AANP Diagnostic Slide Session 2021

Case #4

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The authors have no disclosures

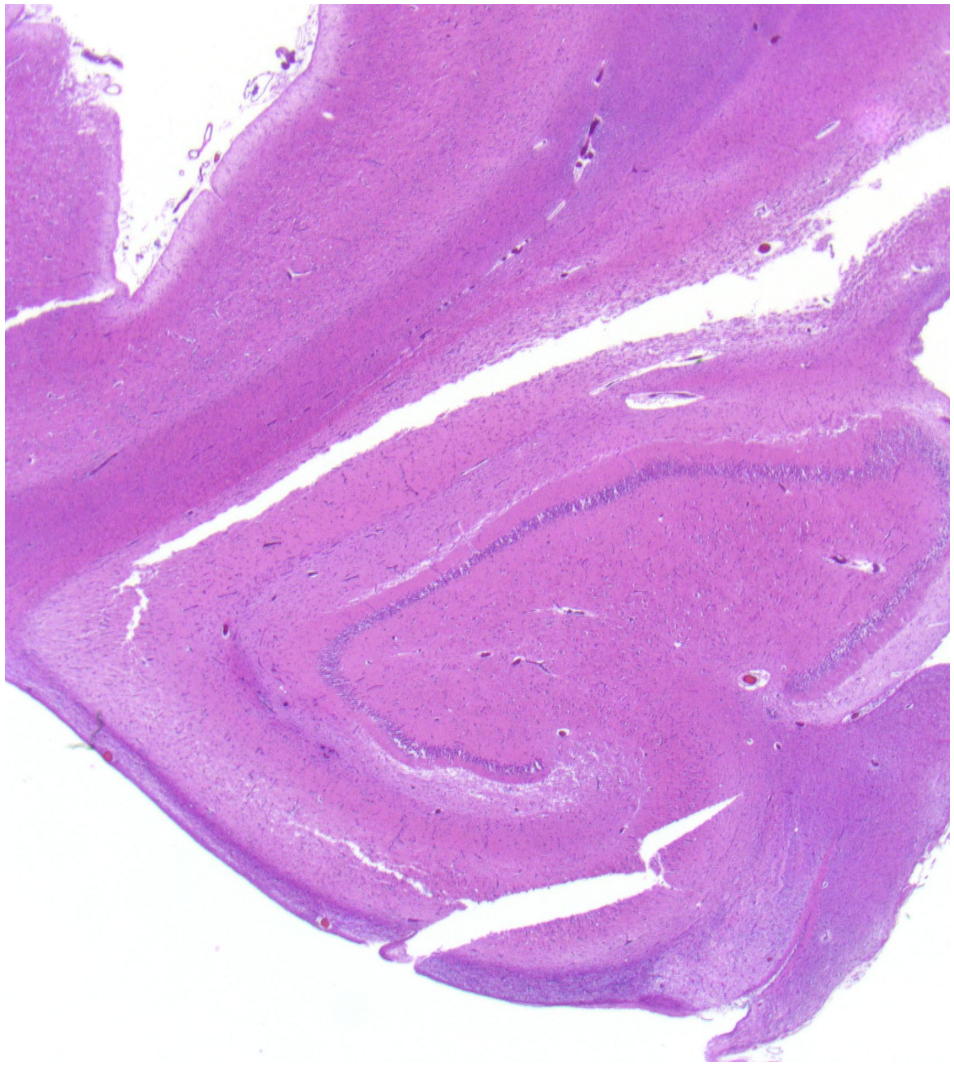
Clinical History

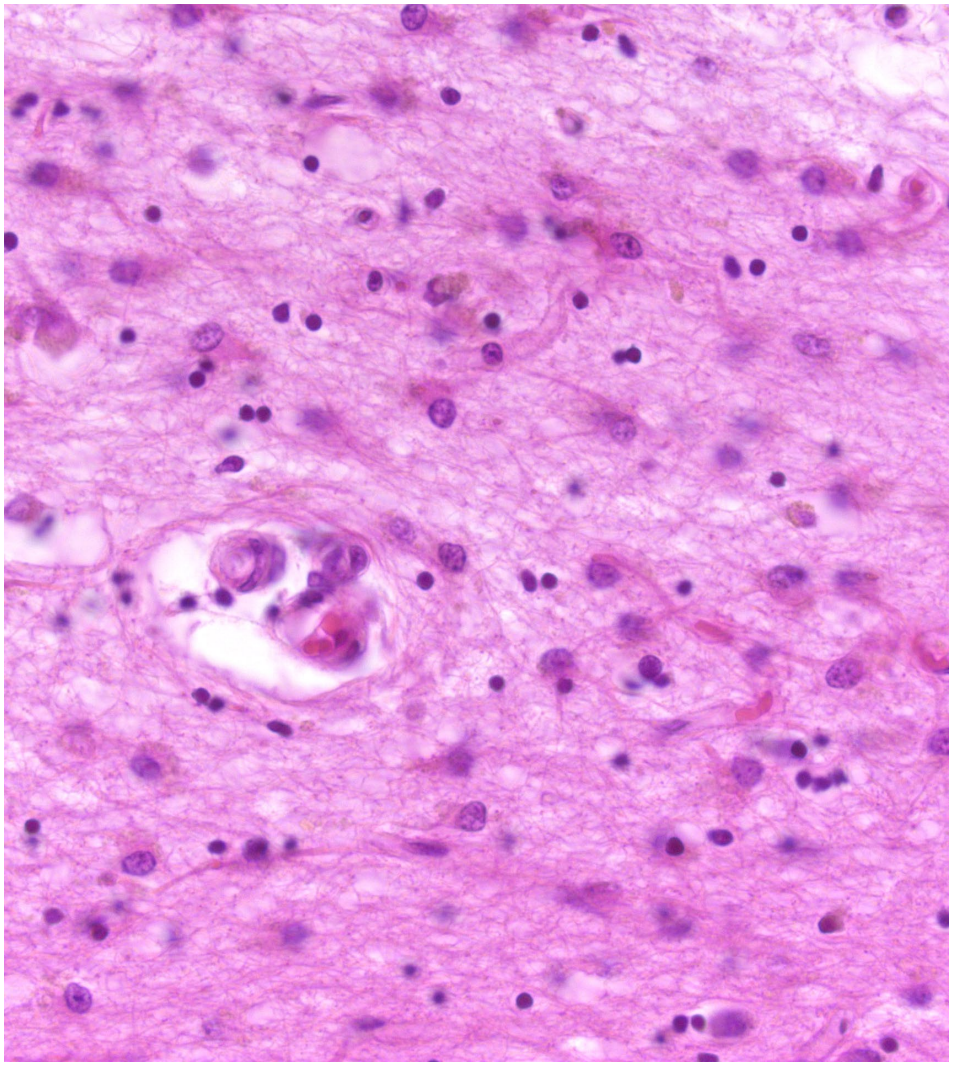
- 67-year-old woman died with clinical diagnosis of behavioral variant of frontotemporal dementia (bvFTD)
  - Progressive cognitive and personality changes starting in her late 50s
  - Several seizure episodes (without prior seizure history)
