DSS Case 2020-4

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Disclosures

We have no relevant financial disclosures.

Clinical history

27-year-old female

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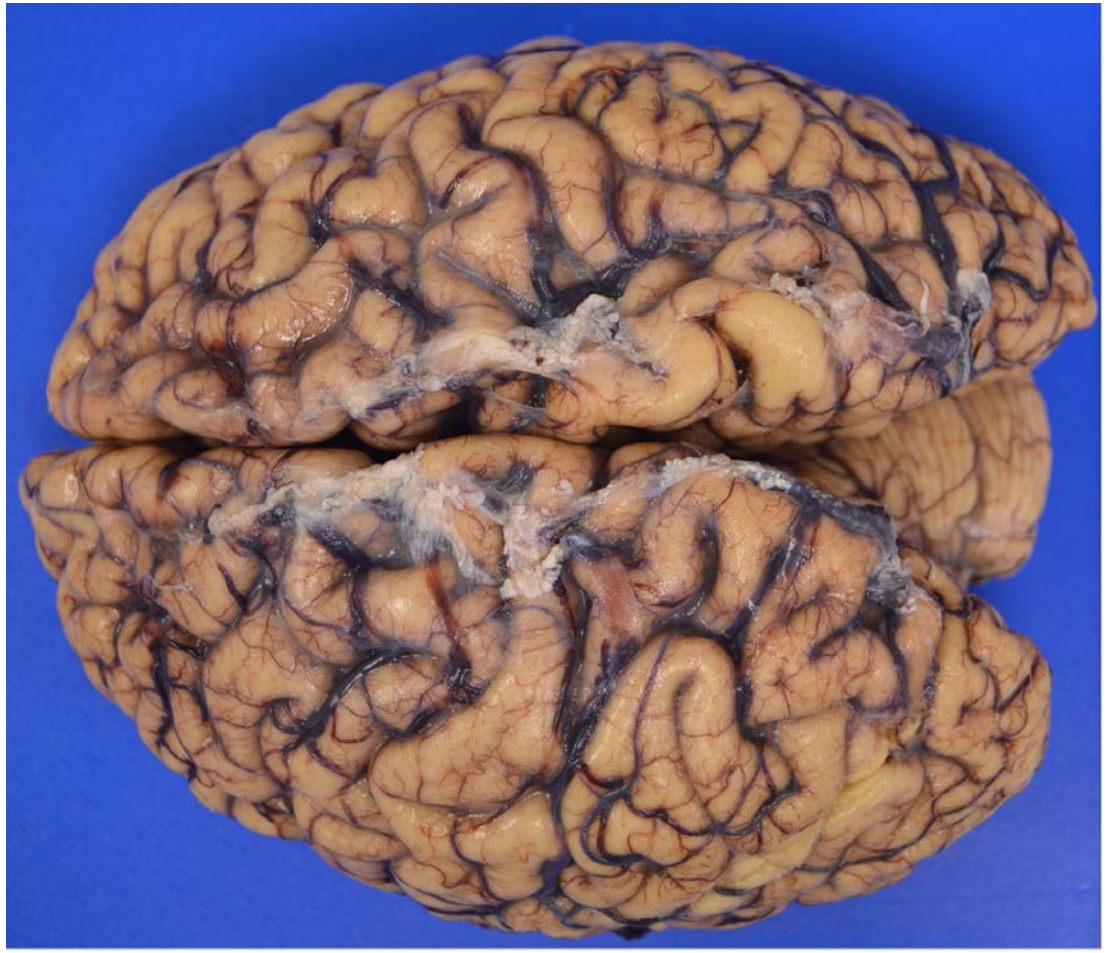
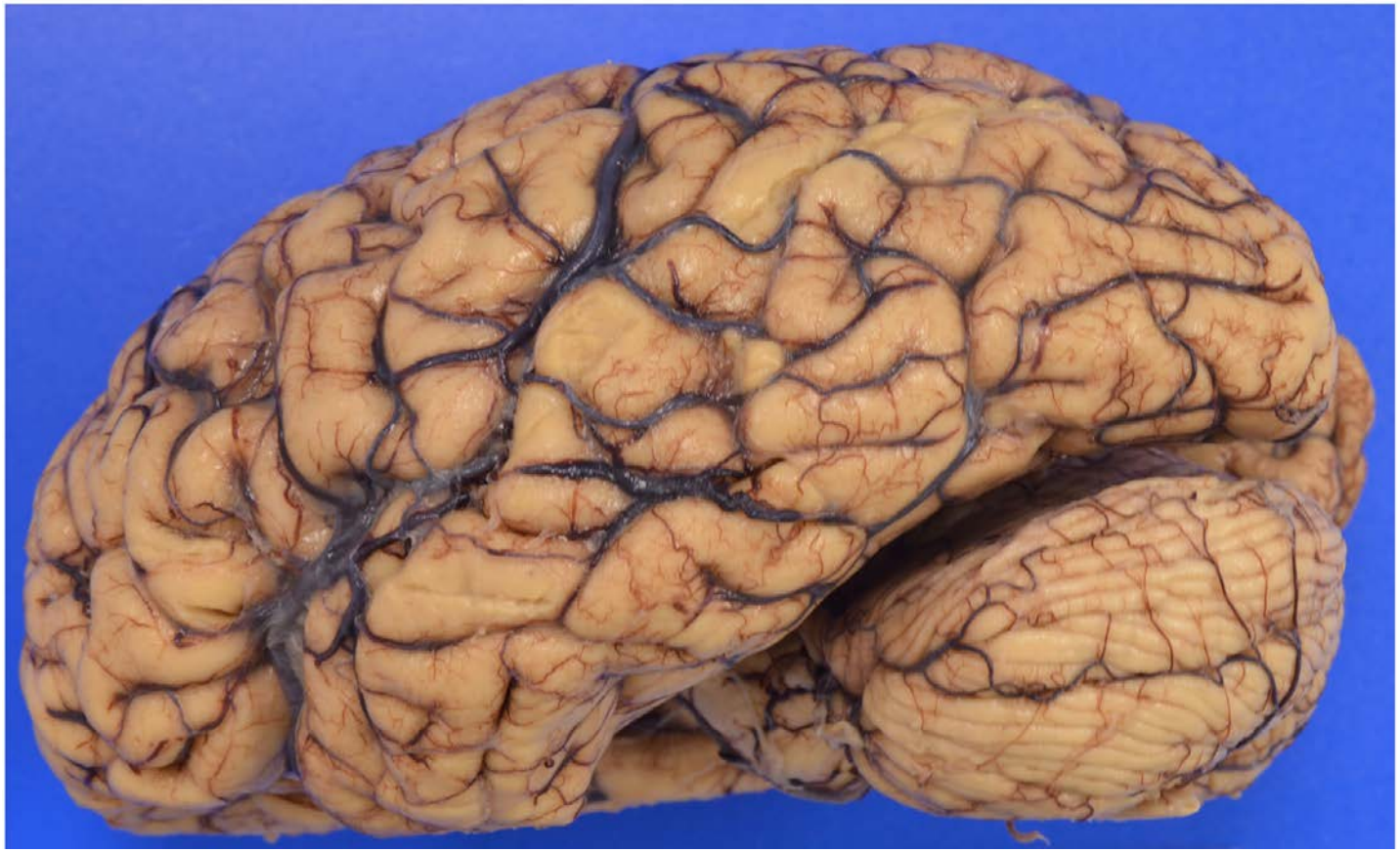
- Cousin diagnosed with RP- no other pertinent PMH/family history

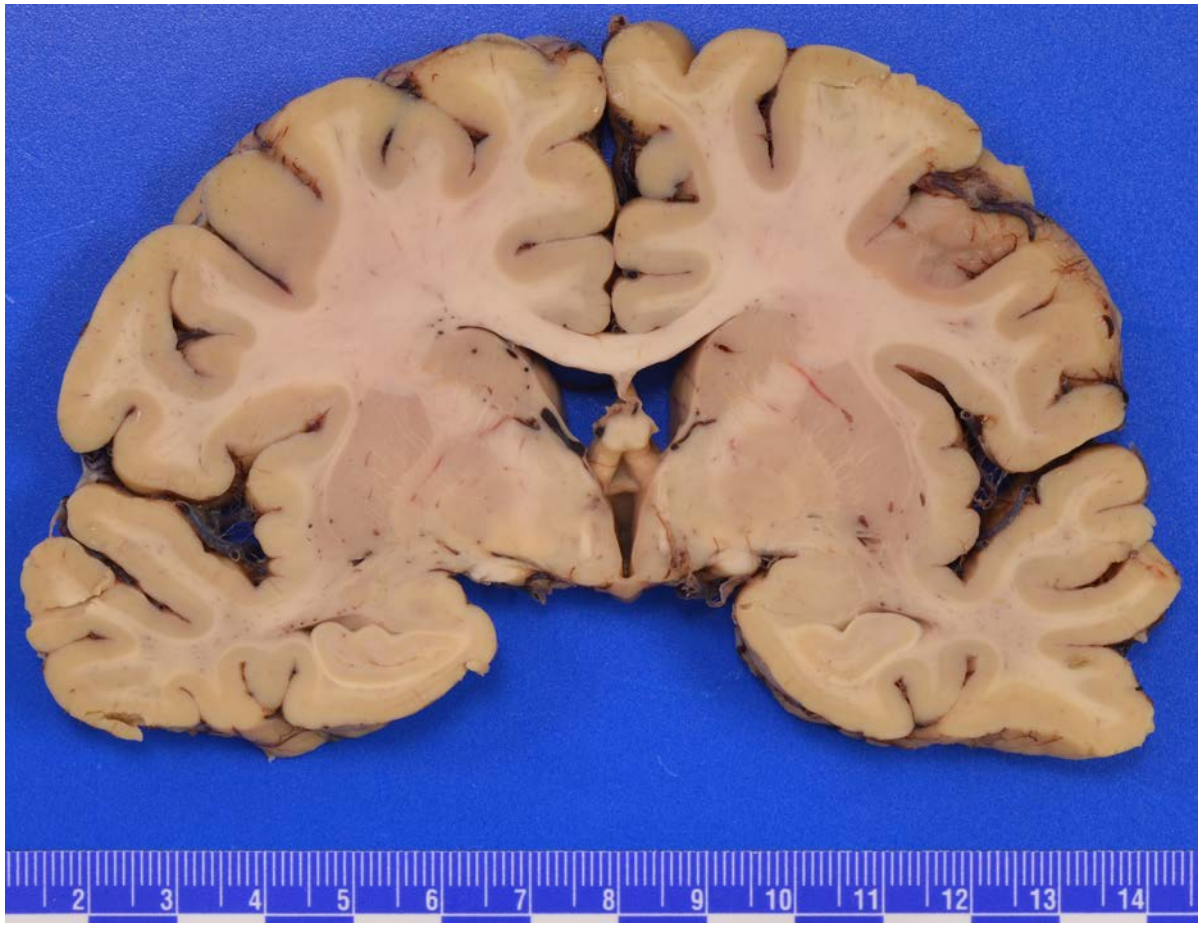
Autopsy

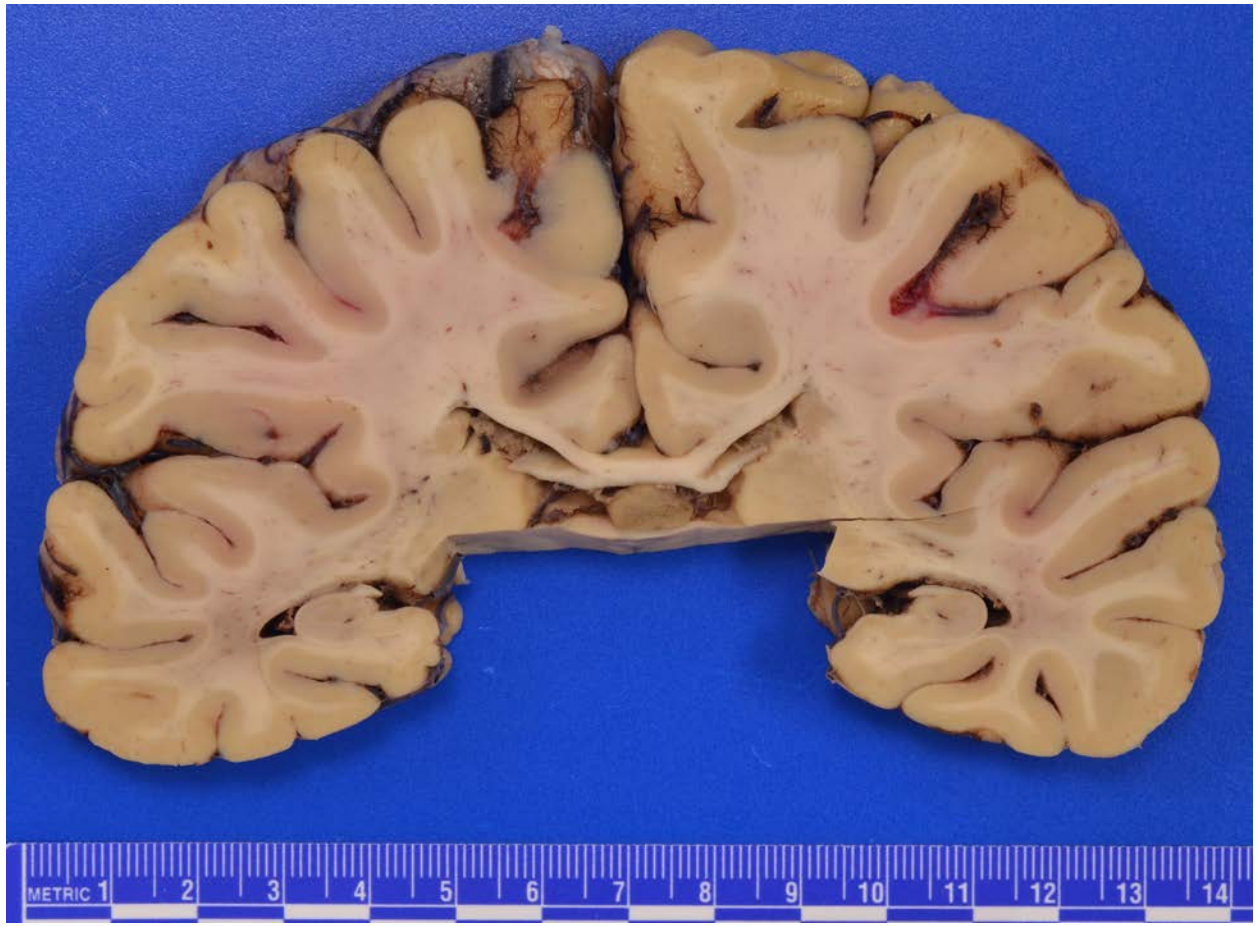




- Brain weight 950 g (expected ~1200 g for adult female)
- Generalized cortical atrophy

