100th Annual Meeting

American Association of Neuropathologists

Diagnostic Slide Session, Case 2024-2

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Disclosures

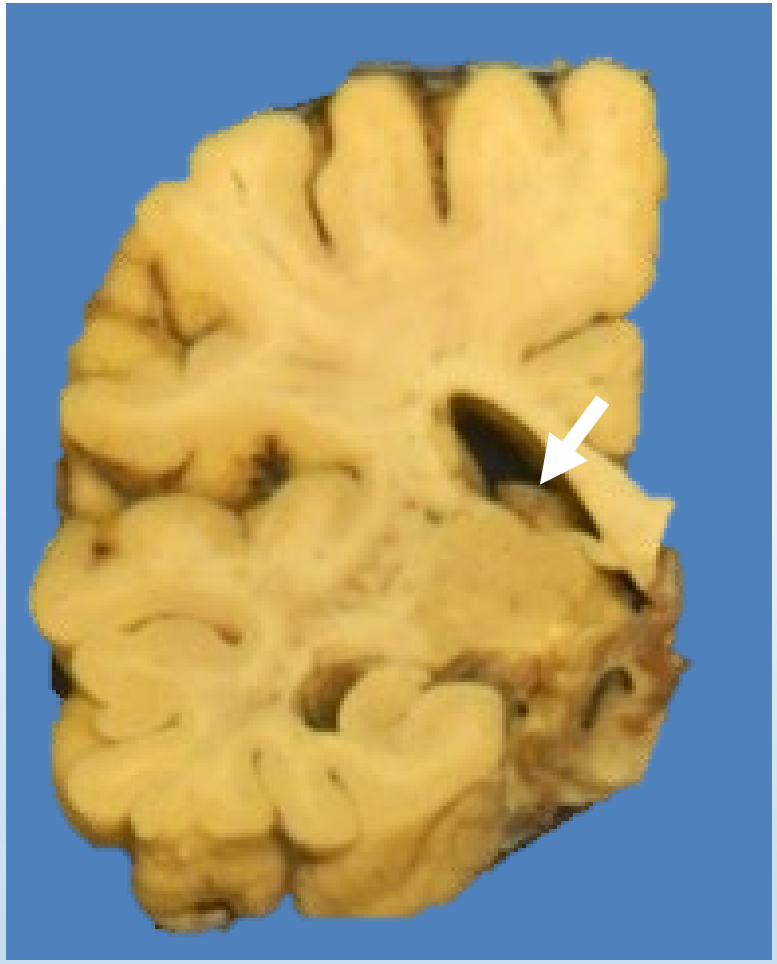
- I have no relevant financial relationships to disclose

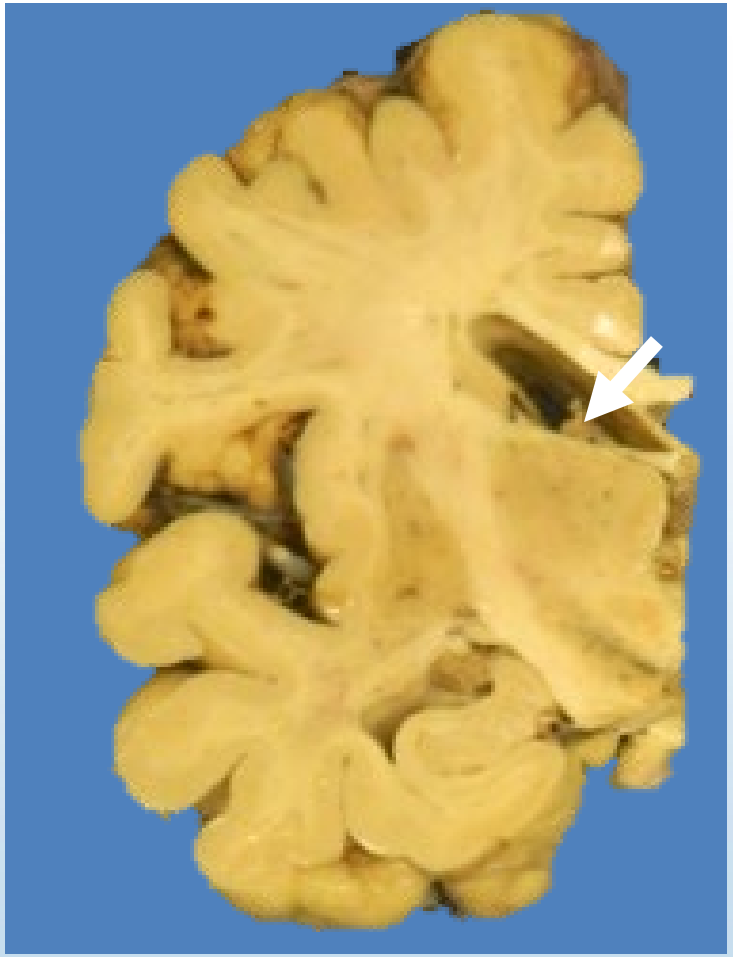
Clinical history

- Gentleman in his 70's, retired from work in his late 40's, due to progressively worsening cognitive decline. A diagnosis of seizures was also rendered at the same time.
- He has a significant family history of early onset dementia in seventeen family members.
- He progressively worsened, with severely impaired decision-making skills, requiring assistance with activities of daily living and frequent falls.
- Lastly, he had a fall, developed a fractured hip which was surgically managed, however he progressively declined and passed away.