- FH: Parkinson's disease with dementia, primary progressive aphasia, corticobasal syndrome

Autopsy Findings

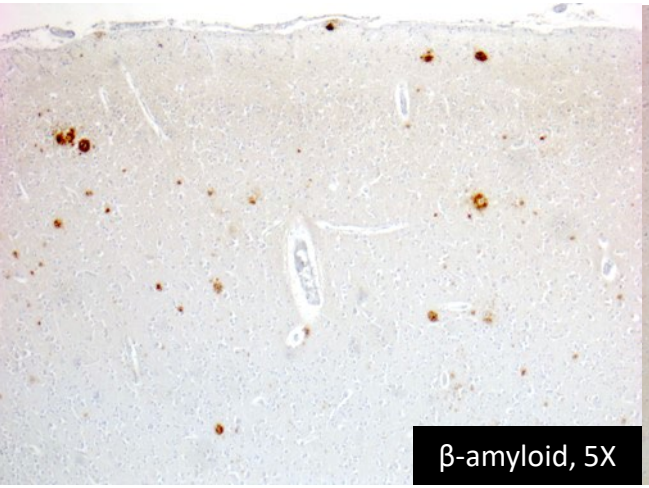
- Gross:
  - Brain weight 981 g
  - Severe atrophy
    - Including hippocampus and amygdala
  - Mildly de-pigmented substantia nigra
  - Severely de-pigmented locus ceruleus
- Microscopic:
  - Moderate to severe neuronal loss and gliosis in frontal cortex ***(see virtual slide)***
  - Hippocampal sclerosis ***(see virtual slide)***