Autopsy





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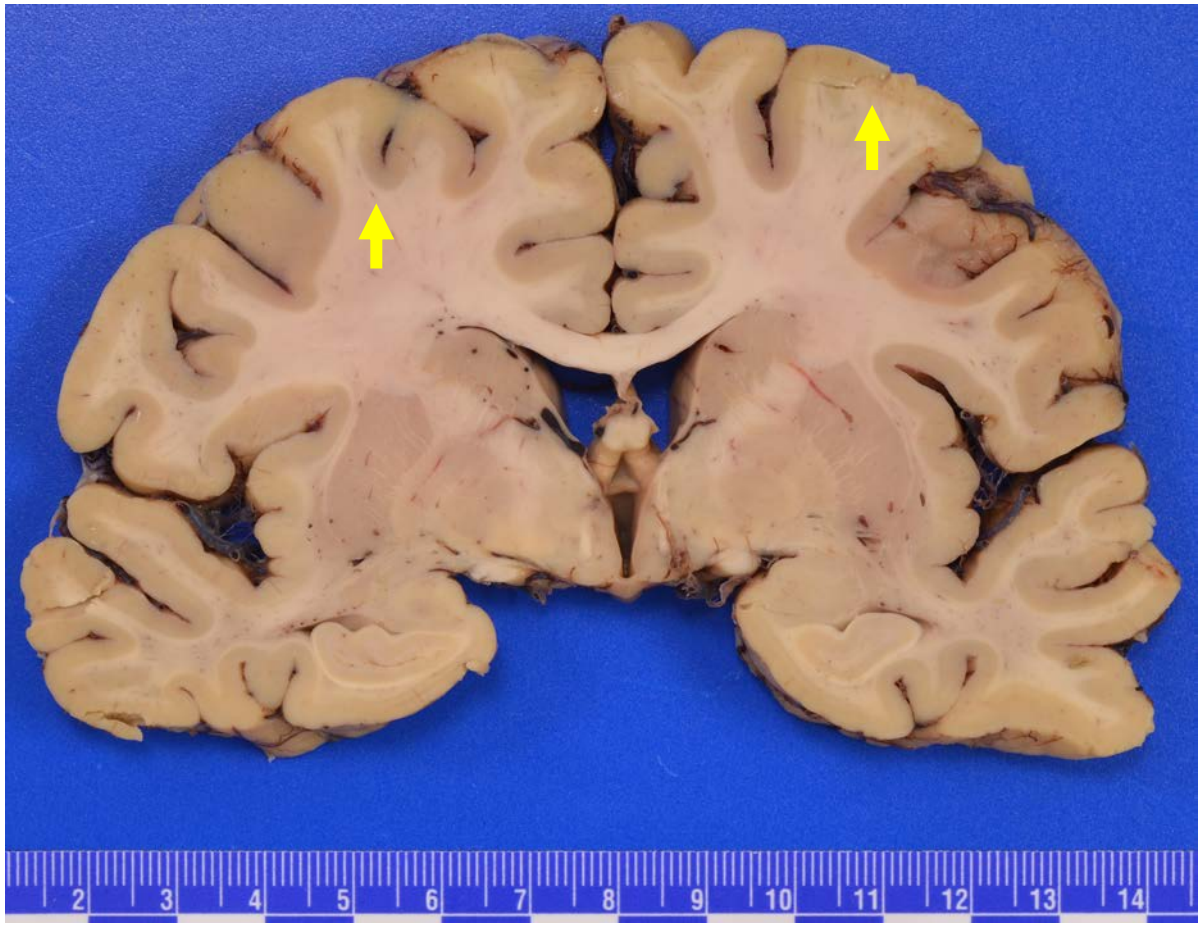
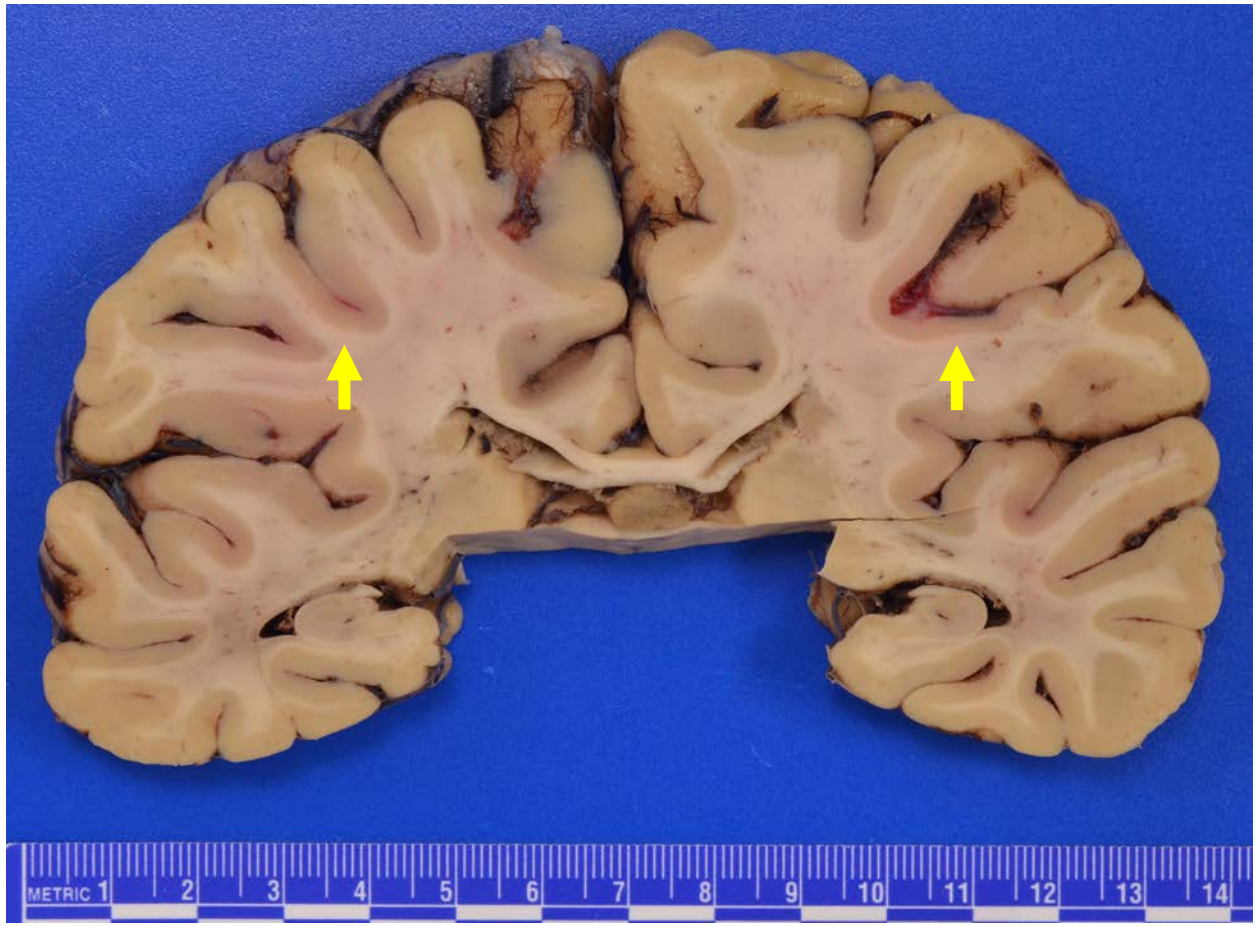
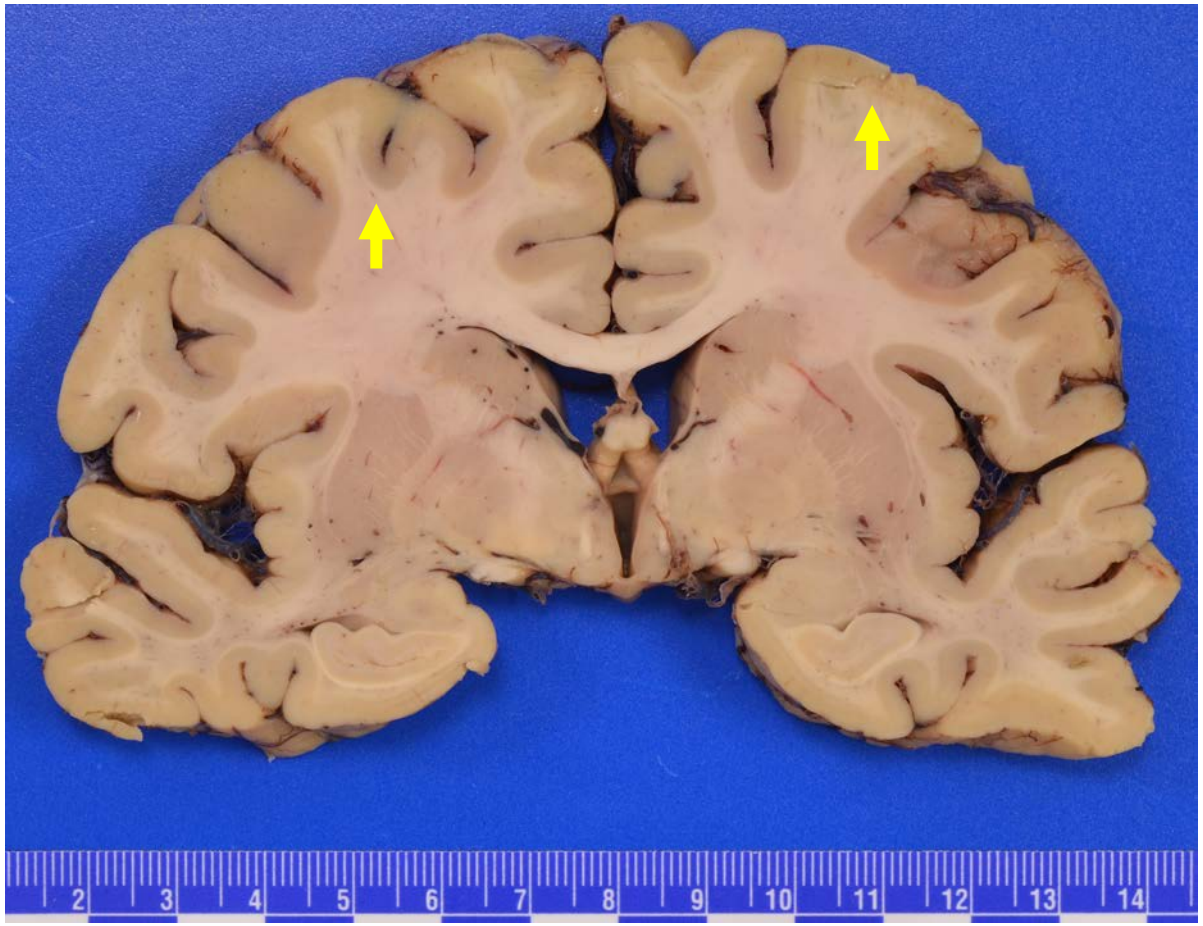
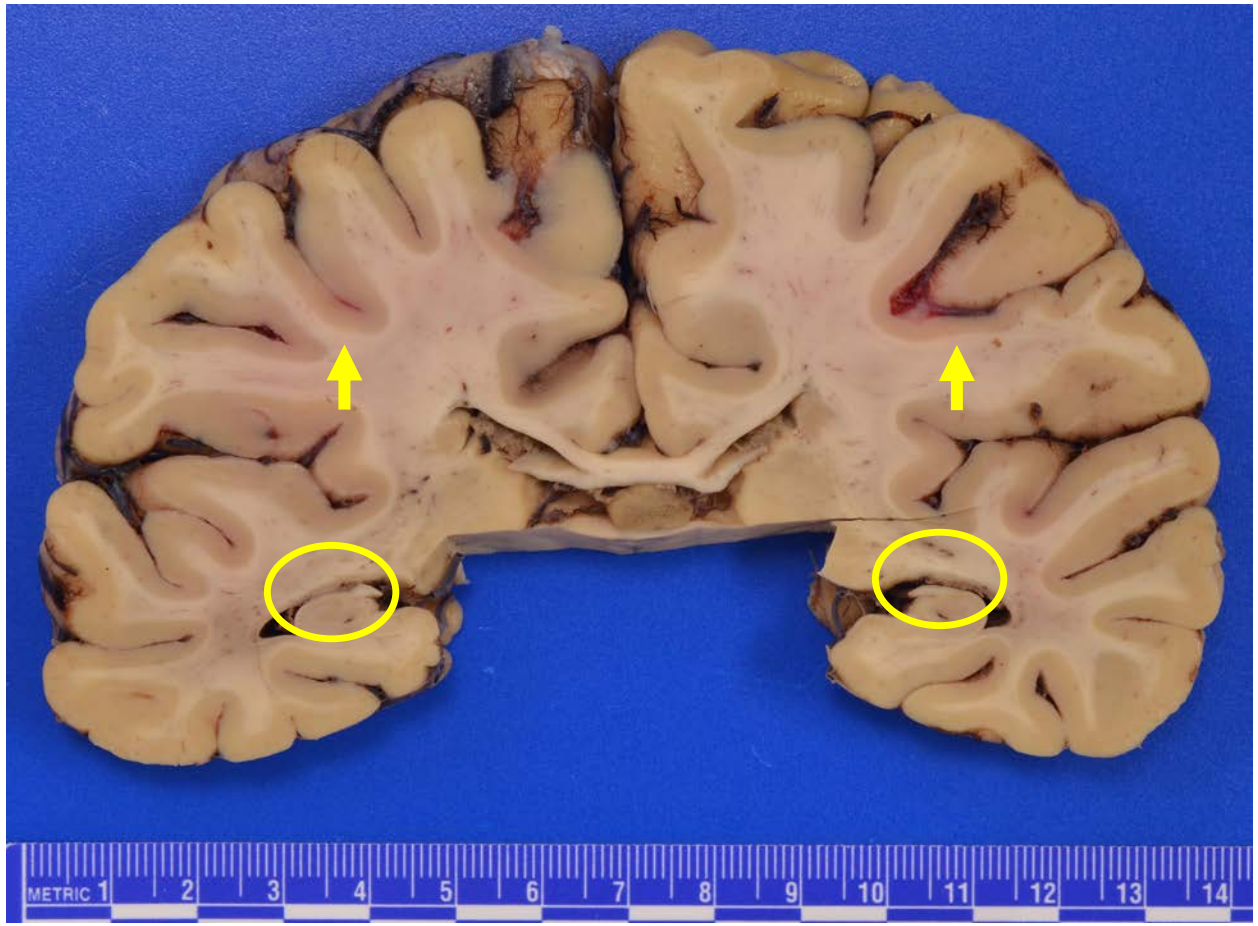




- Mildly thin cortical ribbon

Autopsy

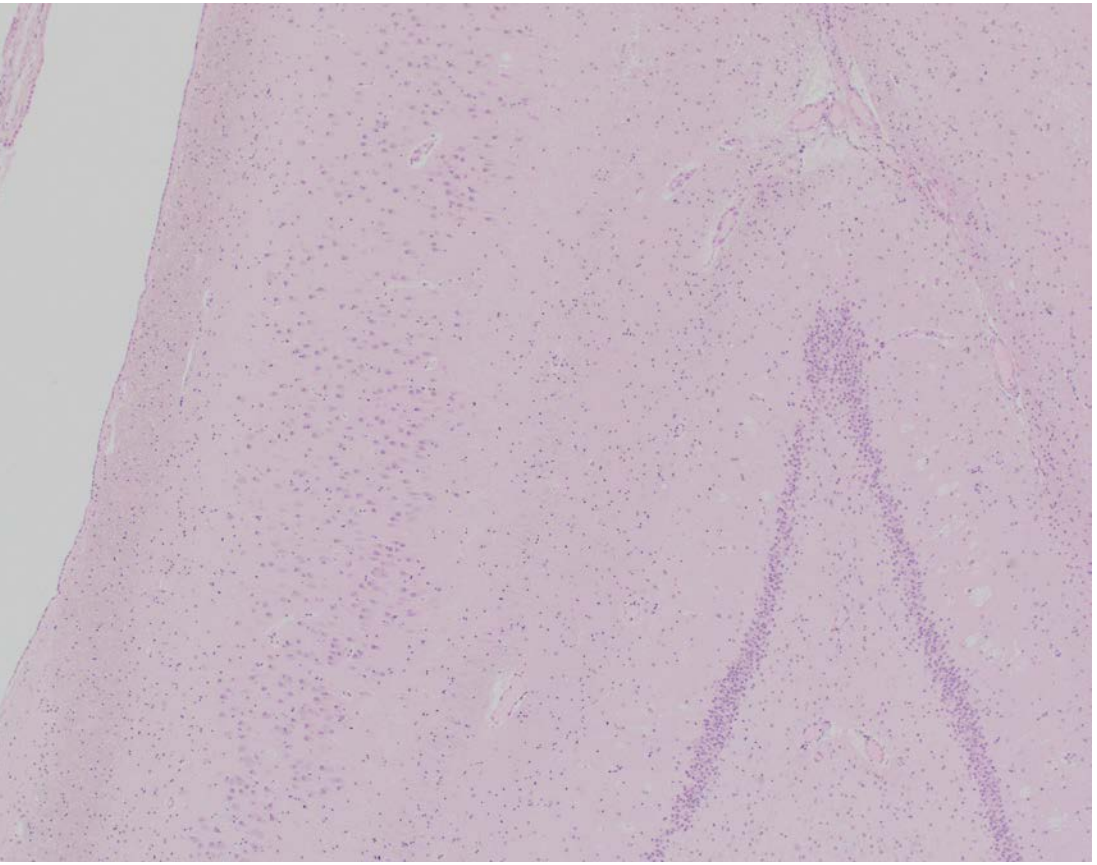


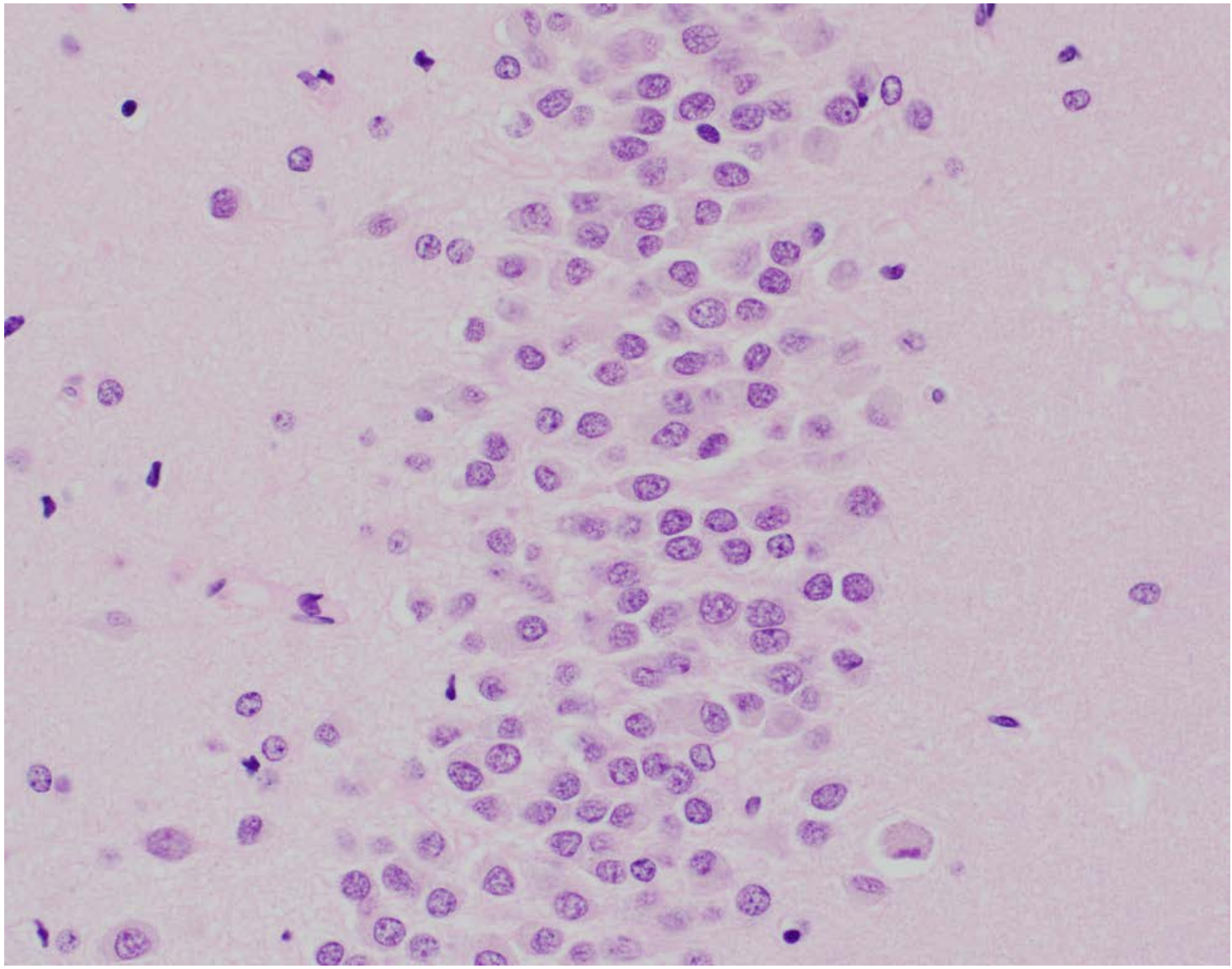


- Mildly thin cortical ribbon
- Highly atrophic bilateral lateral geniculate nuclei