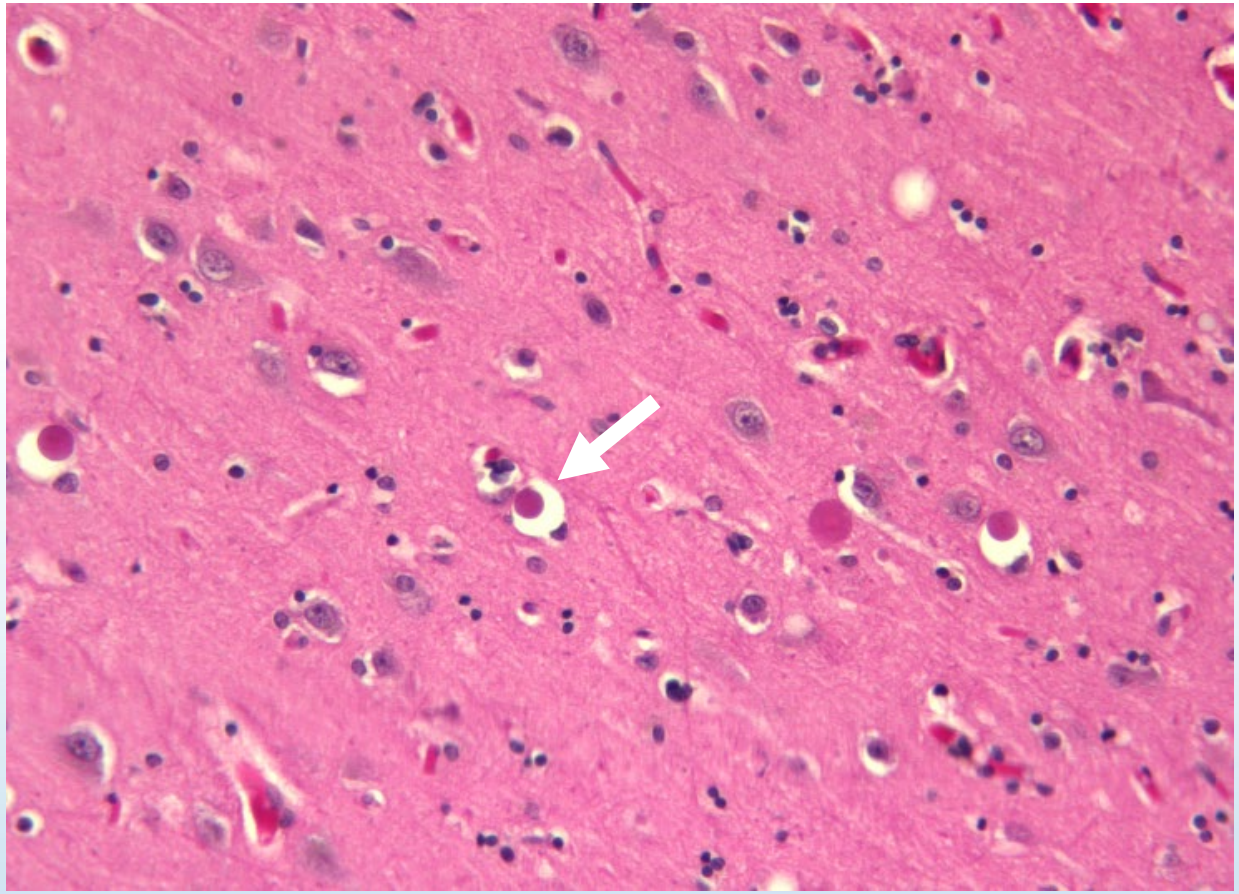
External examination

- The fixed brain weight: 1430 g (reference range 1100-1700 g)
- Coronal sections show mild symmetric hydrocephalus of the lateral ventricles