Hippocampus

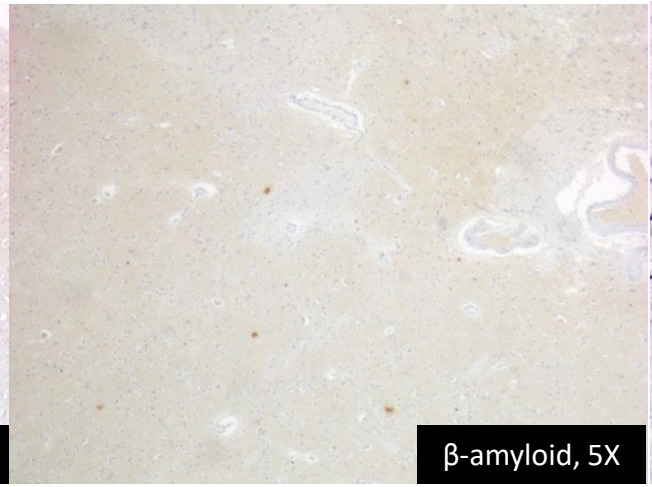




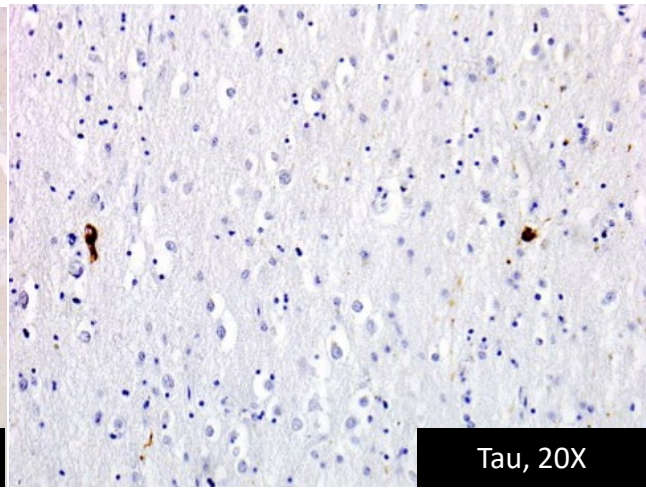
Results of Standard Workup



Neocortical (temporal)



Subcortical (putamen)