Microscopy

Hippocampus





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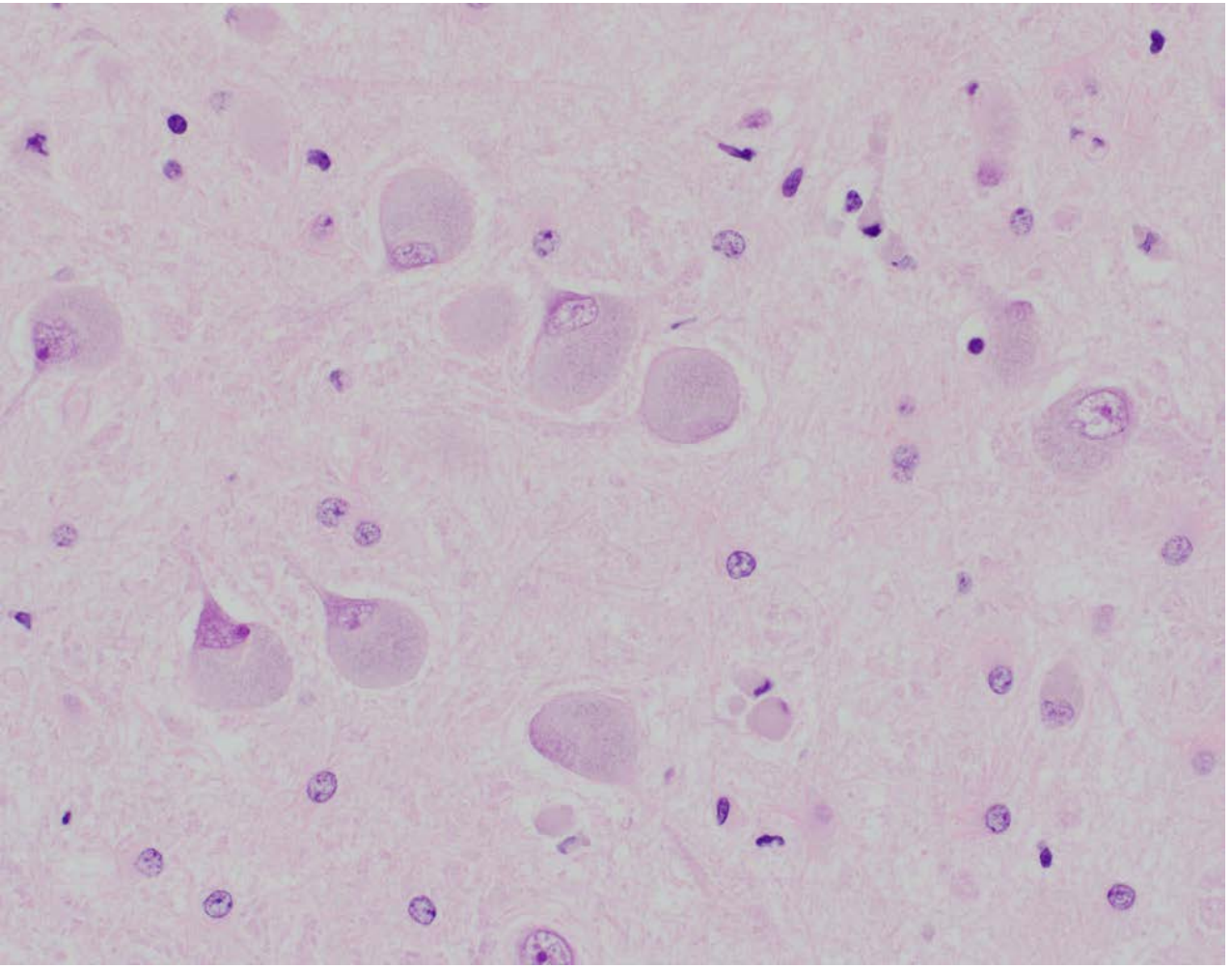
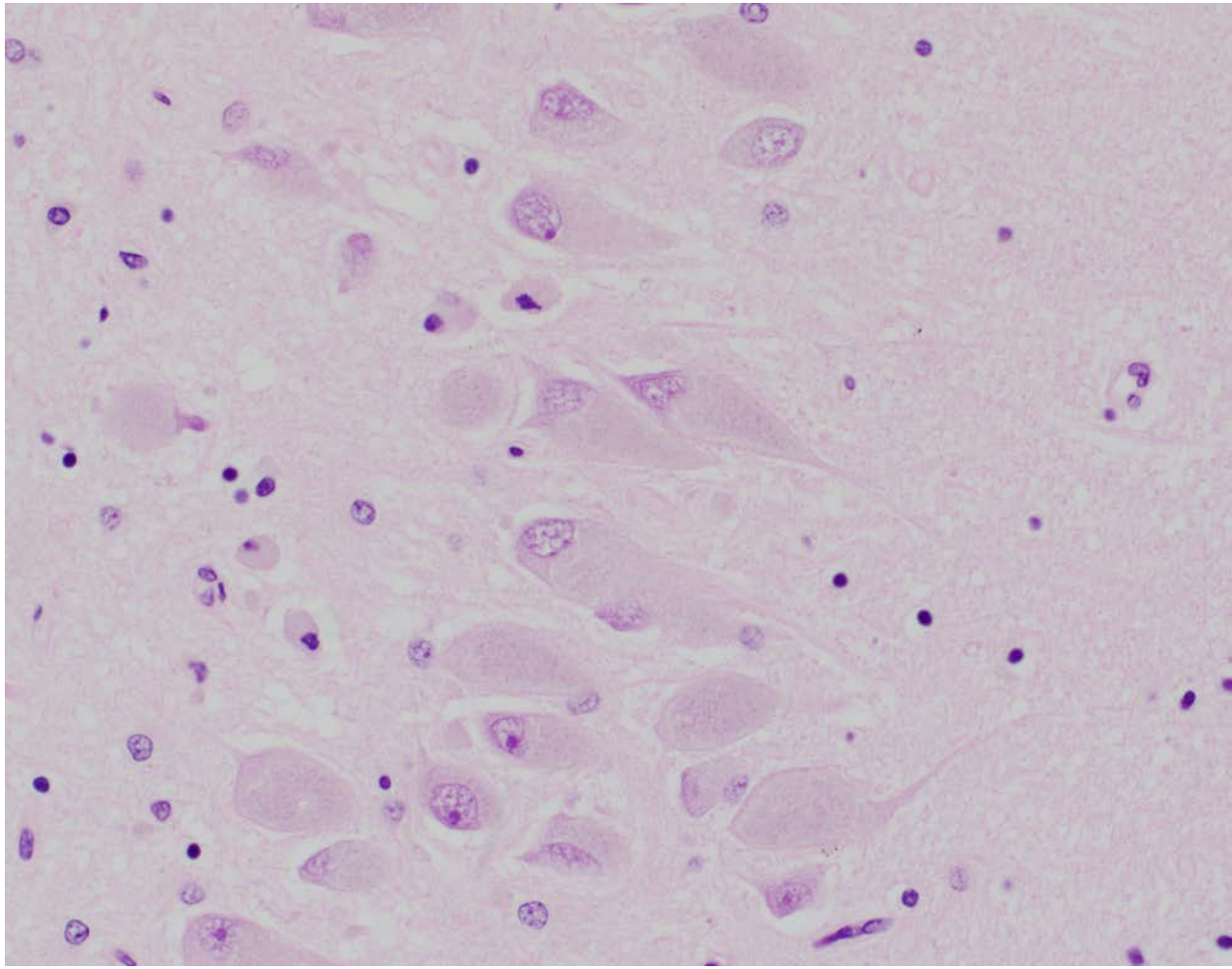
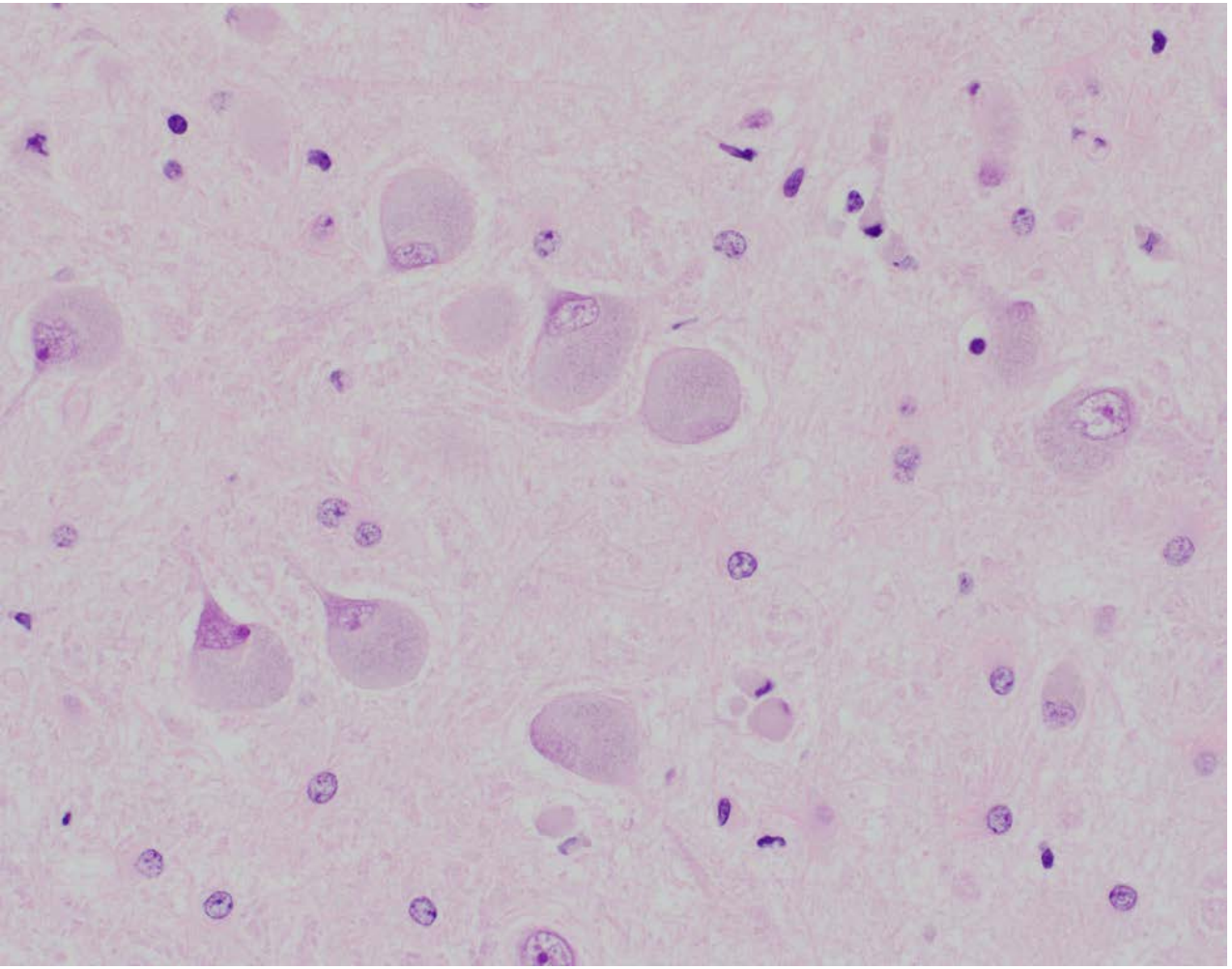