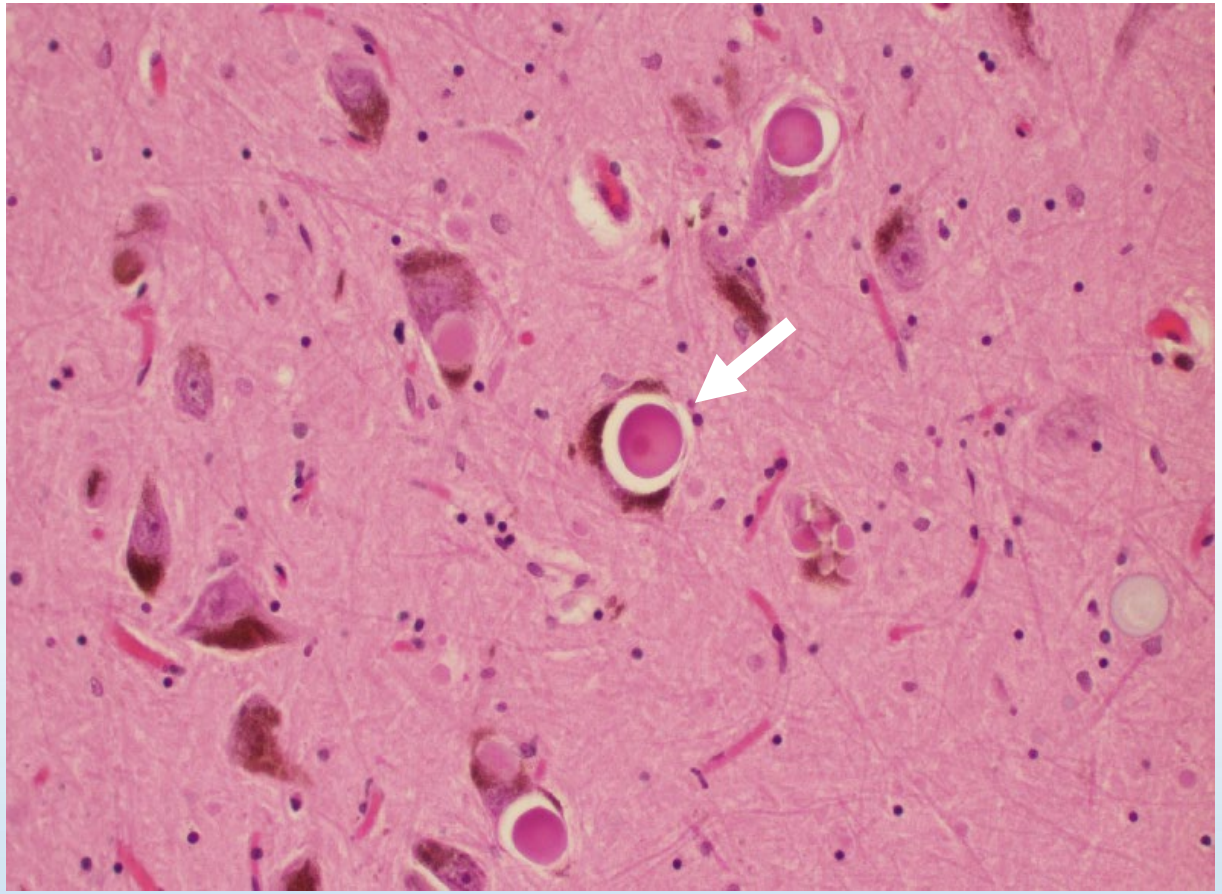




Histology



H&E (20x) Cortical grey matter



H&E (20x) Substantia Nigra