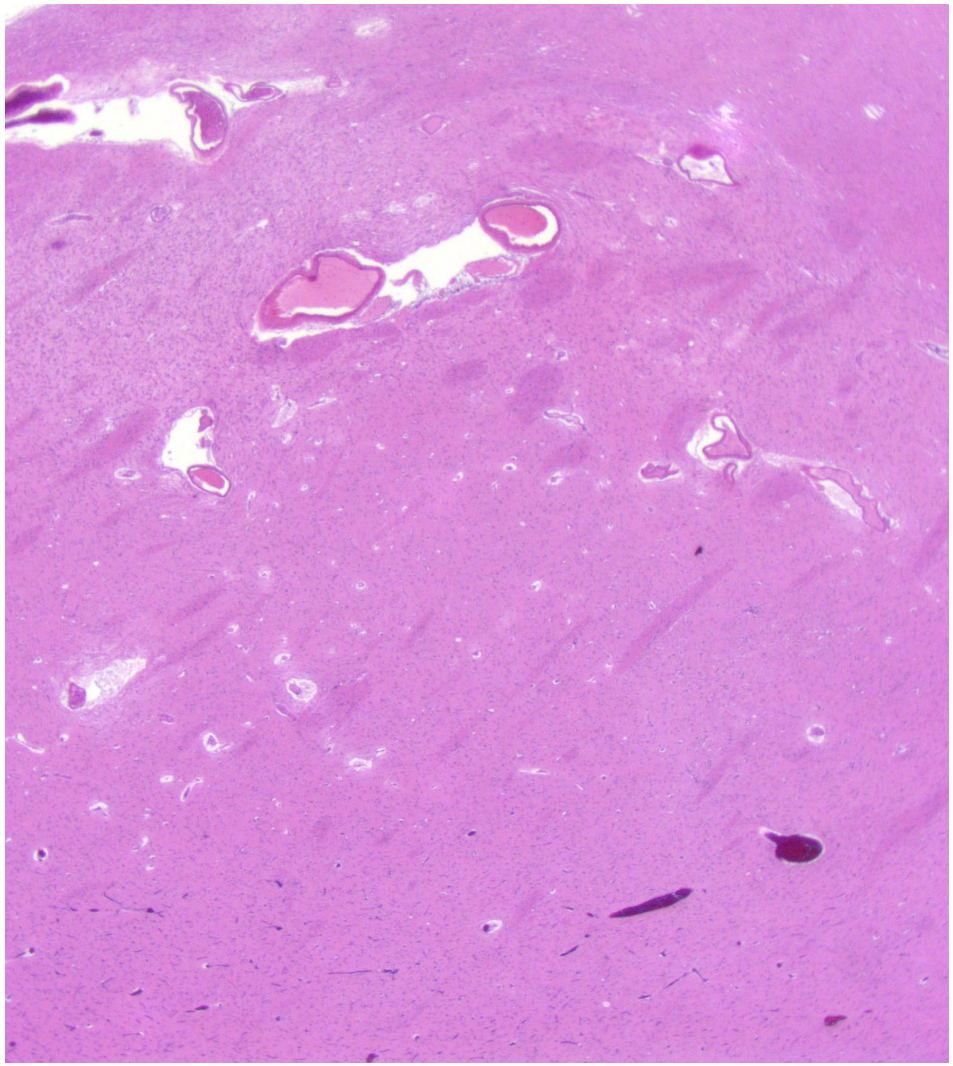
Entorhinal

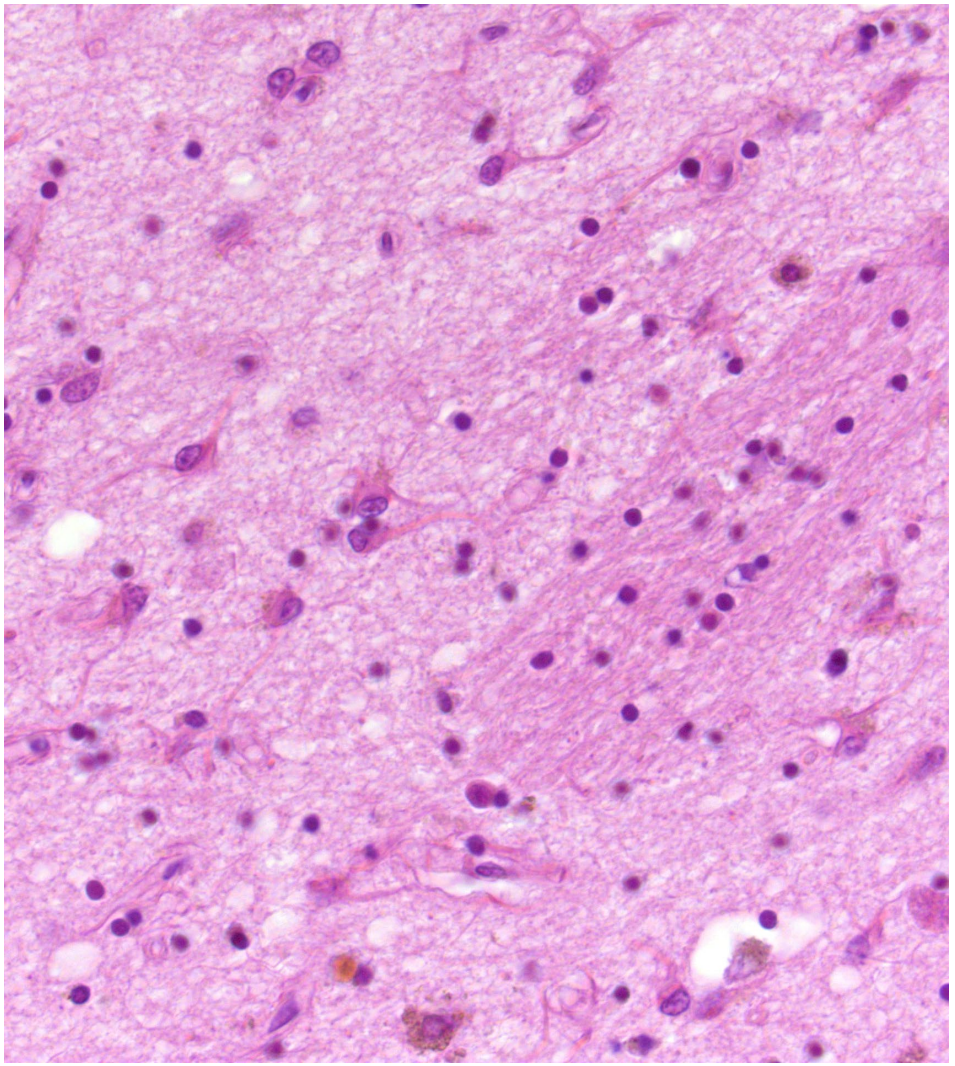
- Low-level Alzheimer's disease neuropathologic change: A2, B1, C1
- No α-synuclein or TDP-43-positive inclusions