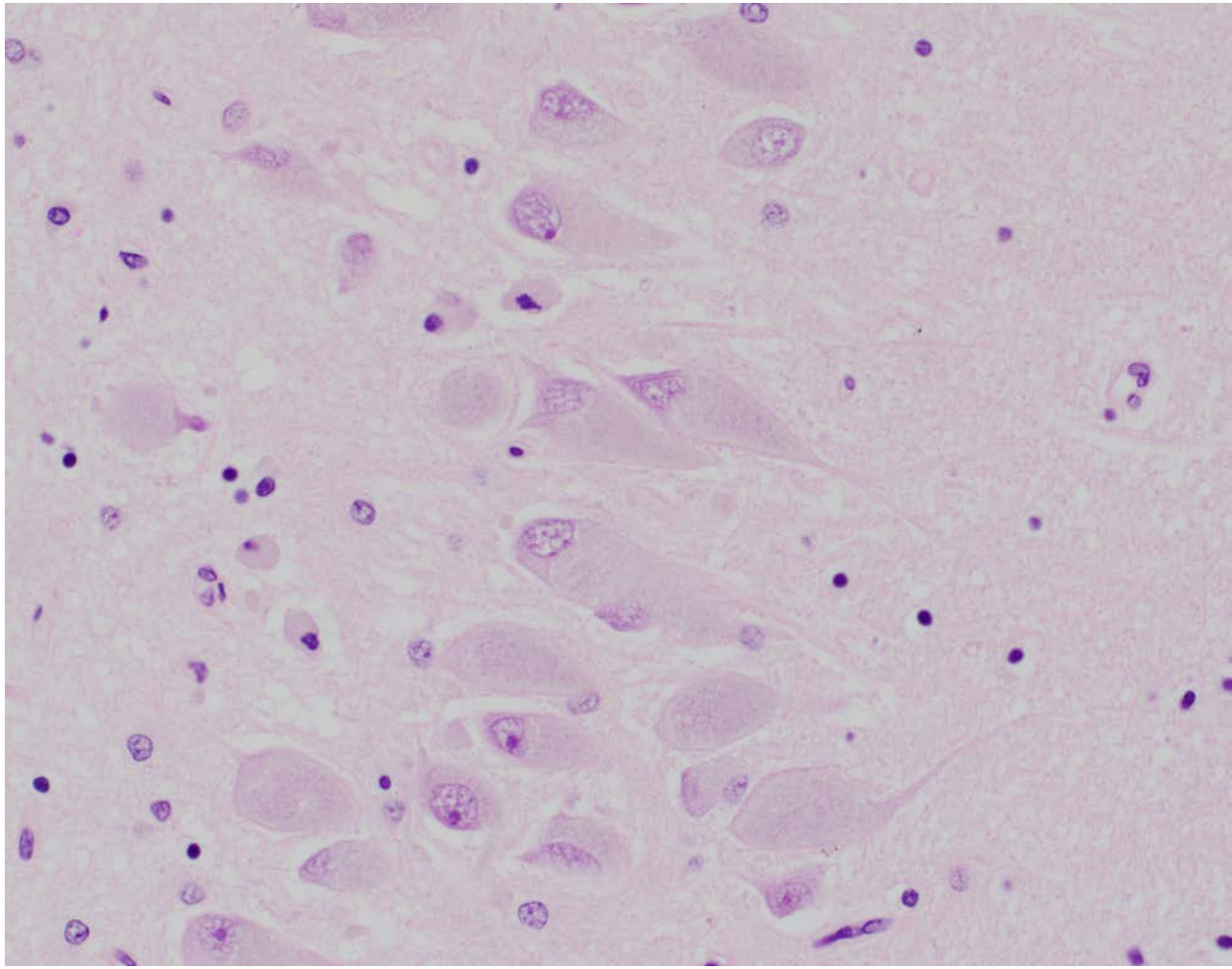


Discussion

Microscopy

Hippocampus

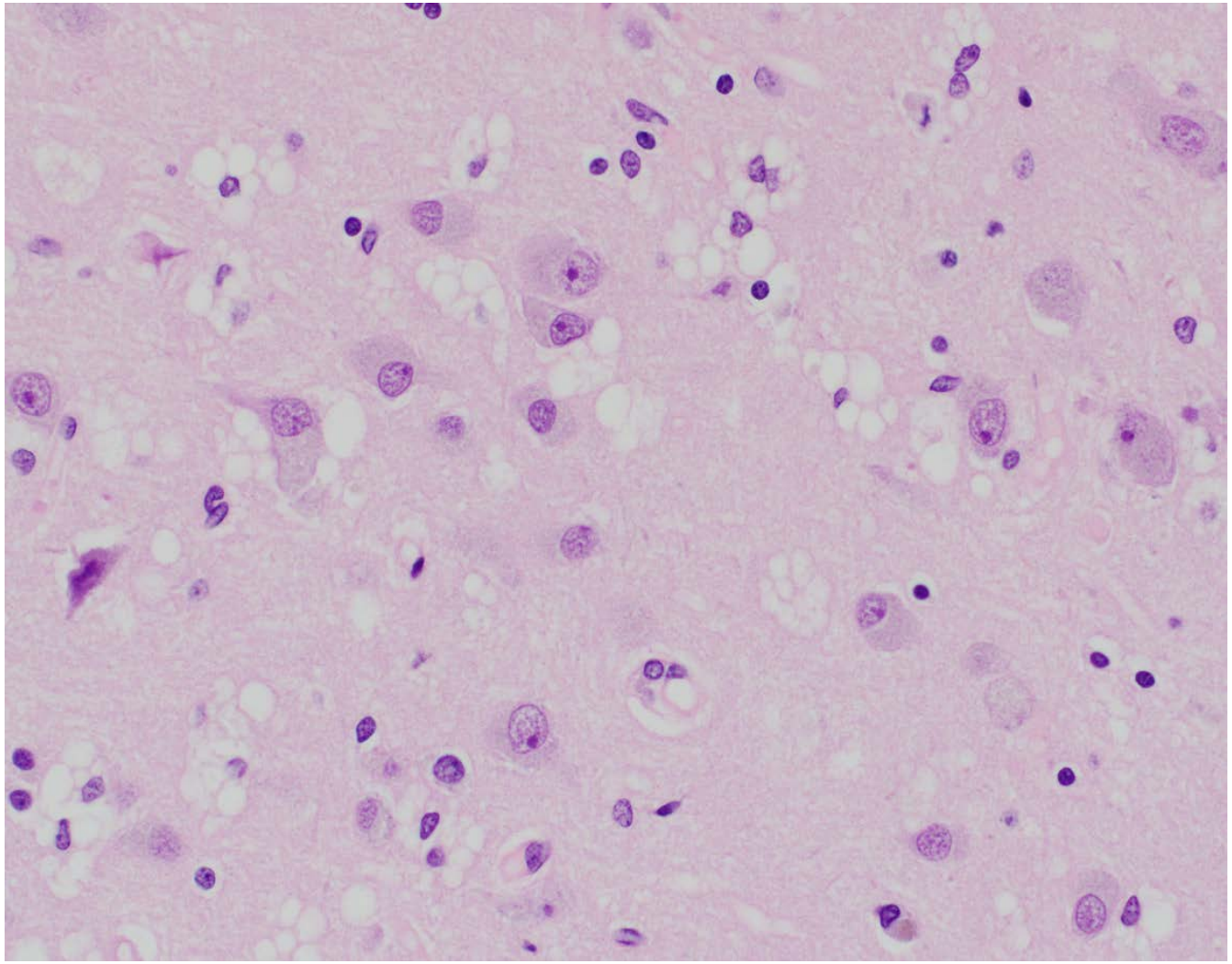




- Neurons filled with granular storage material/intracellular lipopigment

Microscopy

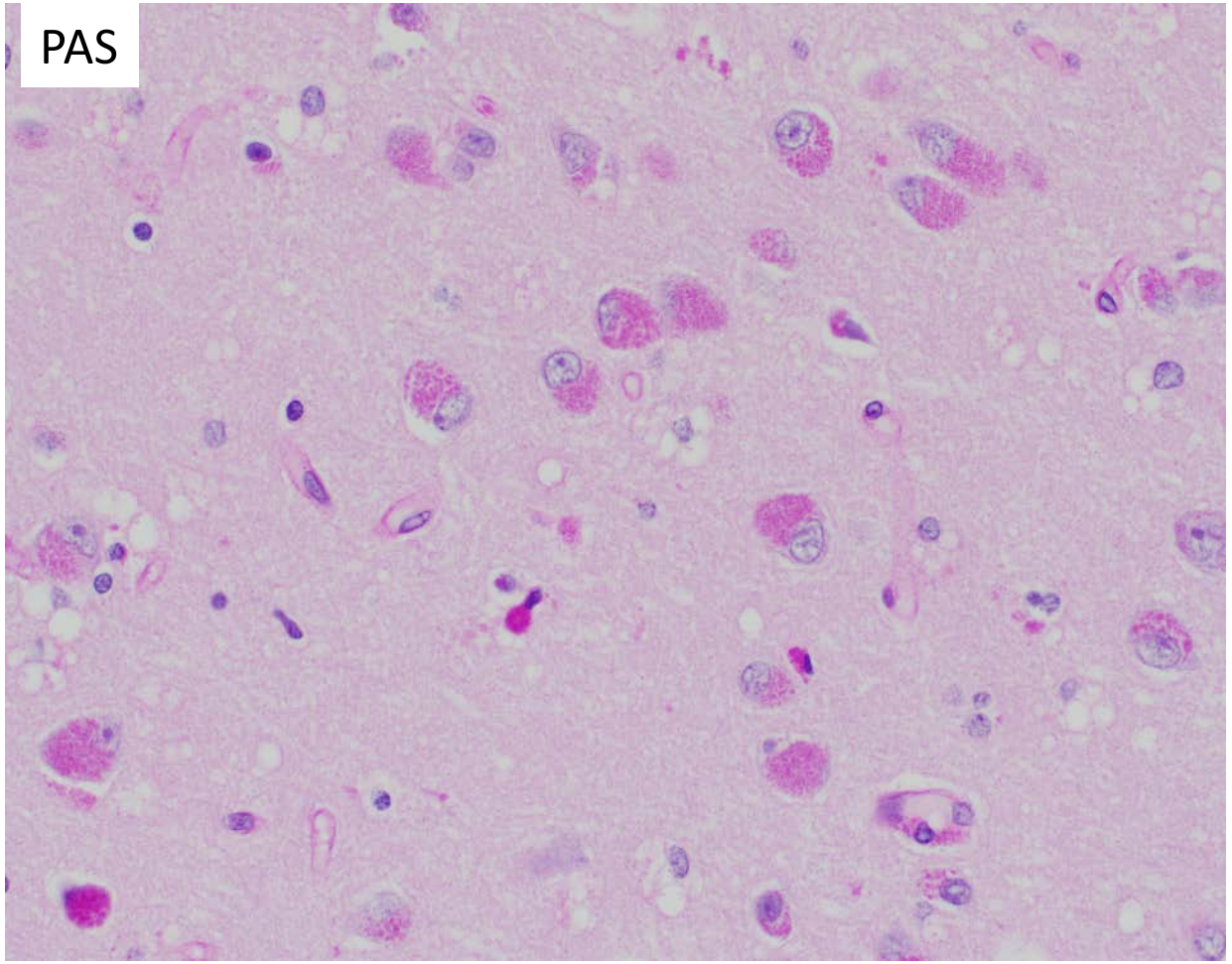
Cingulate gyrus

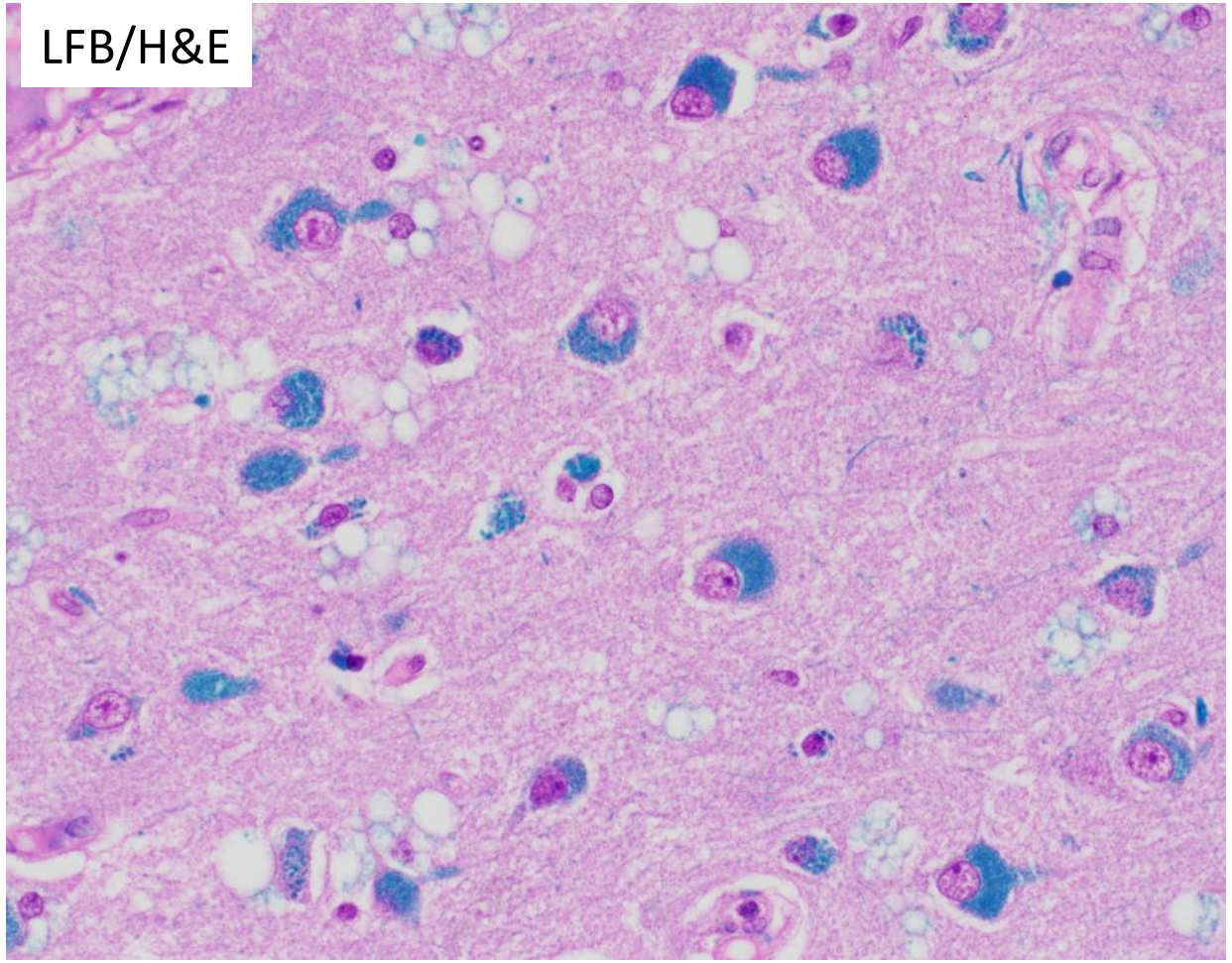


- Neurons filled with granular storage material and neuropil vacuolization

Microscopy

Cingulate gyrus

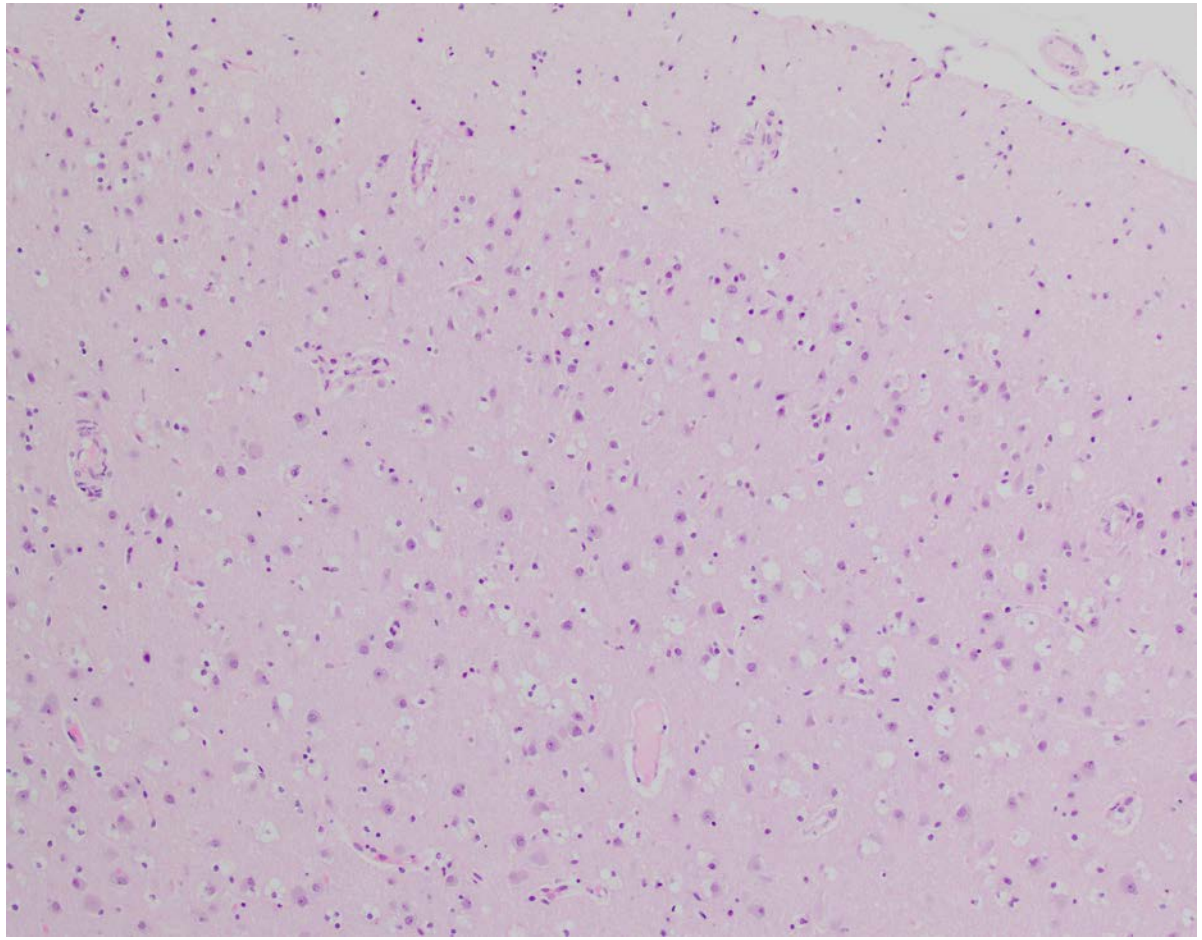


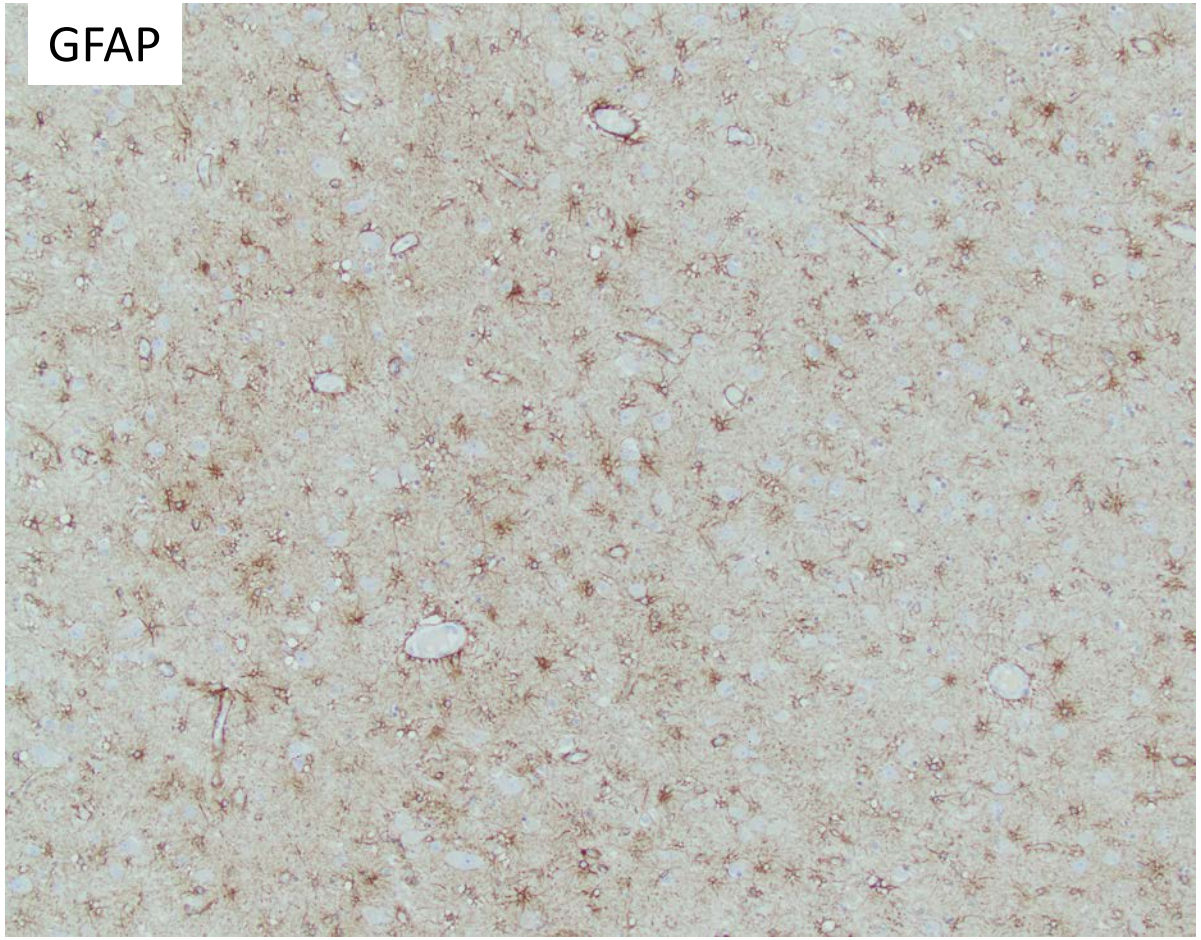


- Neurons filled with PAS and LFB positive granular storage material
- Neuropil vacuolization