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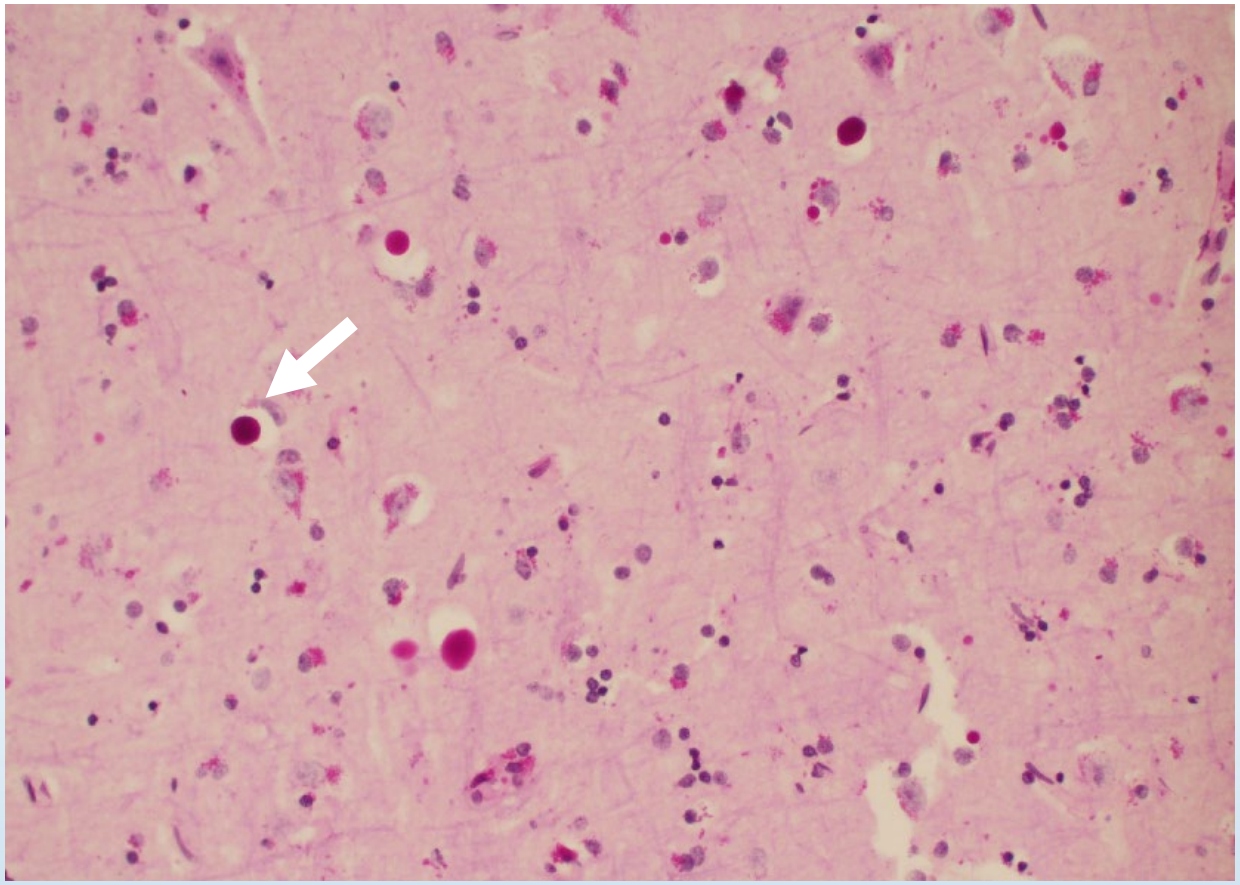
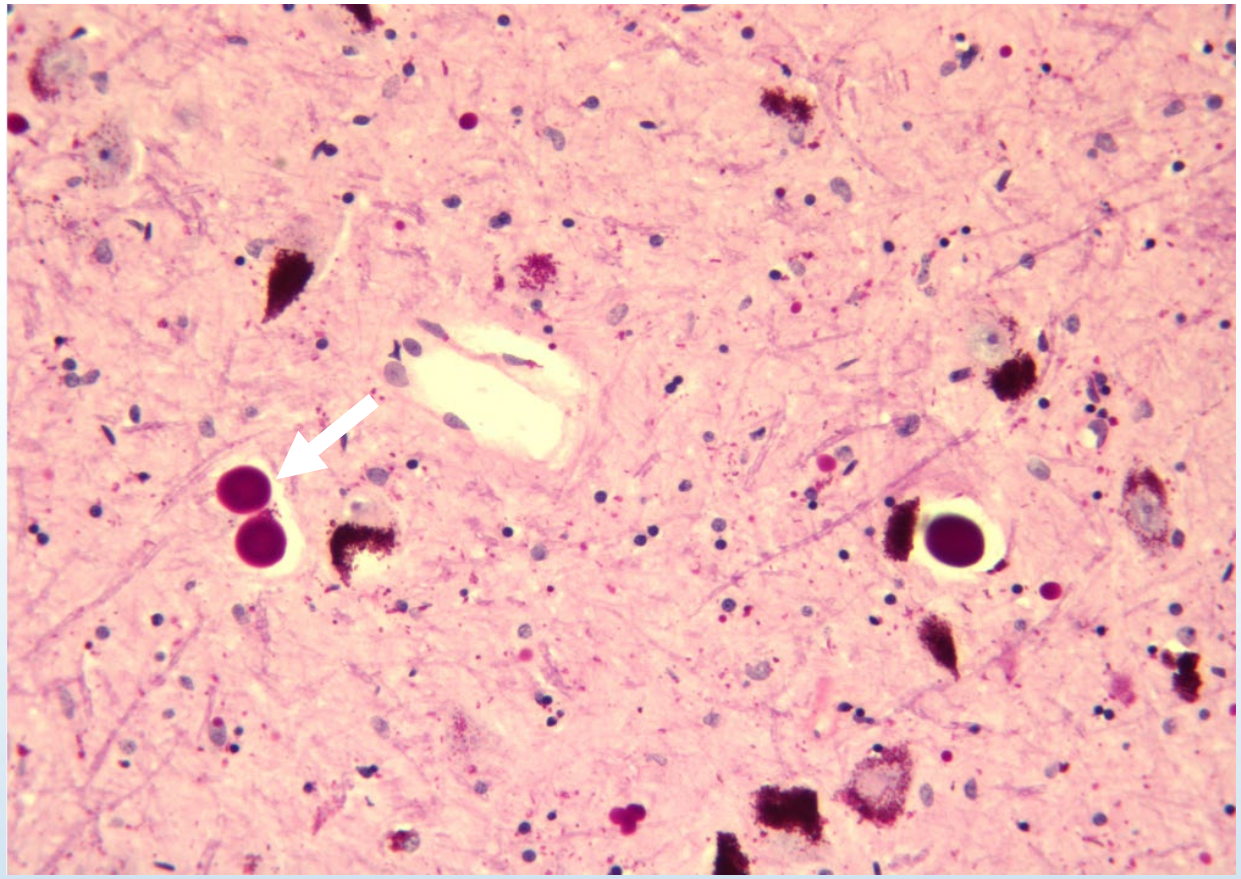
Discussion