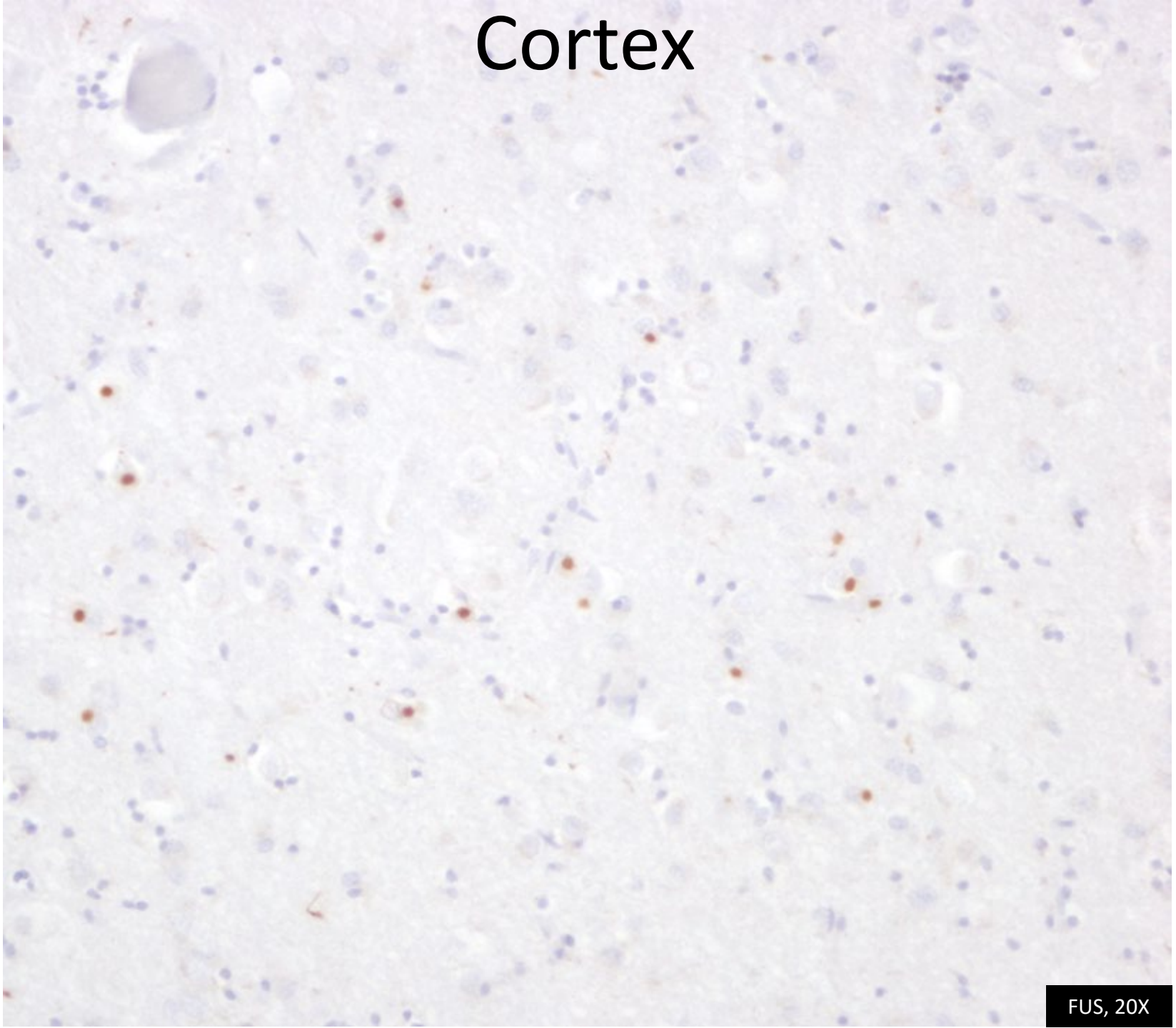
Differential Diagnosis?