Microscopy

Cingulate gyrus

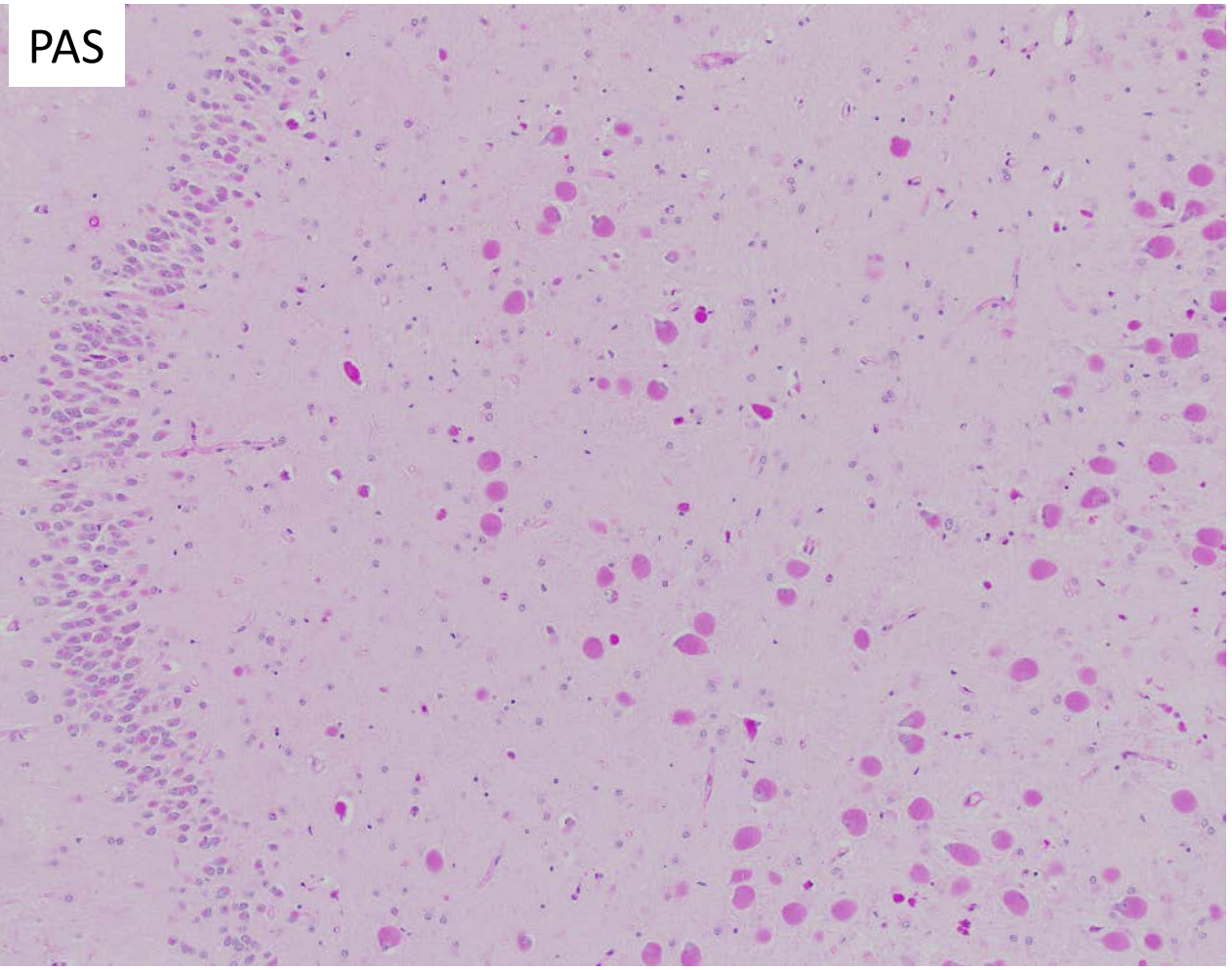


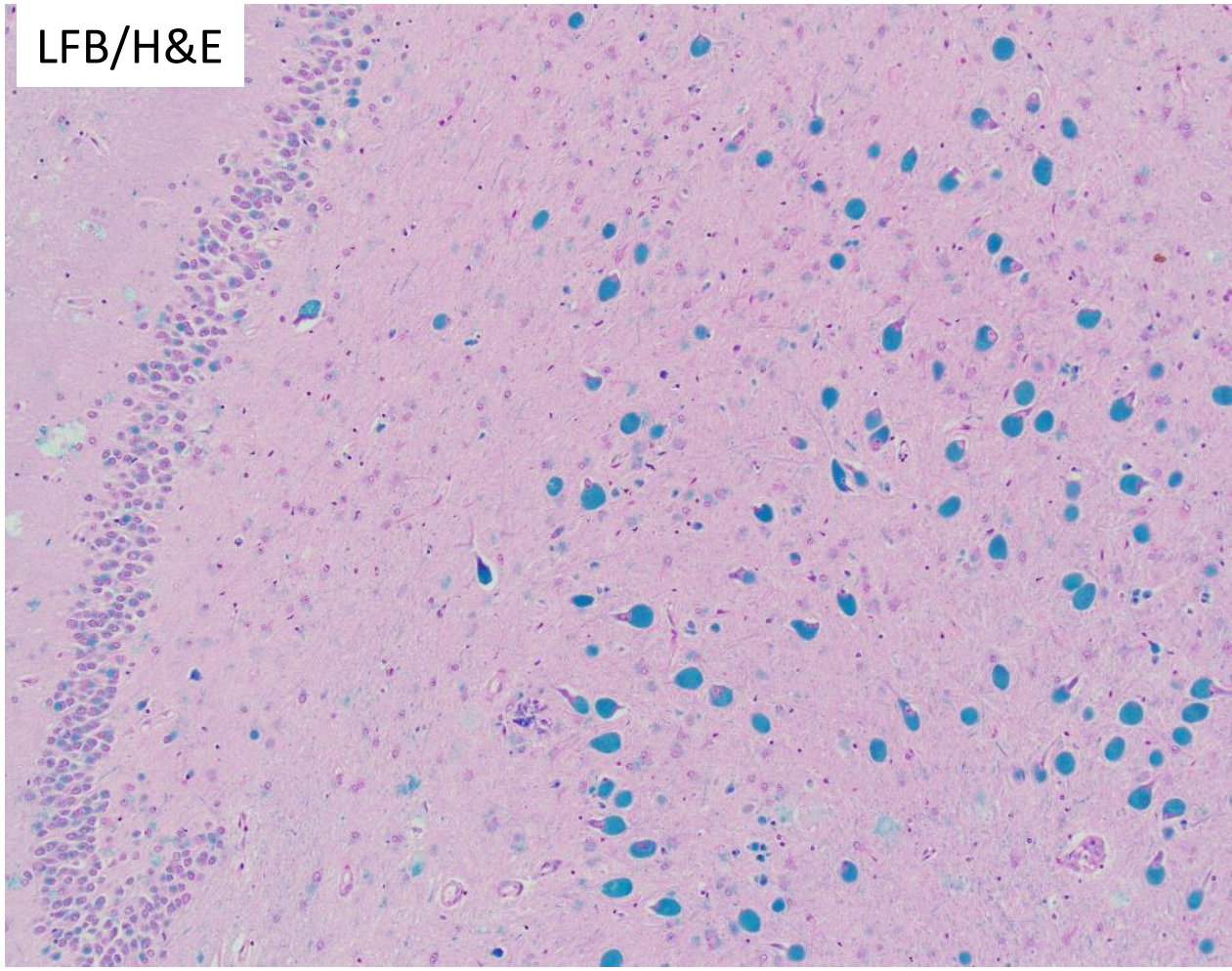


- Reactive gliosis

Microscopy

Hippocampus





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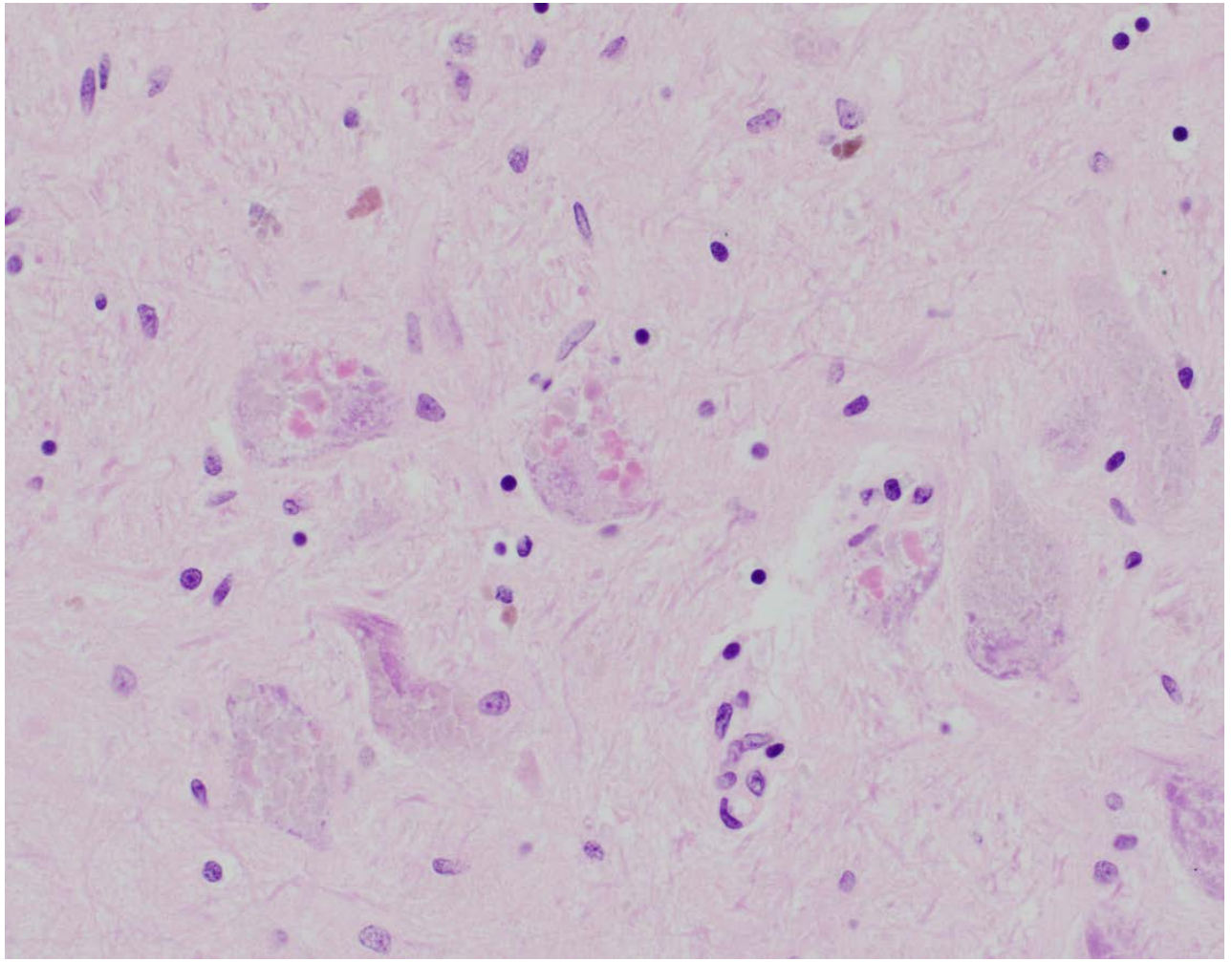
Microscopy

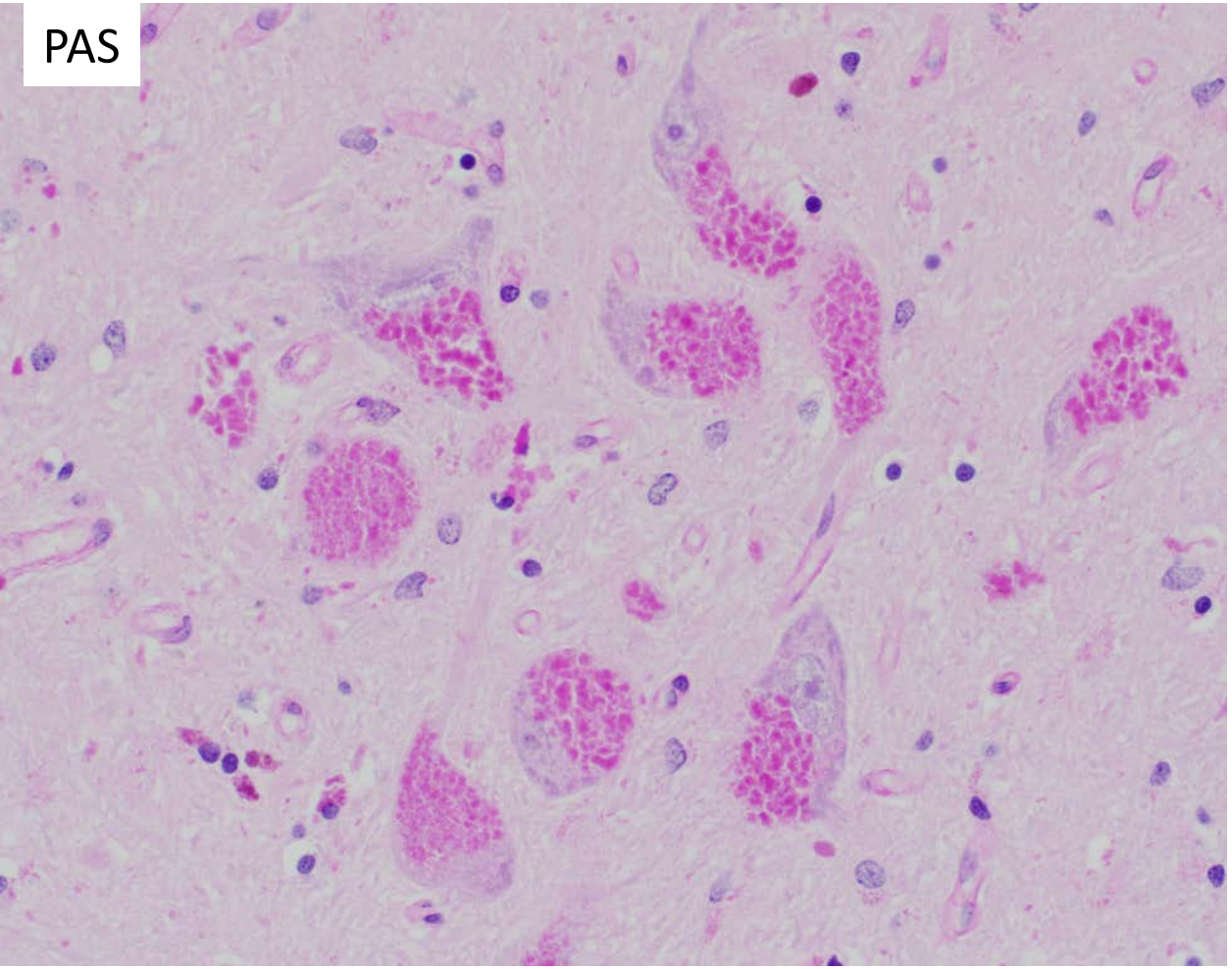
Midbrain

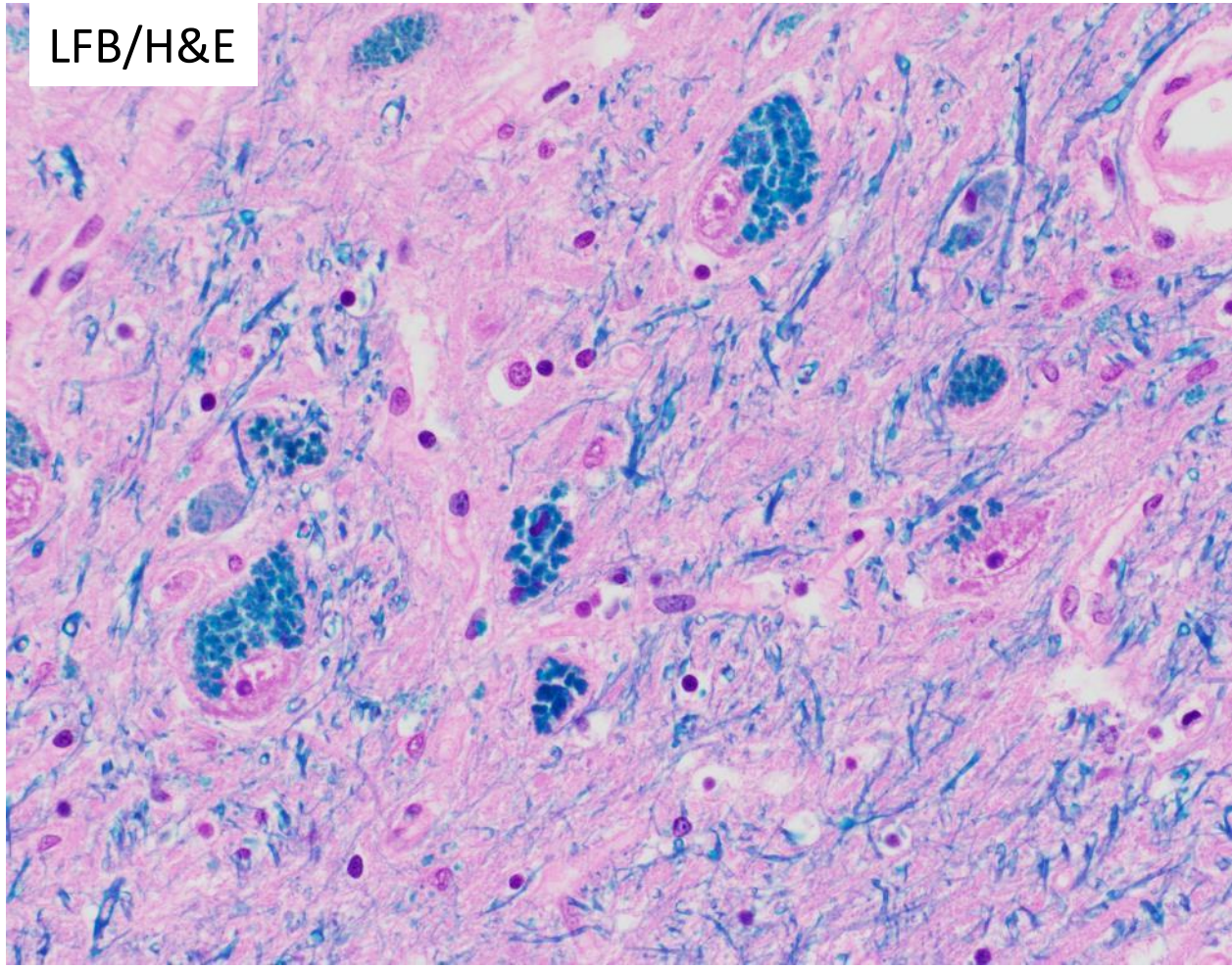


- Neurons filled with larger aggregates of eosinophilic inclusion material
- Pallor in substantia nigra neurons