Histology

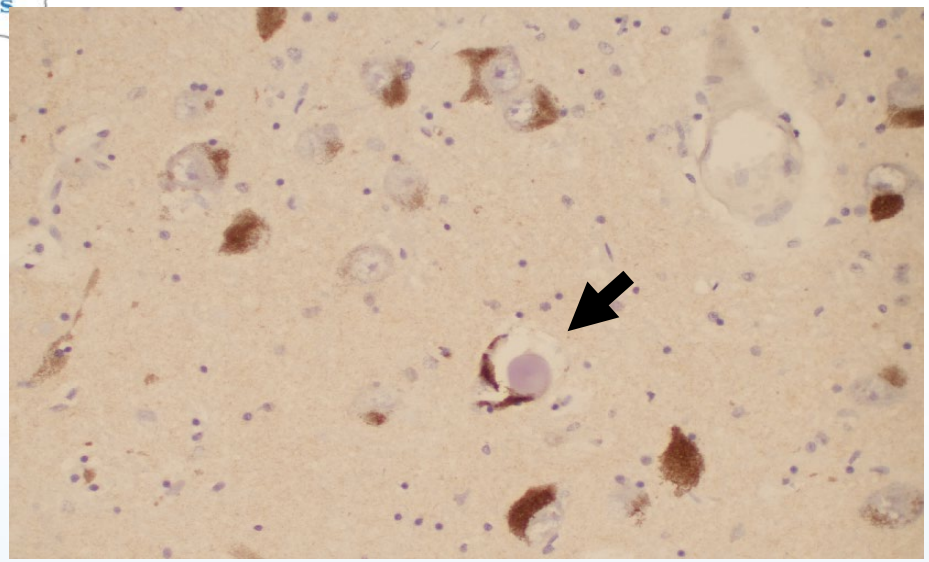


PAS-D (20x) Cortical grey matter

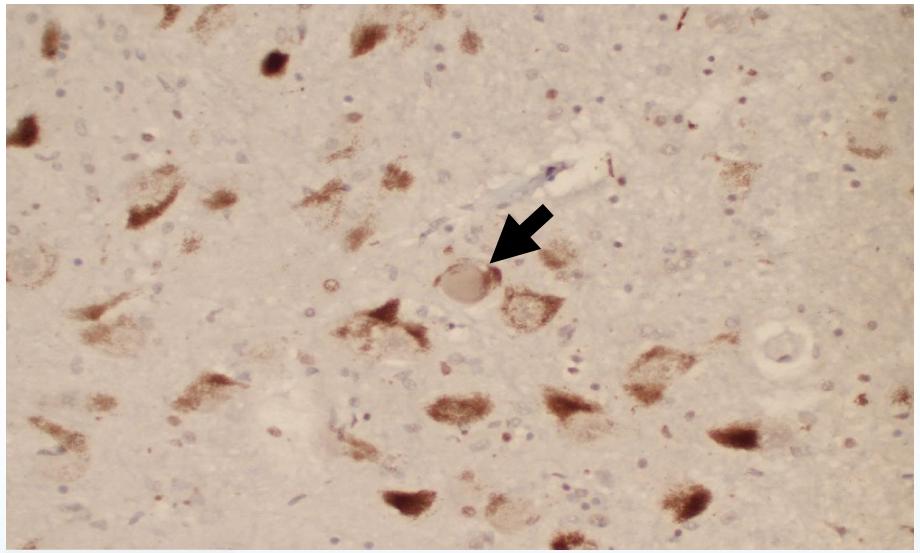


PAS-D (20x) Substantia Nigra

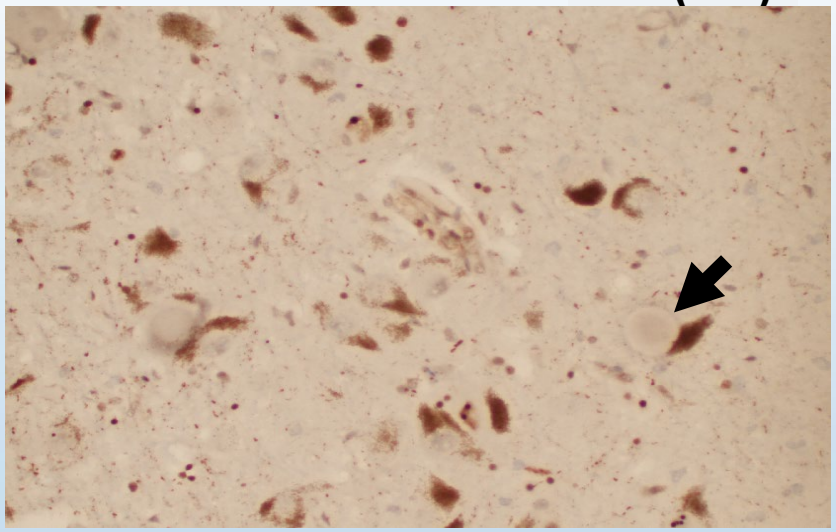
Immunohistochemistry-pertinent negative stains



Synuclein (20x)

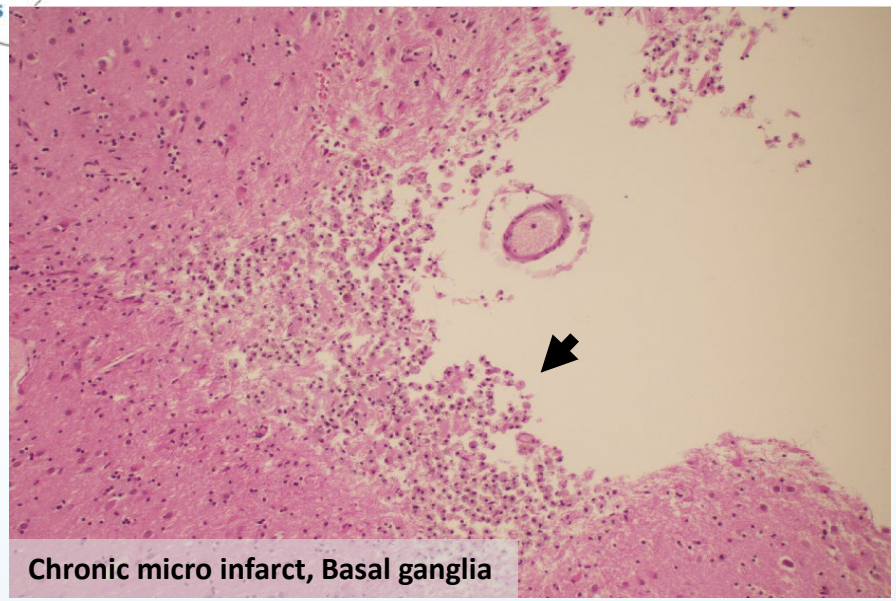


Tau (20x)

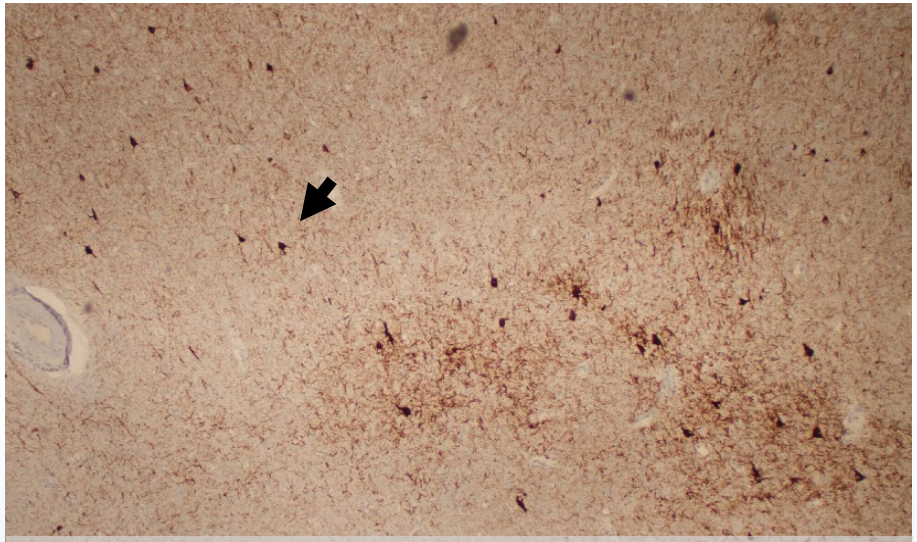


Ubiquitin (20x)