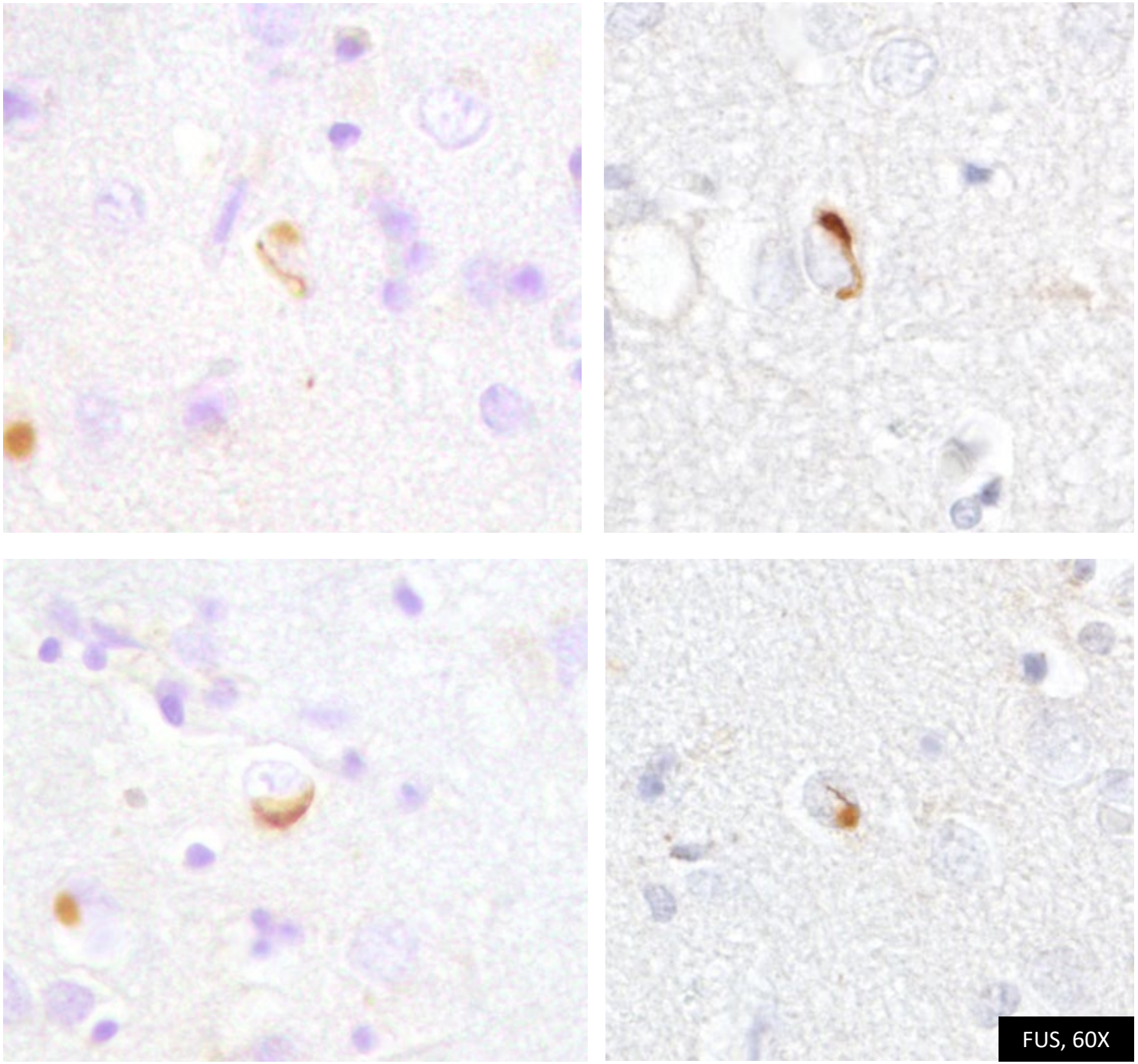
Additional Workup?