Microscopy

Substantia Nigra

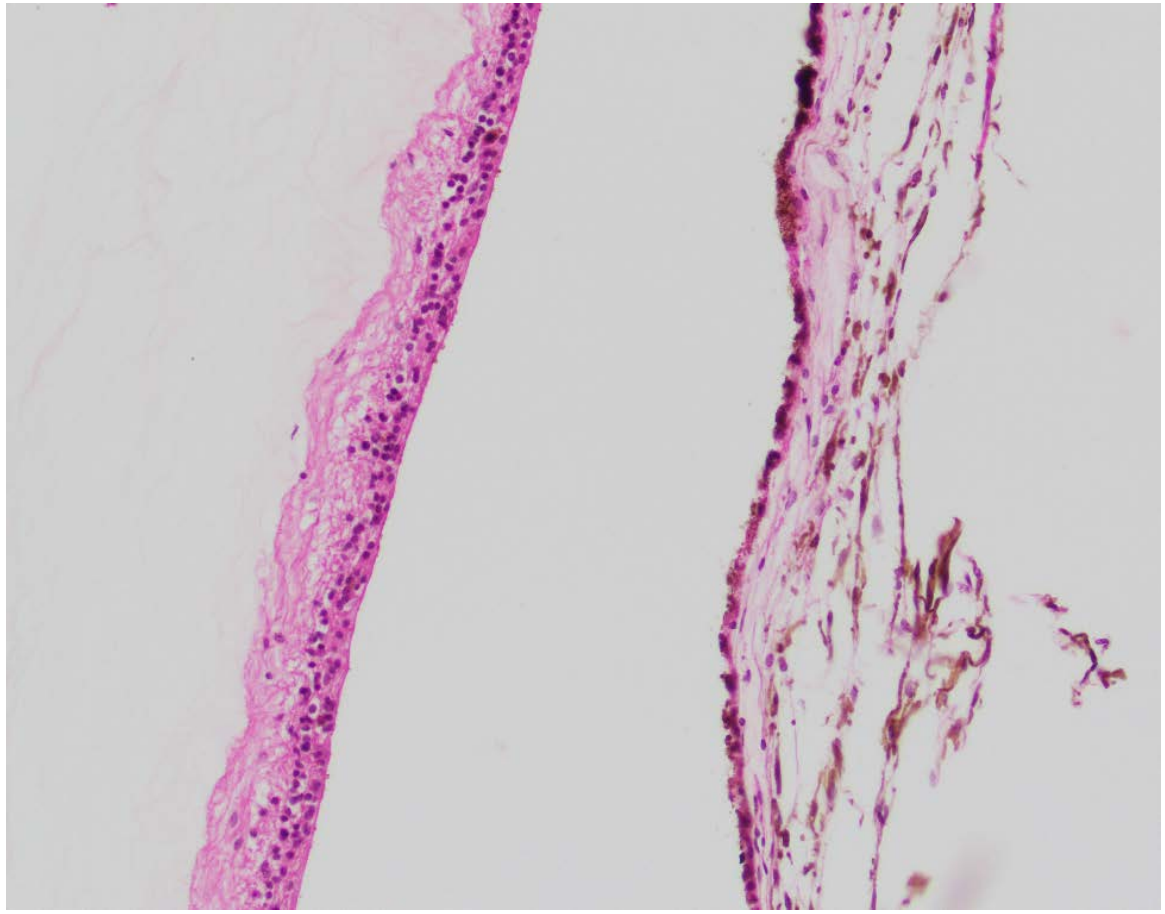


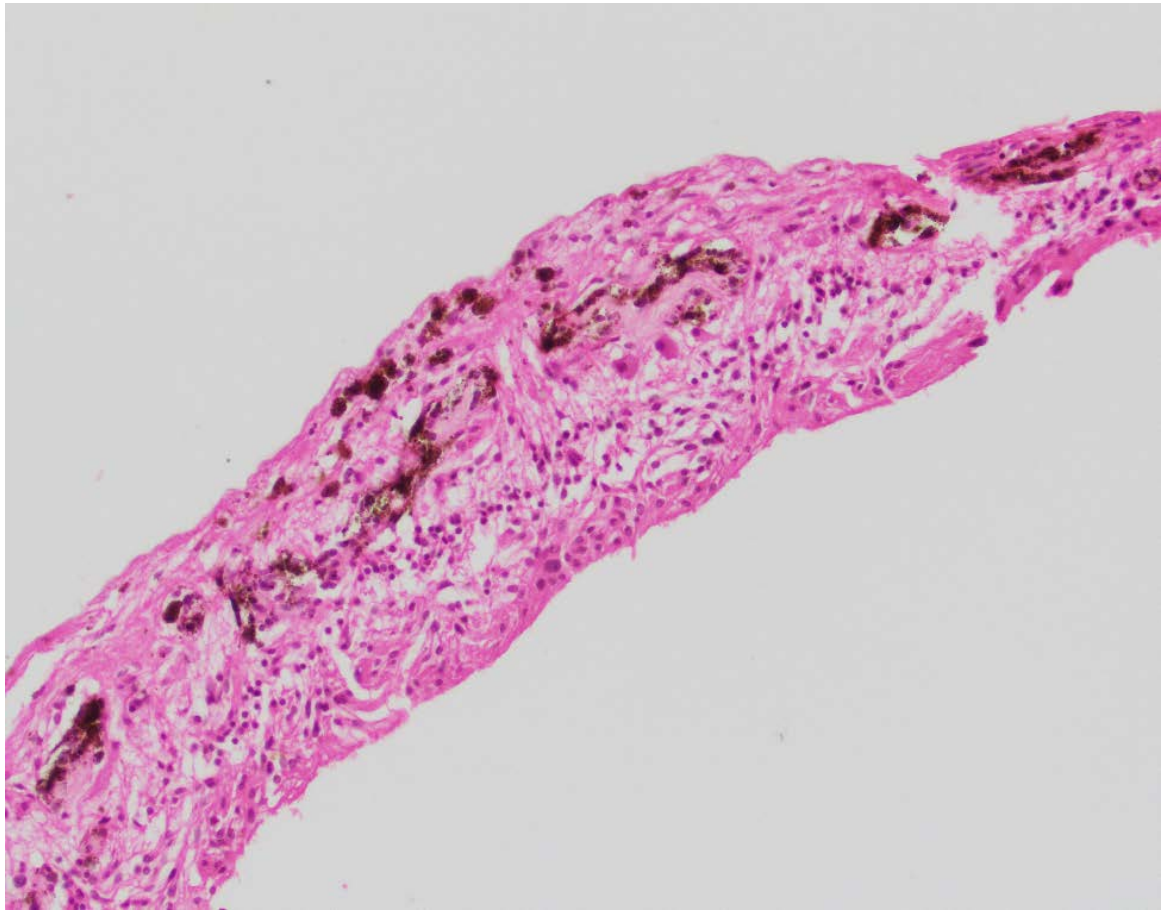


- Neurons filled with larger aggregates of eosinophilic inclusion material

Microscopy

Retina





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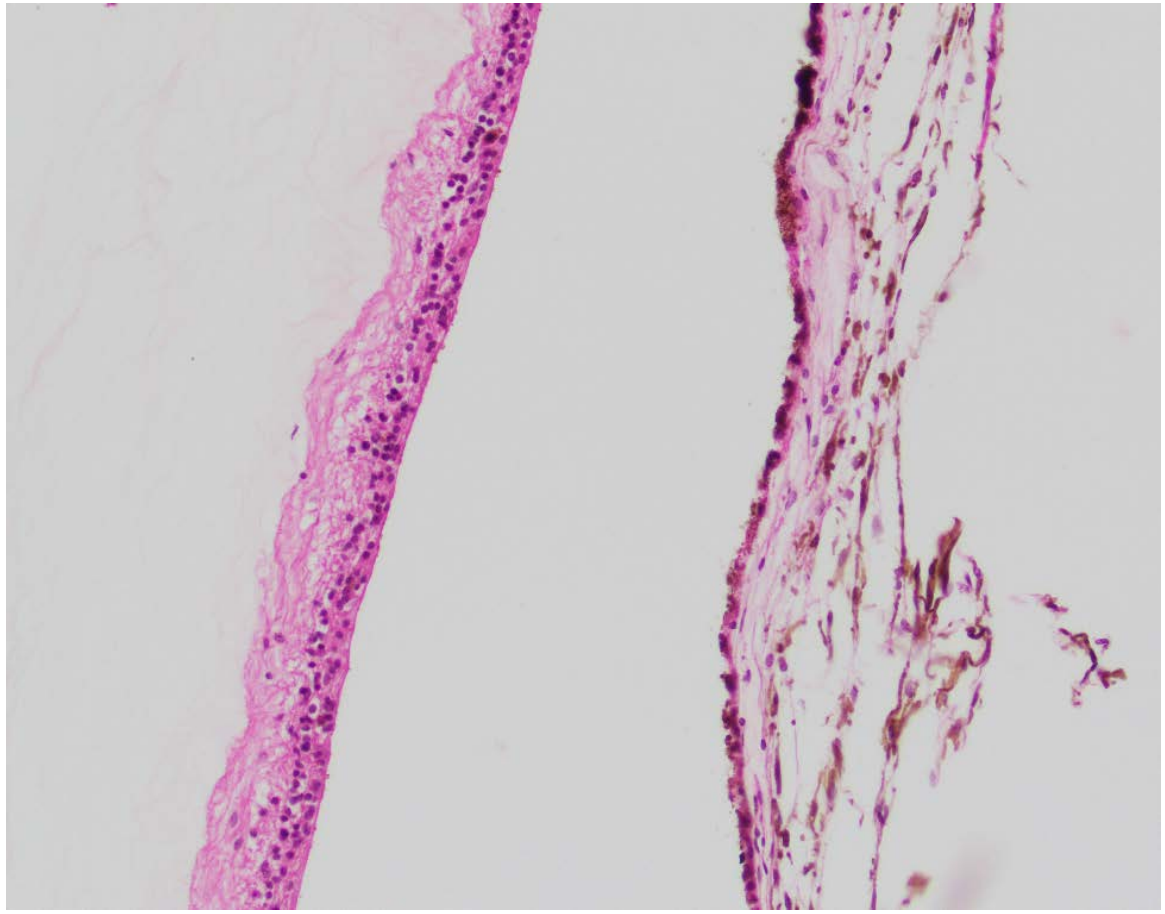

