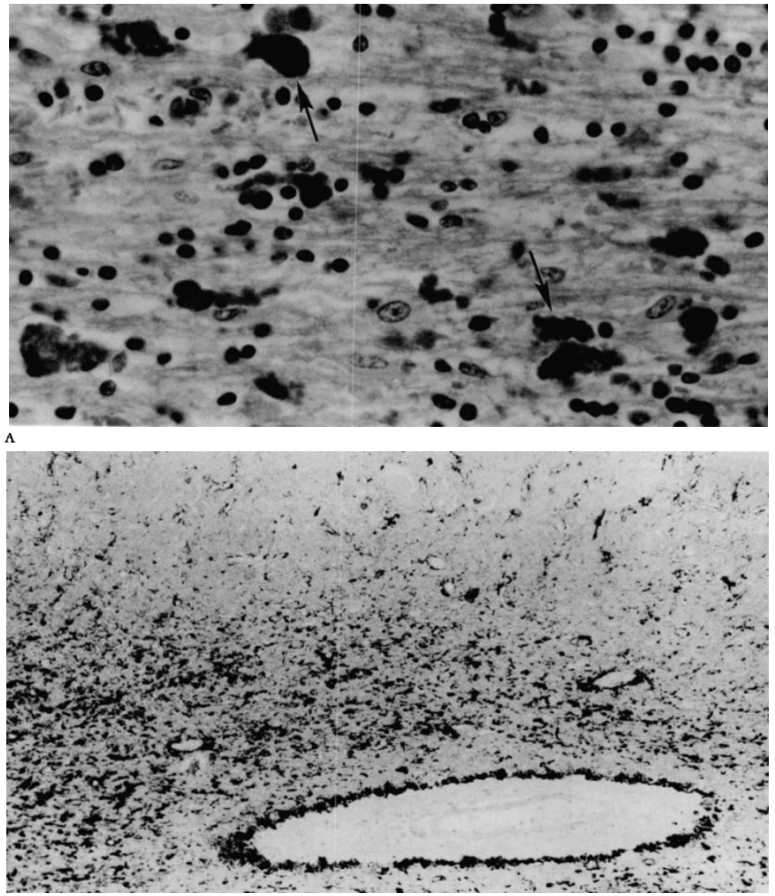
The gene encoding gigaxonin, a new member of the cytoskeletal BTB/kelch repeat family, is mutated in giant axonal neuropathy

Pascale Bomont[1], Laurent Cavalier[2], François Blondeau[1], Christiane Ben Hamida[3], Samir Belal[3], Meriem Tazir[4], Ercan Demir[5], Haluk Topaloglu[5], Rudolf Korinthenberg[6], Beyhan Tüysüz[7], Pierre Landrieu[8], Fayçal Hentati[3] & Michel Koenig[1]

Nat Genet. 2000 Nov;26(3):370-4

Giant Axonal Neuropathy: Correlation of Clinical Findings with Postmortem Neuropathology

C. Thomas, MD,* S. Love, MB, BCh, PhD,*
H. C. Powell, MD,* P. Schultz, MD,†
and P. W. Lampert, MD*



Ann Neurol 22:79-84, 1987

Take Home Messages

- Alexander disease can occasionally occur in adults and present with different clinical and radiological pictures.
- The manifestations may resemble other neurodegenerative disorders.
- There are no pathogenic GFAP mutations detected in a small percentage (~5%) of the cases.
- Other genetic or non-genetic contributors may exist; further studies are required.

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