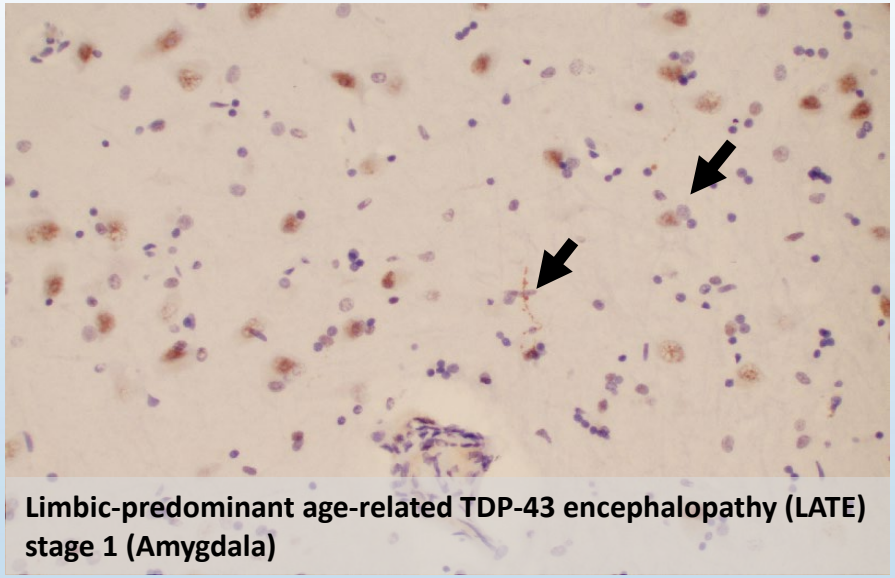
Co-occurring age related pathology



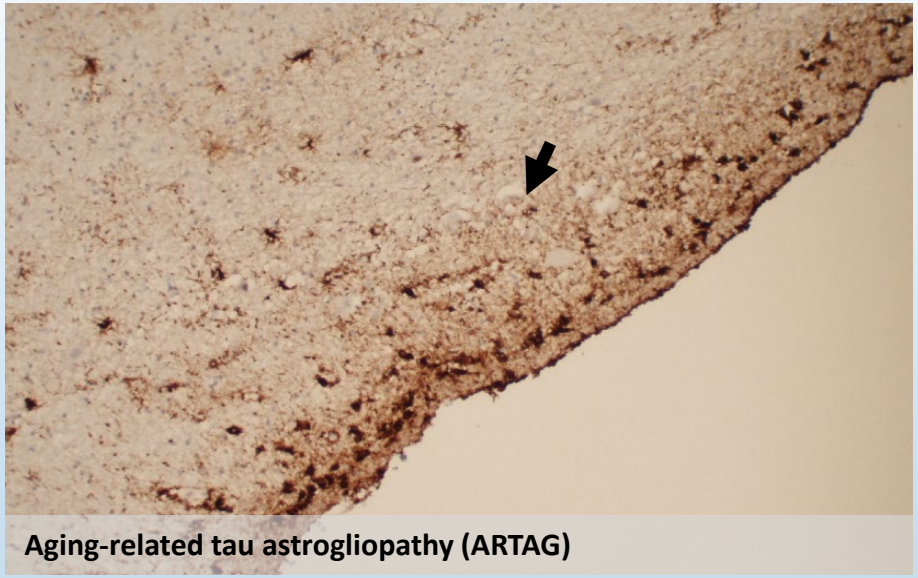
Chronic micro infarct, Basal ganglia



Primary age-related tauopathy (PART); TAU (Entorhinal cortex)



Limbic-predominant age-related TDP-43 encephalopathy (LATE) stage 1 (Amygdala)



Aging-related tau astrogliopathy (ARTAG)

Differential diagnosis

- Storage disease
  - Gaucher's Disease
  - Niemann–Pick disease
  - Neuronal Ceroid Lipofuscinosis/Batten's disease

- Alzheimer's disease
- Parkinson's Disease
- Frontotemporal lobar degeneration
- Familial encephalopathy with Neuroserpin Inclusion Bodies (FENIB)

Clinical history- Key family history

- Parent diagnosed with Familial Encephalopathy with neuroserpin inclusion bodies (FENIB).

Final Diagnosis

- Familial encephalopathy with Neuroserpin Inclusion Bodies (FENIB).

Familial encephalopathy with Neuroserpin Inclusion Bodies (FENIB)