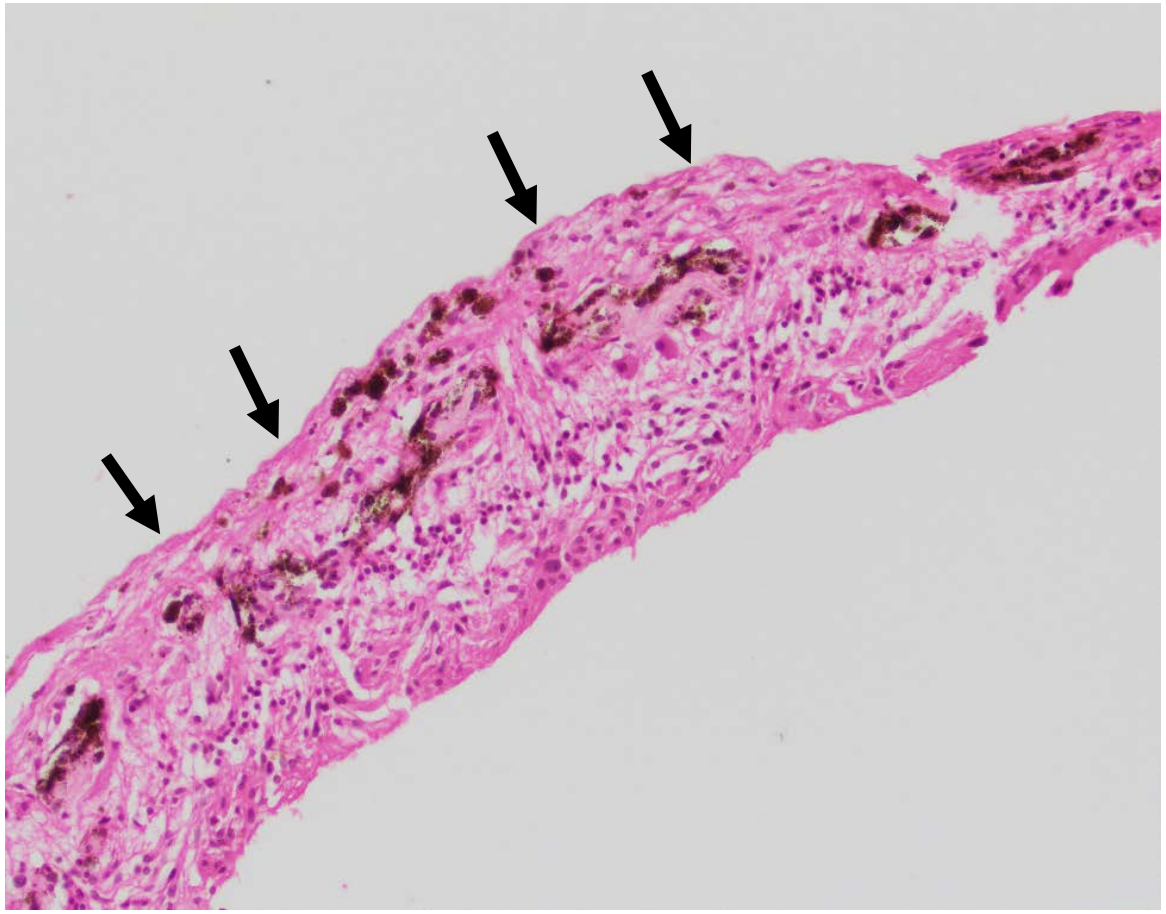

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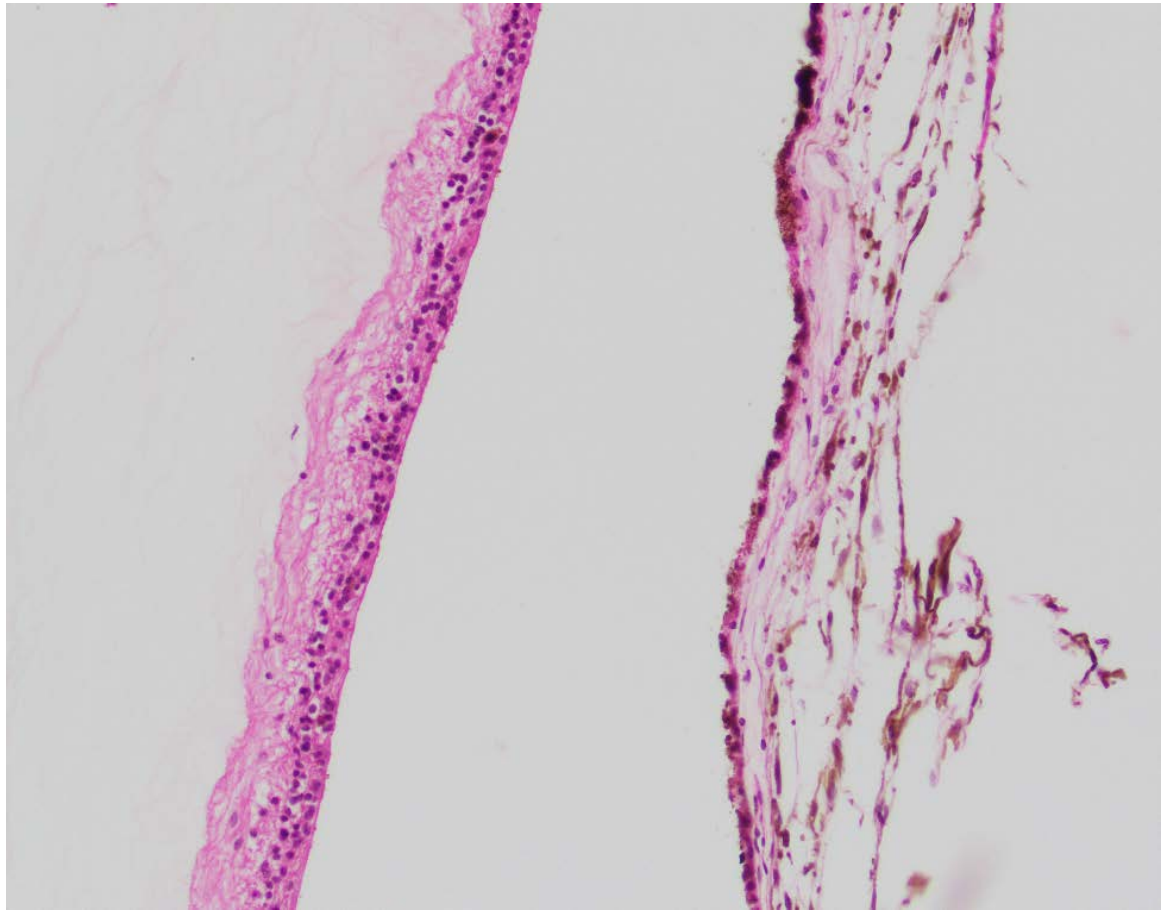
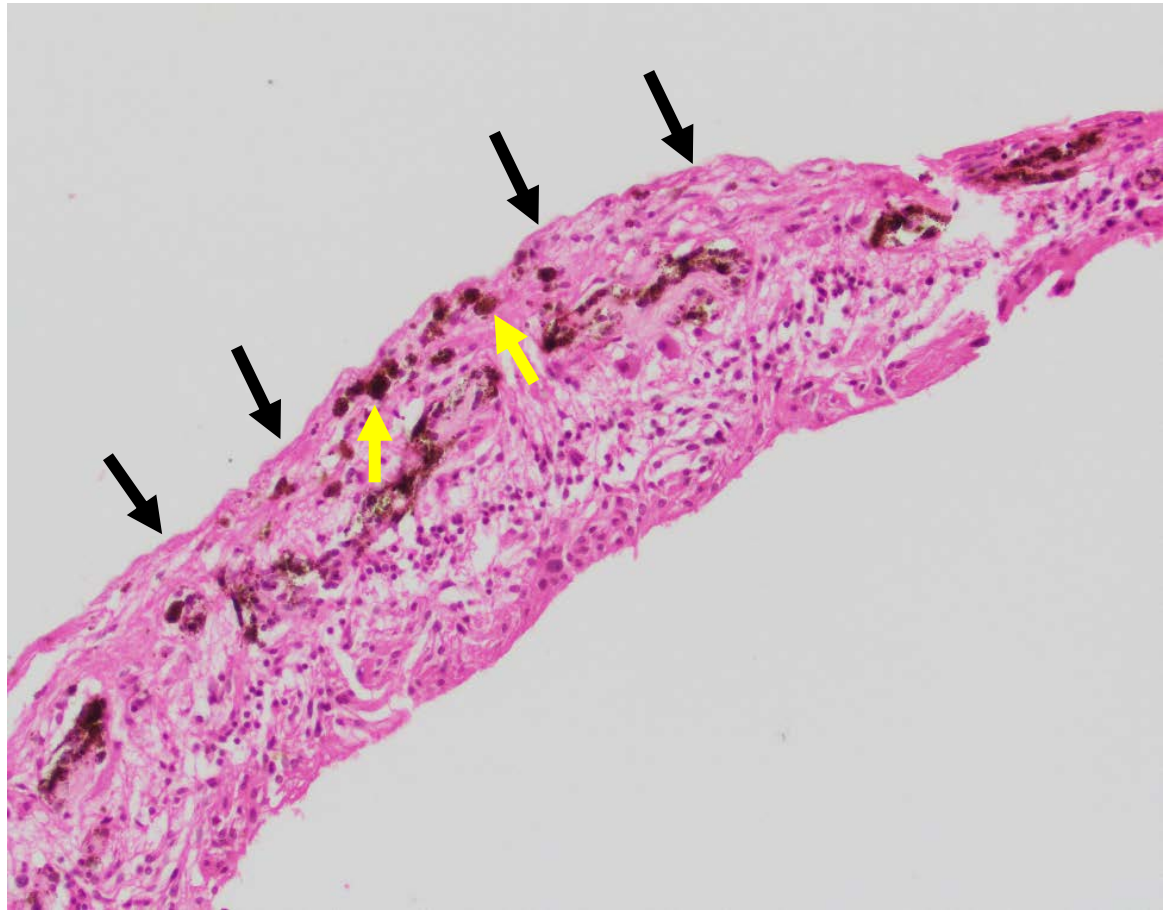
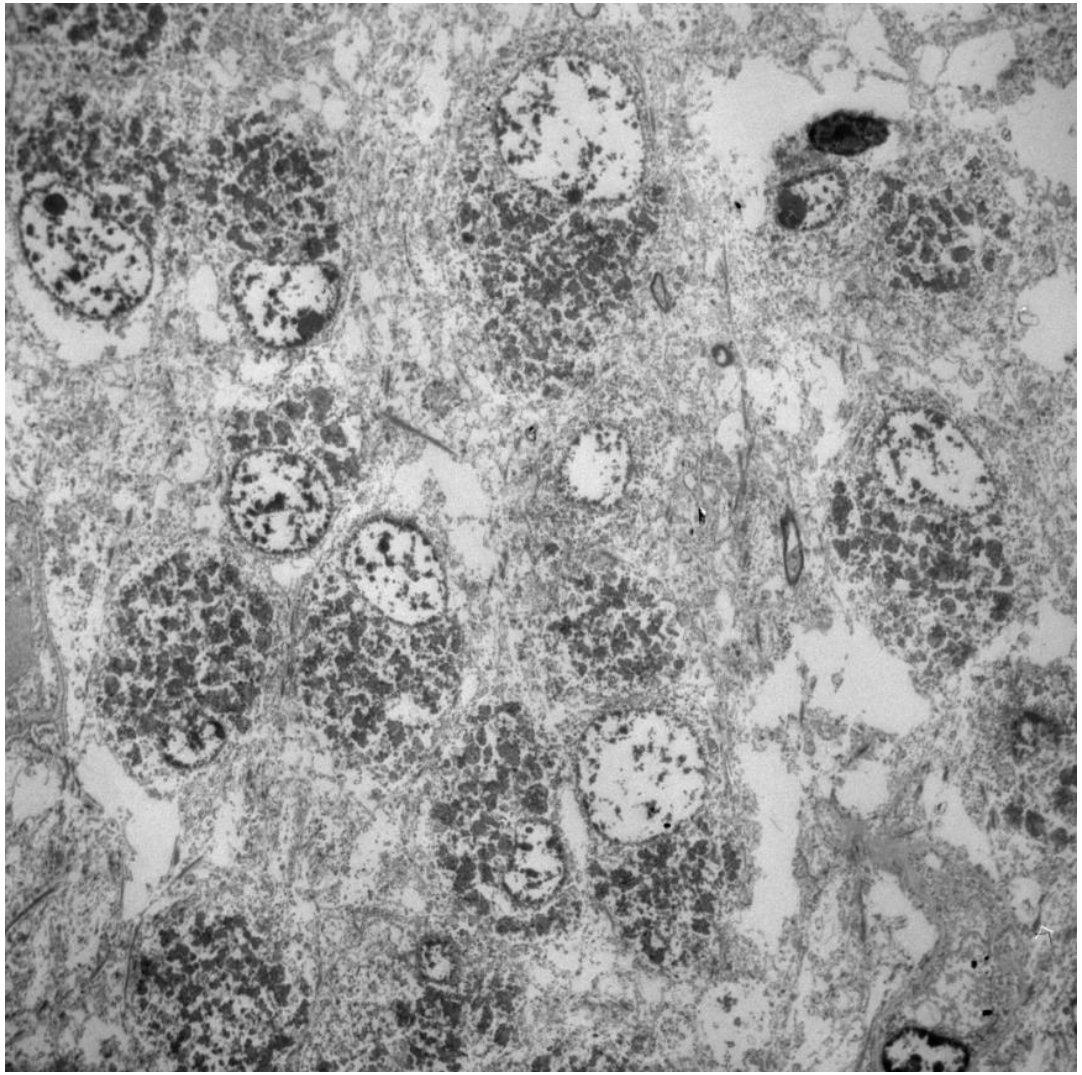




- Severe degeneration of retinal layers → glial scar
- Pigment-laden macrophages/pigment epithelium

Electron Microscopy

Brain



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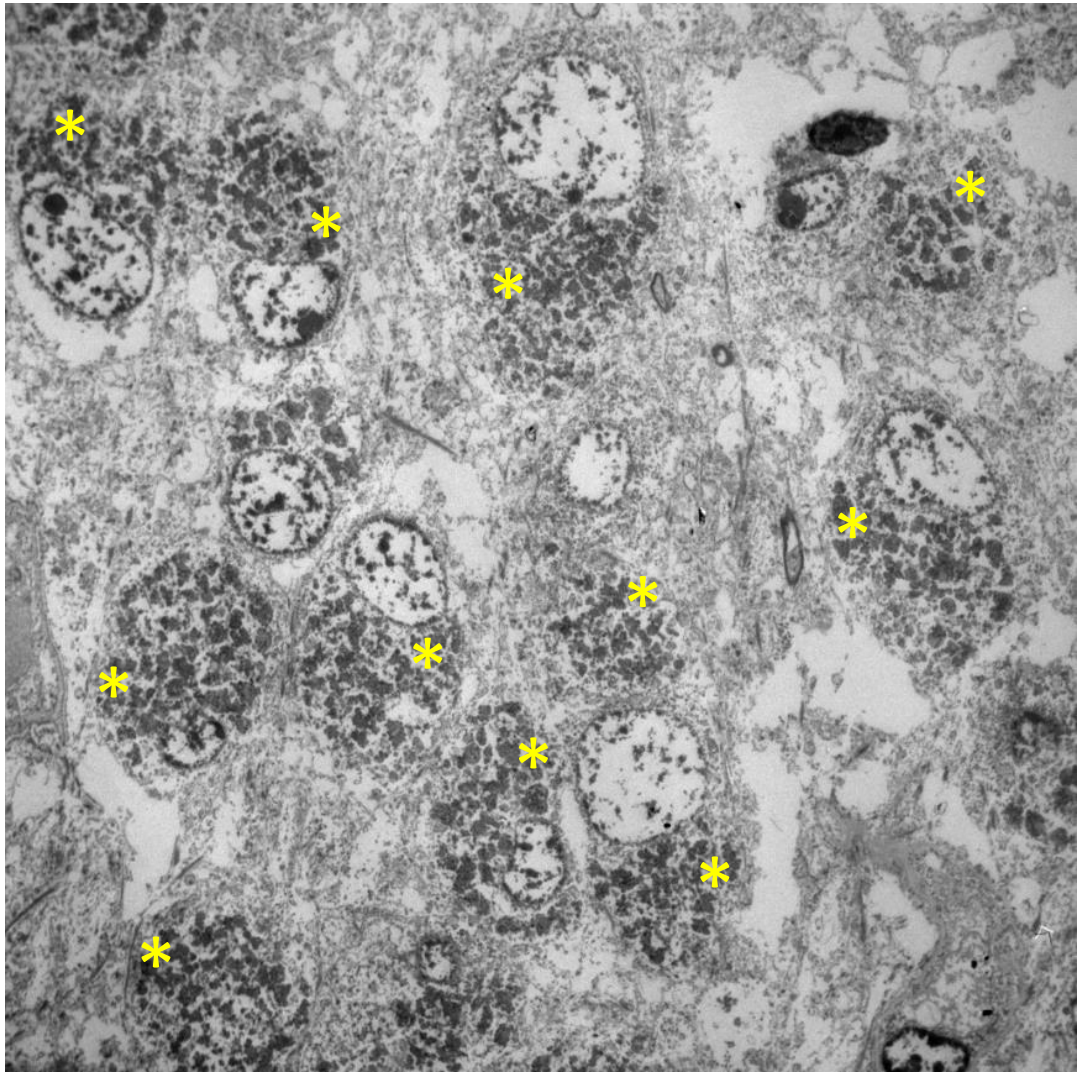

- Neuronal cytoplasmic inclusions

Electron Microscopy

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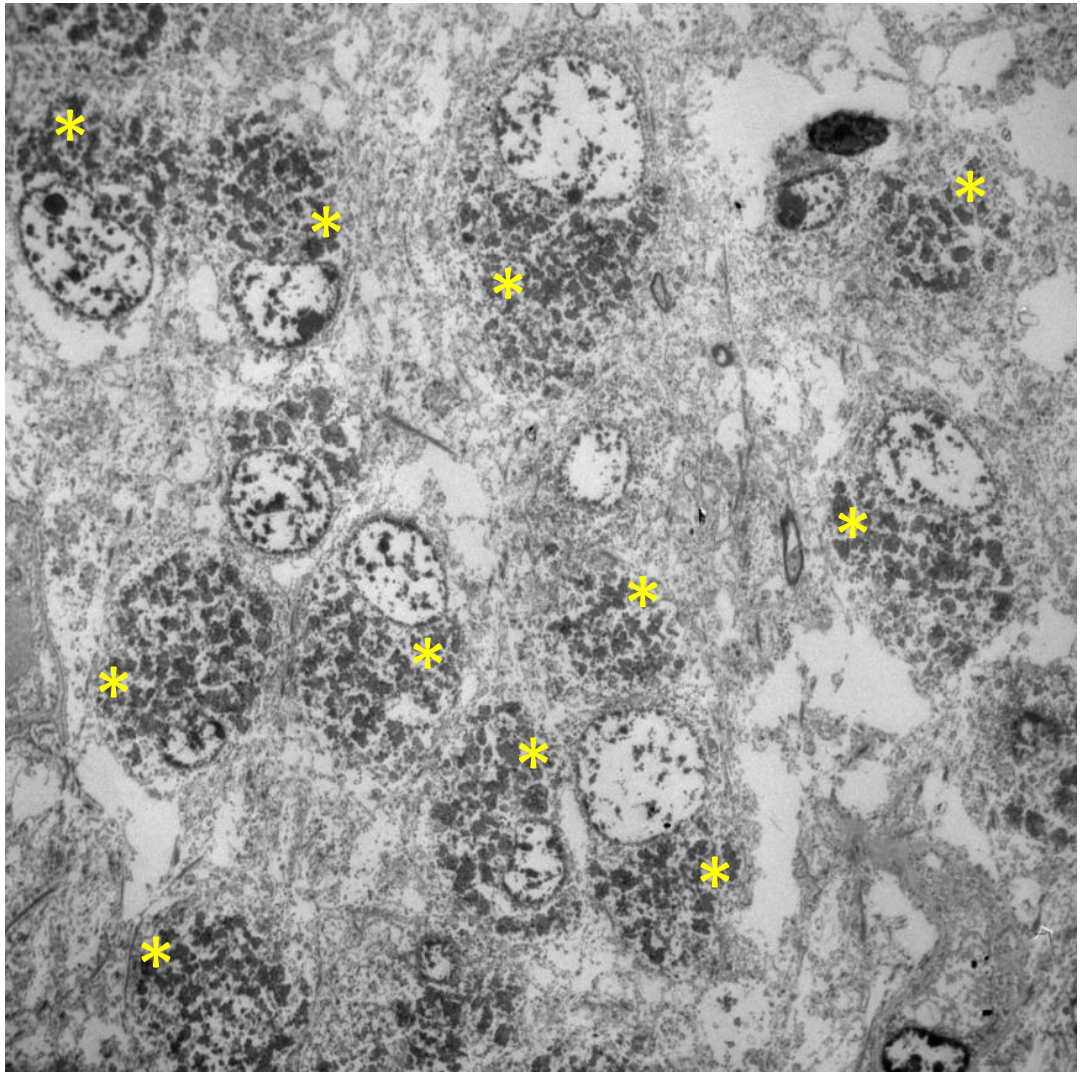