Striatum

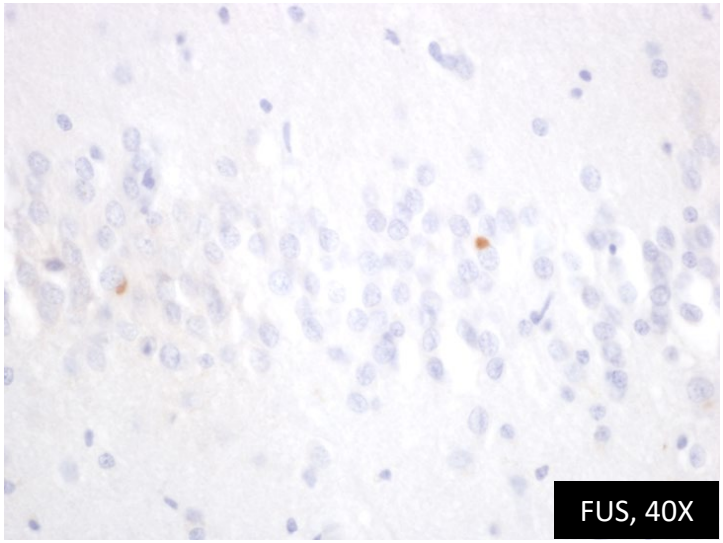


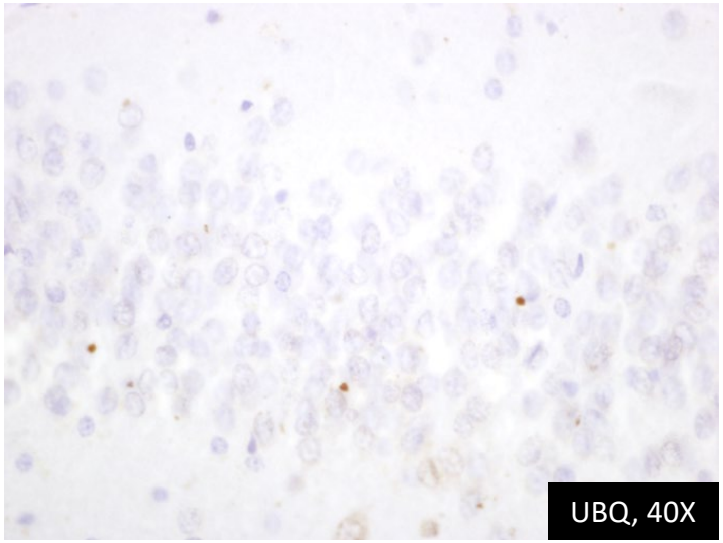


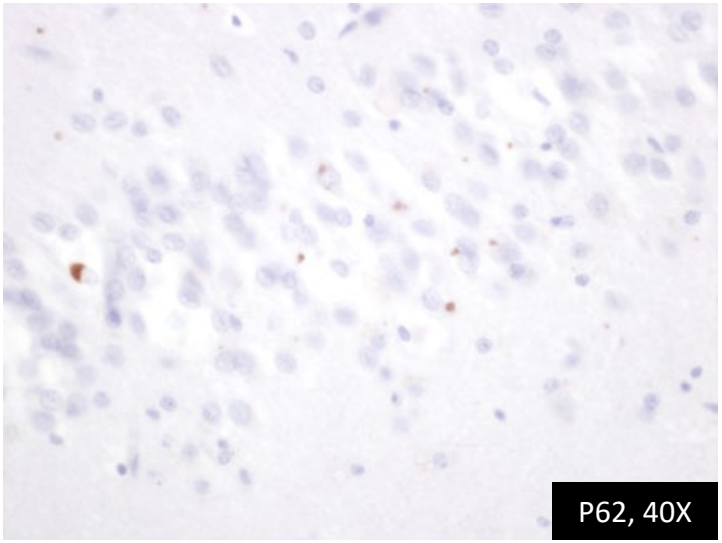

Cortex
FUS, 20X


FUS, 60X

Hippocampus







- Frontotemporal lobar degeneration with FUS-positive inclusions (FTLD-FUS)
- Atypical FTLD with ubiquitin-positive inclusions (aFTLD-U) subtype

Discussion

- ~5-10% of clinical FTD cases are FTLD-FUS
- FUS is part of FET protein family of DNA/RNA binding proteins
  - Ewing's sarcoma protein (EWS)
  - TATA-binding protein-associated factor 15 (TAF15)
  - Transportin
- Loss of normal FUS function? Or gain of novel toxic function?
- Only a few pathologically confirmed FTLD-FUS cases have had genetic testing, and none have shown variants in the FUS gene