Clinical presentation

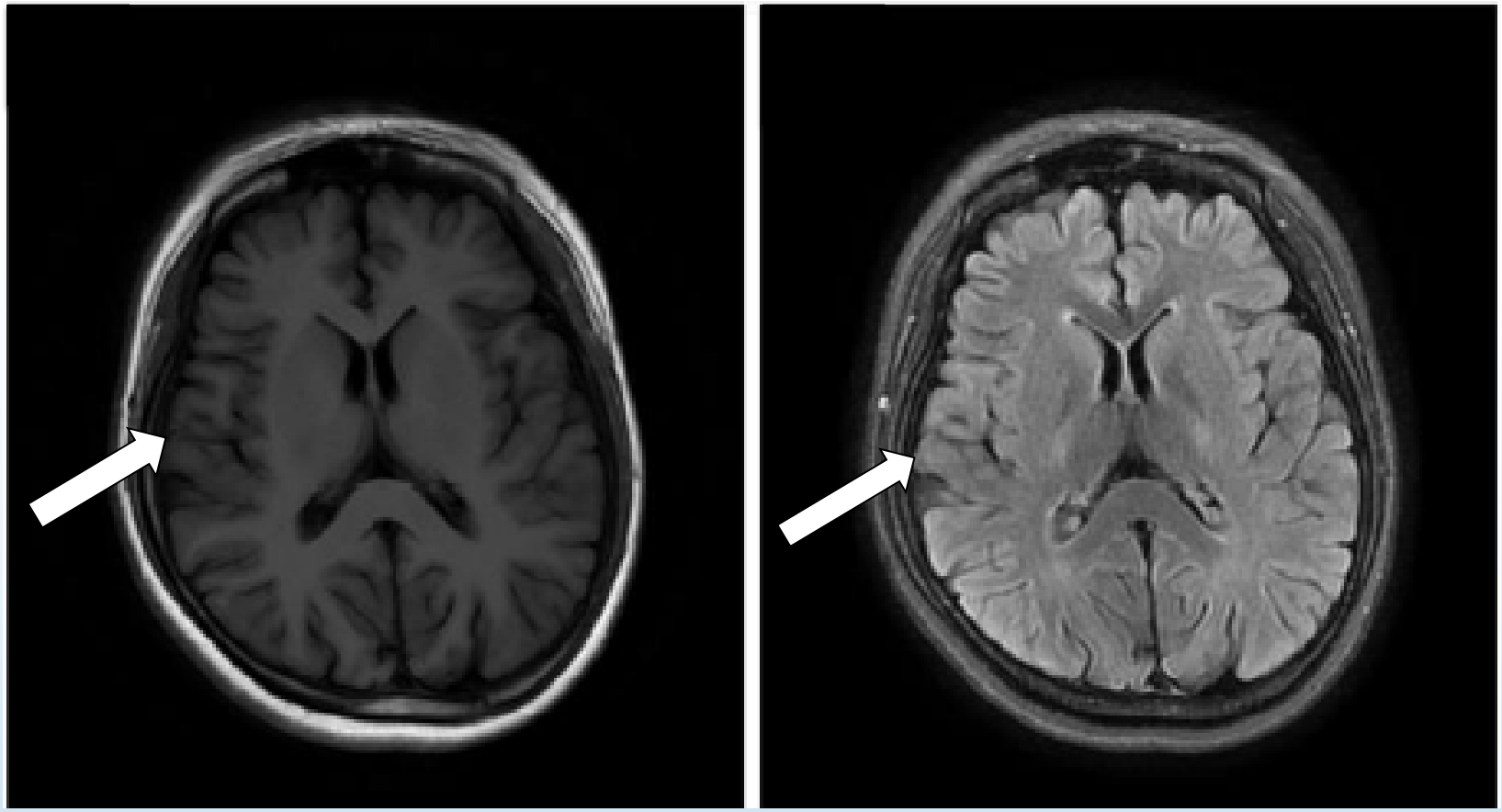
- Progressive dementia typical onset in 4th- 5th decade of life
- Myoclonic jerks and seizures

Typical MRI findings

- cerebral and/or cerebellar atrophy

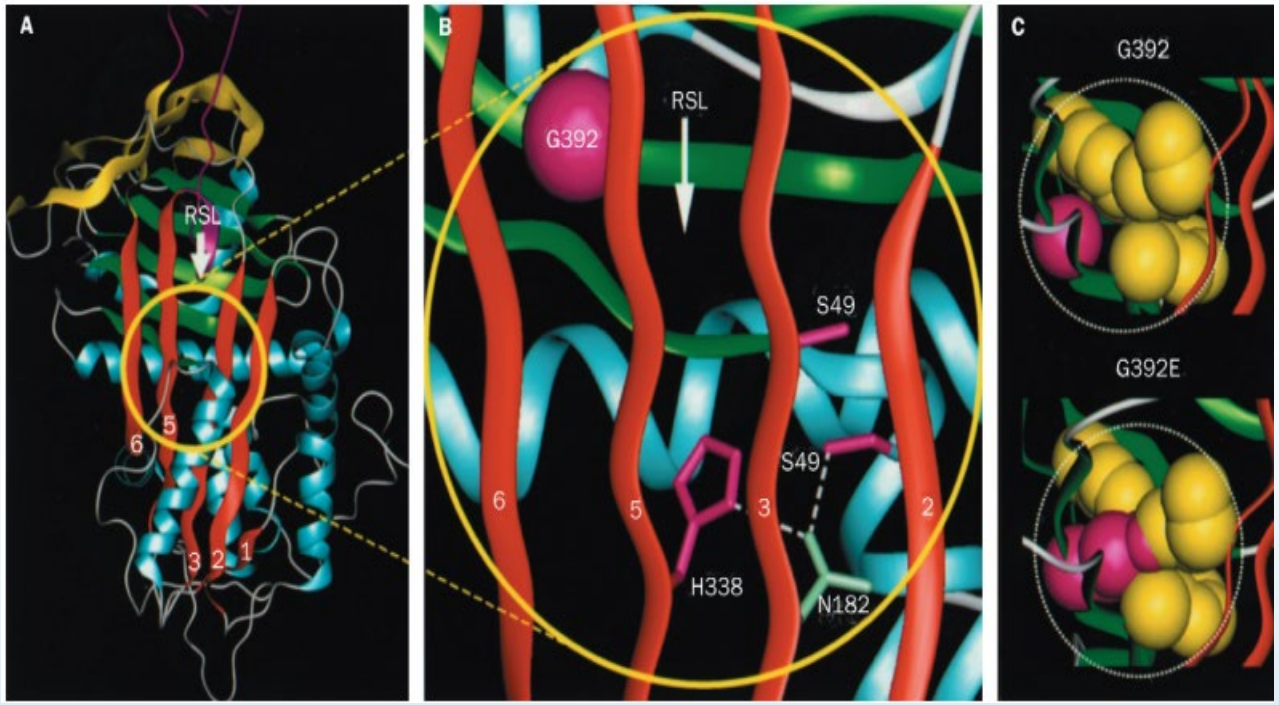
Ancillary Studies

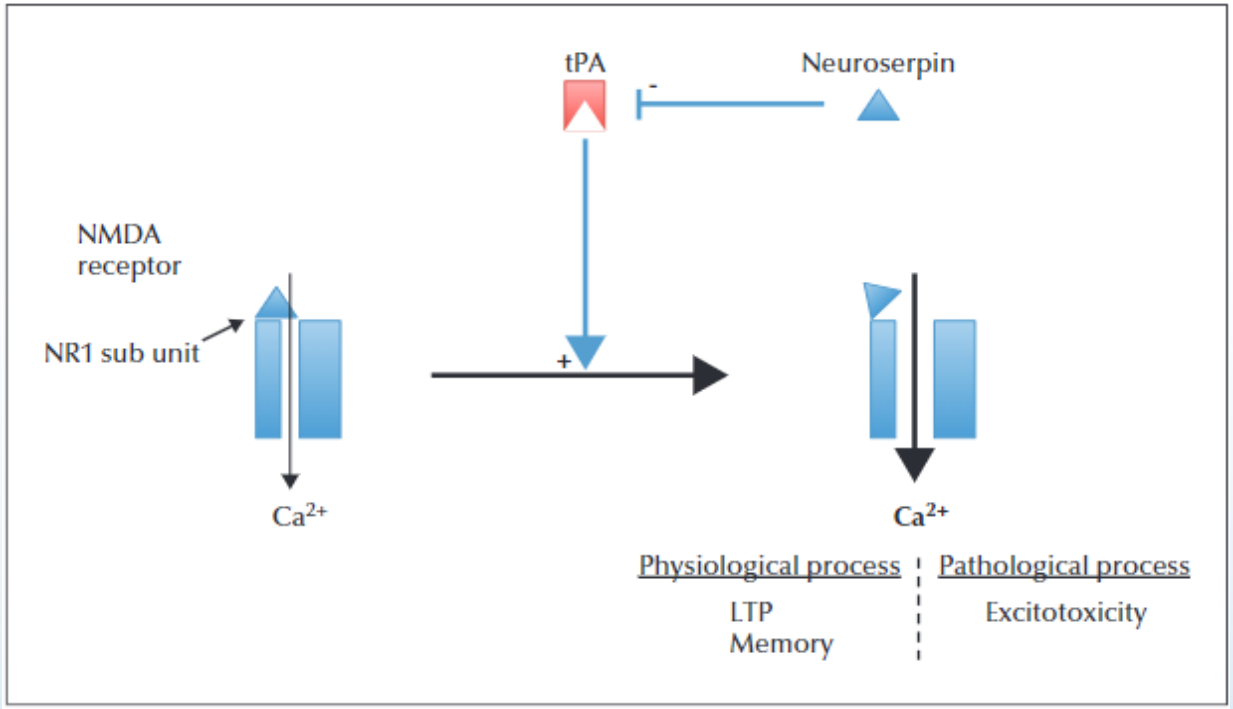
- Light microscopic examination: Detection of PAS-D-positive, neuronal inclusion bodies in the cerebral cortex and substantia nigra
- Genetic studies



Yang *et al. Seizure*. 2022

Pathophysiology and Mutations in Neuroserpin protein





Davis et al.. *The Lancet.* 2002

B.D. Roussel et al.. *Epileptic Disord.* 2016

Summary of FENIB

- Familial encephalopathy with Neuroserpin inclusion bodies (FENIB), is a very rare autosomal dominant neurodegenerative disease.
- Clinically, patients often present with early onset cognitive decline and myoclonic seizures.
- FENIB is characterized by periodic acid/Schiff reagent (PAS)-positive, diastase-resistant neuronal inclusion bodies in the cerebral cortex and substantia nigra called Collins bodies (aggregates of neuroserpin protein).
- While the mechanisms of disease are not entirely clear, loss of neuroserpin-mediated inhibition of tissue plasminogen activator in the brain, which can exacerbate NMDA receptor excitotoxicity could result in seizure activity and progression to epilepsy.

References

1. Davis RL, Holohan PD, Shrimpton AE, Tatum AH, Daucher J, Collins GH, Todd R, Bradshaw C, Kent P, Feiglin D, Rosenbaum A, Yerby MS, Shaw CM, Lacbawan F, Lawrence DA. Familial encephalopathy with neuroserpin inclusion bodies. Am J Pathol. 1999 Dec;155(6):1901-13. PMID: 10595921

2. Yang X, Fang Z, Yan L, He X, Luo H, Han Z, Gui J, Cheng M, Jiang L. Role of SERPINI1 pathogenic variants in familial encephalopathy with neuroserpin inclusion bodies: A case report and literature review. Seizure. 2022 Dec;103:137-147. doi: 10.1016/j.seizure.2022.11.008. Epub 2022 Nov 13. PMID: 36417830.

2. Davis RL, Shrimpton AE, Carrell RW, et al. Association between conformational mutations in neuroserpin and onset and severity of dementia [published correction appears in Lancet 2002 Oct 5;360(9339):1102]. Lancet 2002;359(9325):2242–7. https://doi.org/10.1016/S0140-6736(02)09293-0.

4. Roussel BD, Lomas DA, Crowther DC. Progressive myoclonus epilepsy associated with neuroserpin inclusion bodies (neuroserpinosis). Epileptic Disord 2016;18(S2): 103–10. https://doi.org/10.1684/epd.2016.0847.

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Thank You