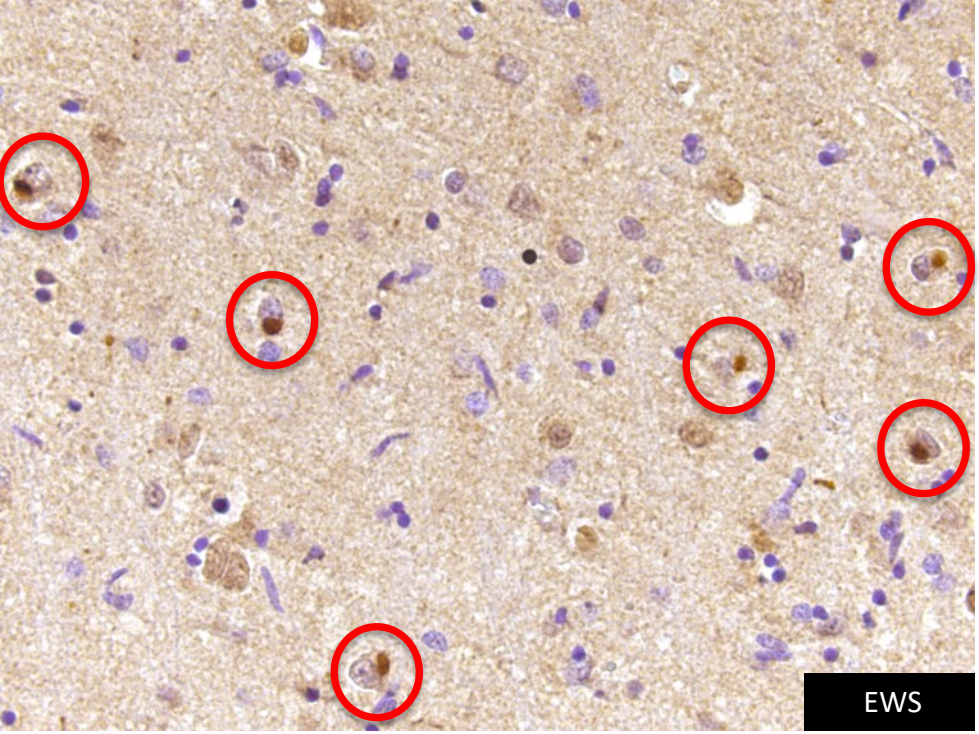
Discussion

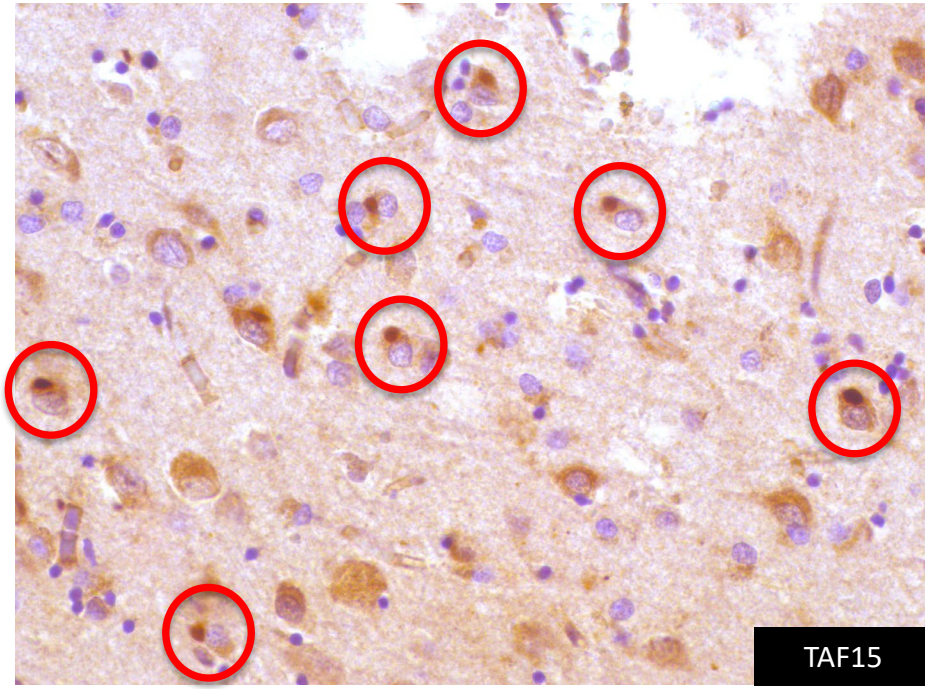
- **FUS-mutated** FUSopathy (ALS-FUS) exhibits FUS-positive inclusions that are *negative* for transportin, EWS and TAF15
  - Pathogenic FUS mutations interfere with normal binding of FUS to transportin -> reduced nuclear import -> accumulation of FUS in the cytoplasm
- **Non-FUS-mutated** FUSopathies (aFTLD-U, NIFID, BIBD) exhibit FUS-positive inclusions that are also *positive* for transportin, EWS and TAF15
  - Possibly more general defect in nuclear import that affects all FET proteins
- *Our patient had significant family hx of FTD-spectrum disease -> sequencing*

Our Patient's Exome Sequencing

- Heterozygous variants of uncertain significance
  - GBA: encodes a lysosomal beta-glucocerebrosidase
    - Biallelic *pathogenic variants* are associated with autosomal recessive Gaucher disease
    - Heterozygous carriers of *pathogenic variants* increased risk of Parkinson's disease and dementia with Lewy bodies
  - SETX
    - *Pathogenic variants* are associated with autosomal recessive spinocerebellar ataxia and autosomal dominant ALS

- **NO FUS mutations**





Consistent with **non-FUS-mutated** FUSopathy

Final Diagnosis

- FTLD-FUS (aFTLD-U subtype), suspicious for genetic etiology
  - Histopathology consistent with non-FUS-mutated etiology

- Hippocampal sclerosis, indeterminate etiology (neurodegenerative vs. seizure)

References

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THANK YOU!