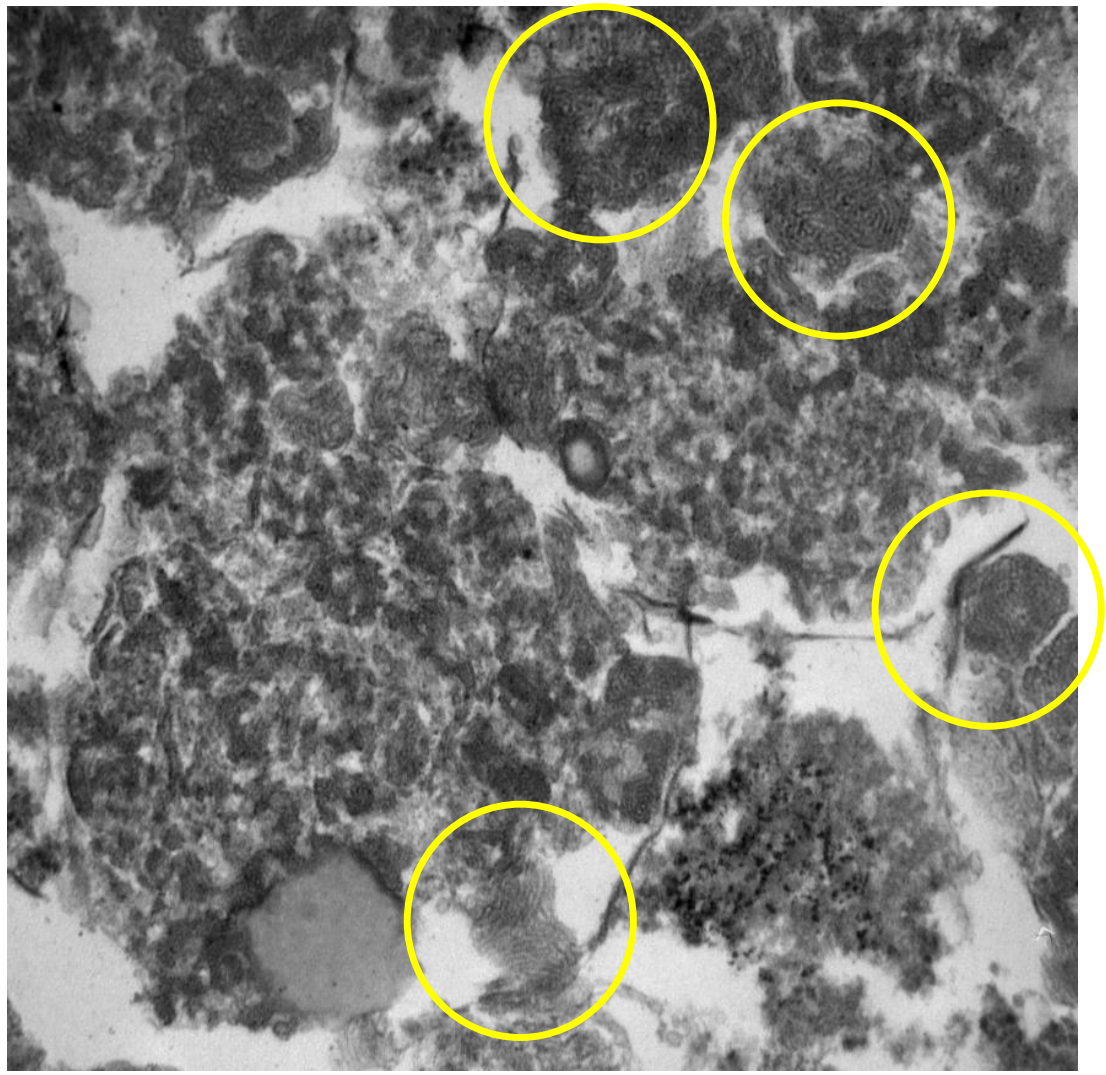

- Neuronal cytoplasmic inclusions including fingerprint bodies

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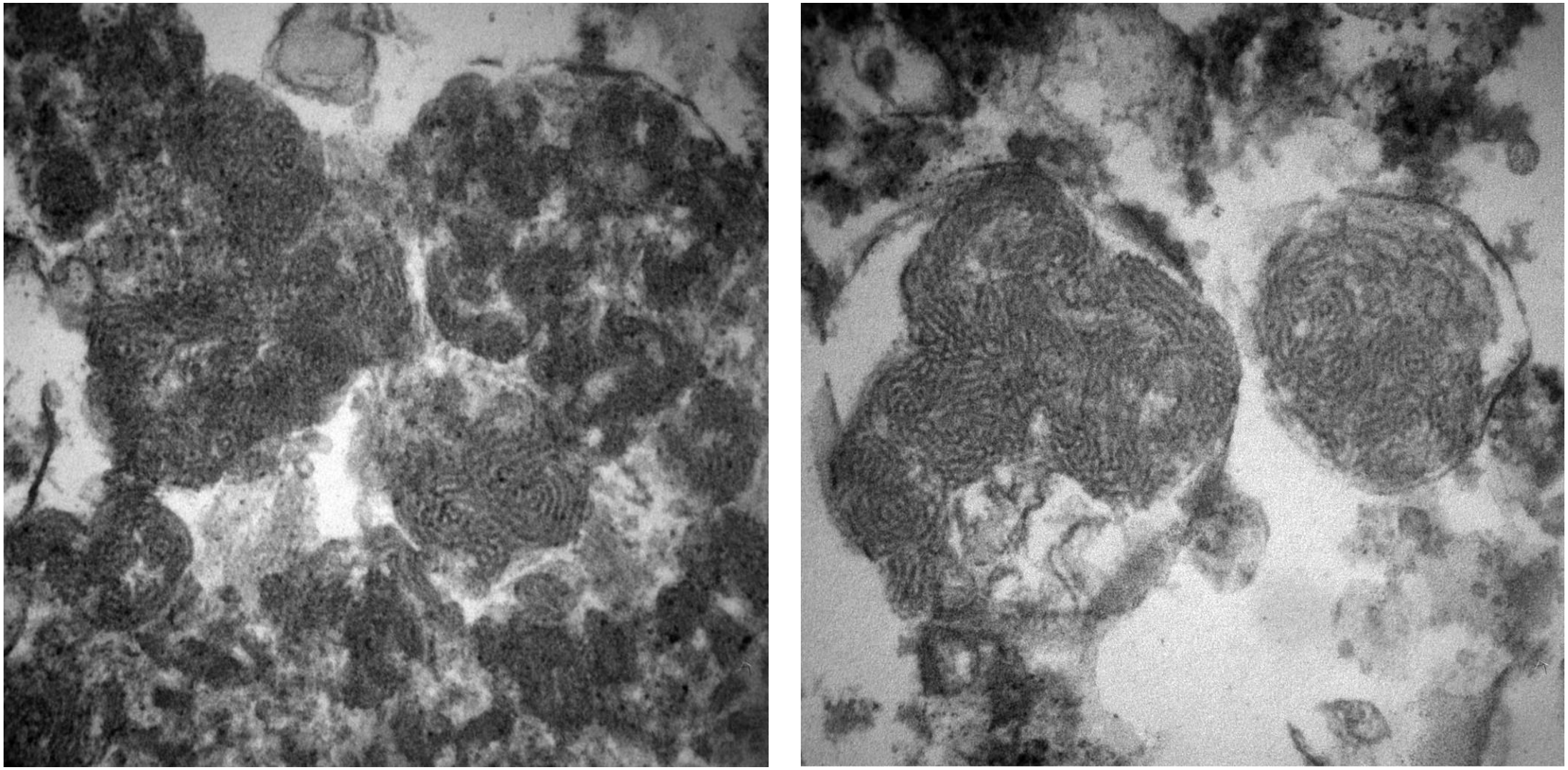

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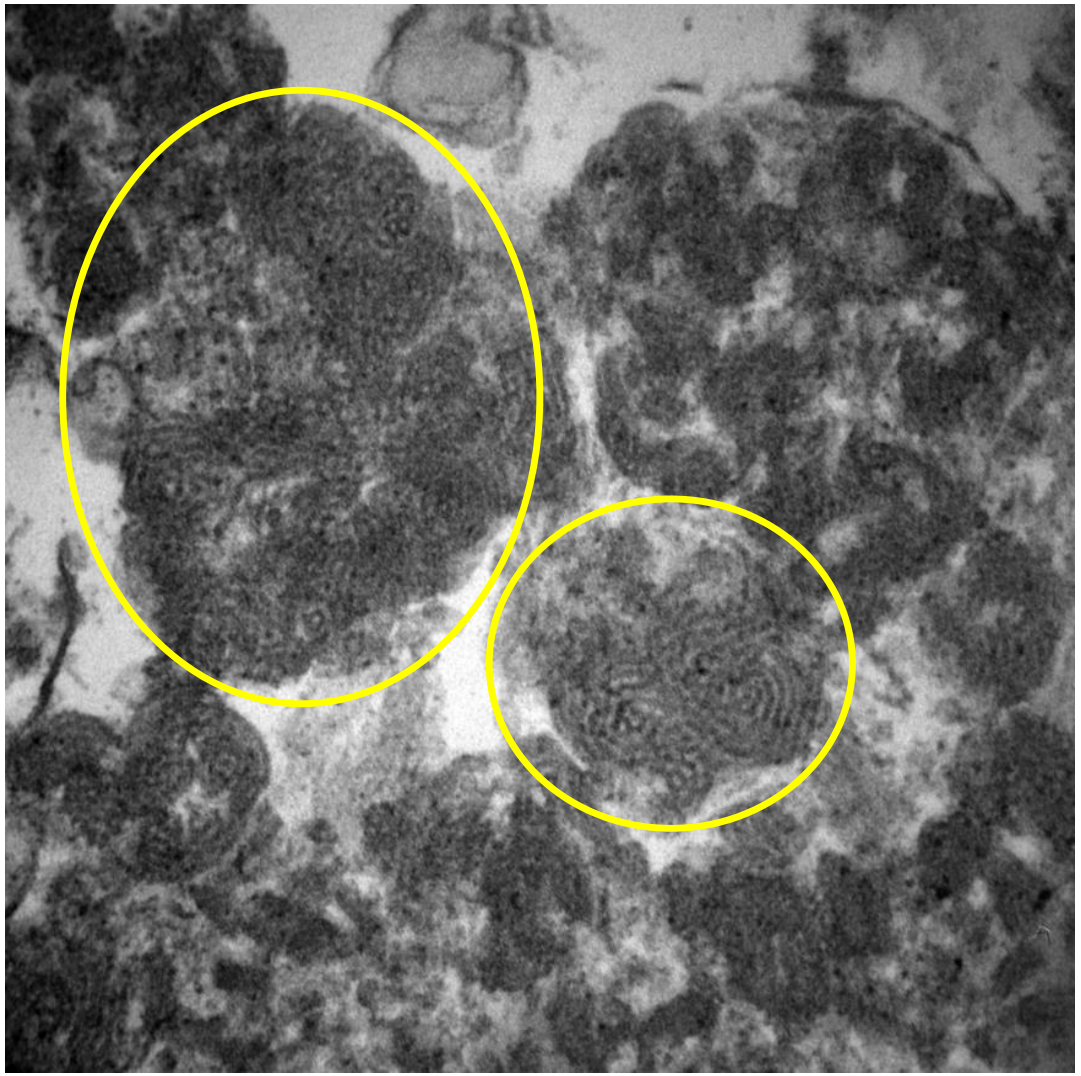

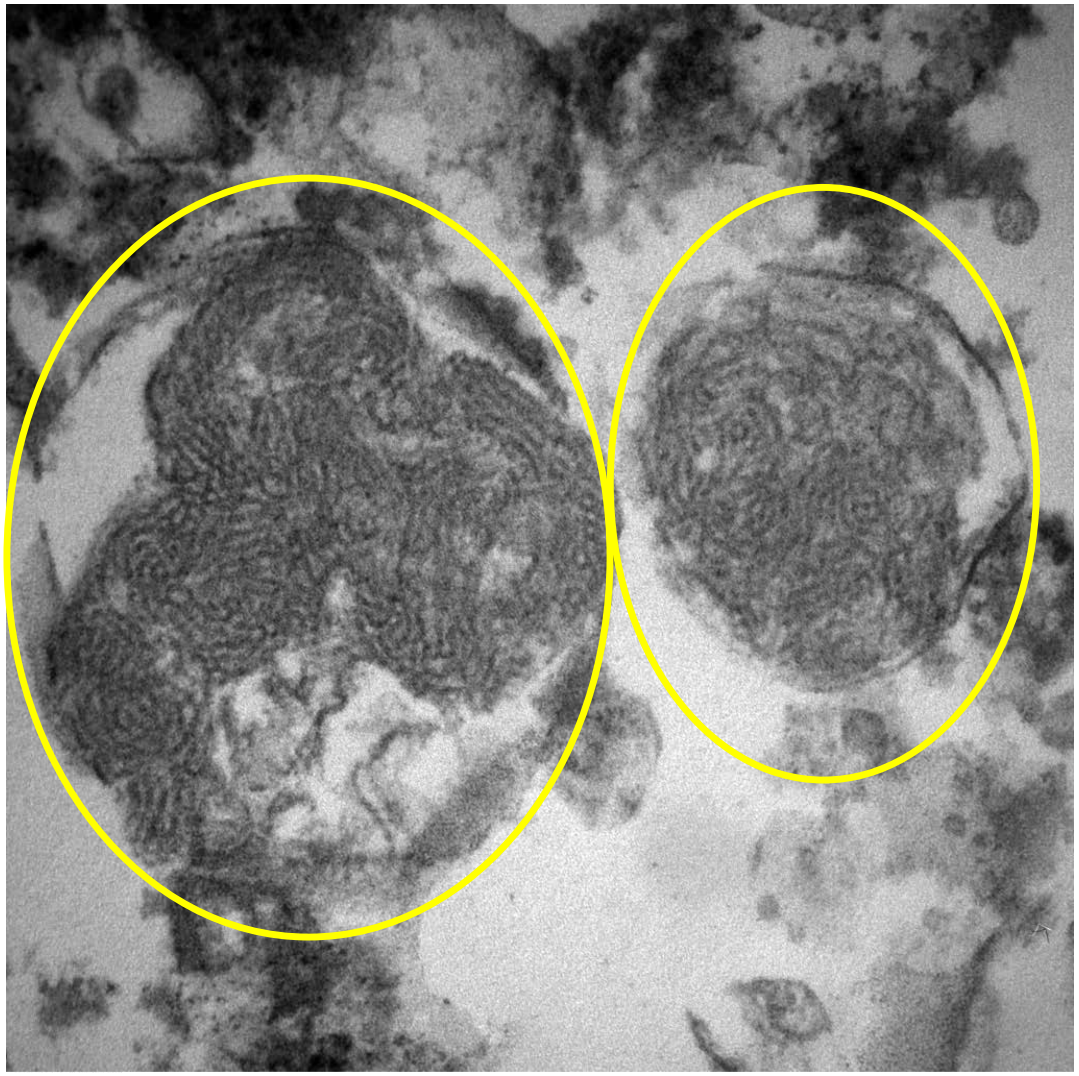

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Genetic testing and Neuropathological Diagnosis

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- **Juvenile neuronal ceroid lipofuscinosis/CLN3 disease (Batten Disease)**

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- Mutations in at least 14 genes
- Variable age of onset, symptoms, pathological findings
- Principle features: visual impairment, cognitive/motor decline, seizures, premature death
- Neuronal loss, reactive gliosis, and lysosomal accumulation of autofluorescent storage material (ASM) or lipopigment

Juvenile NCL/CLN3 Disease

- Autosomal recessive mutation in ceroid-lipofuscinosis, neuronal 3 gene (*CLN3)*
  - Encodes BATTENIN: ubiquitously expressed, transmembrane protein, unknown function
  - 85% have homozygous 1kb deletion→ truncated, nonfunctional protein

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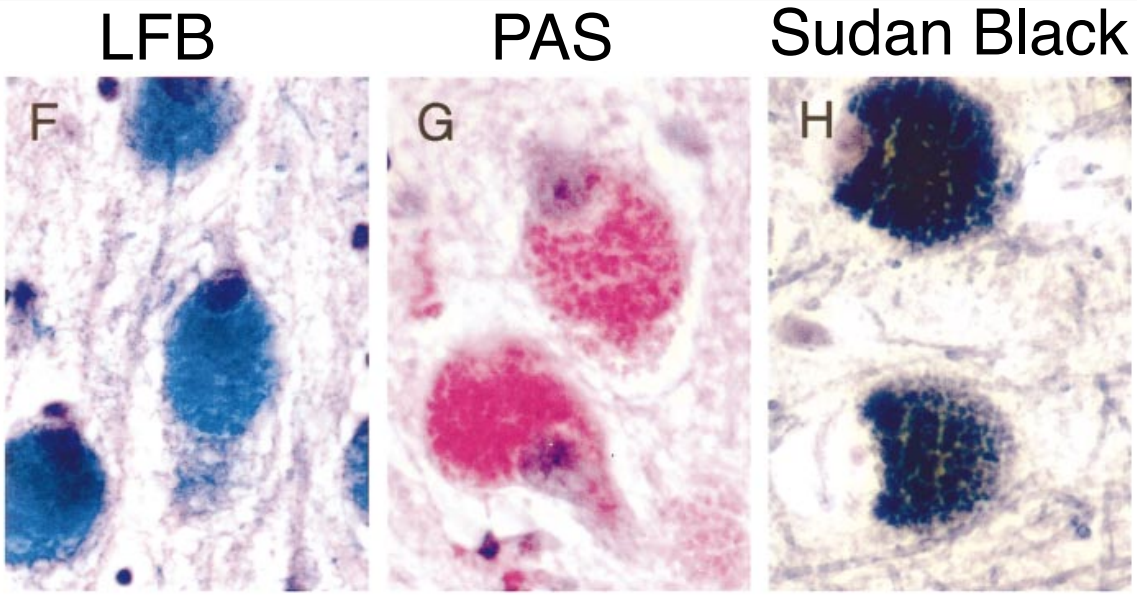
- Vision loss followed by cognitive/motor decline, speech problems, seizures, death in 2nd/3rd decade
- Autopsy
  - Significant neuronal loss
  - Gray matter can appear light brown/yellow/tan due to excessive lipopigment and gliosis?
  - Pallor in substantia nigra
  - Retinal atrophy, optic nerve degeneration, lateral geniculate nuclei degeneration

Juvenile NCL/CLN3 Disease

- Intracellular lipopigment/ASMs
  - Luxol fast blue
  - PAS
  - Sudan black
  - Acid phosphatase
  - Autofluorescence



Haltia, *J Neuropathol Exp Neurol*, 2003

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- Intracellular lipopigment/ASMs
  - Luxol fast blue
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  - Acid phosphatase
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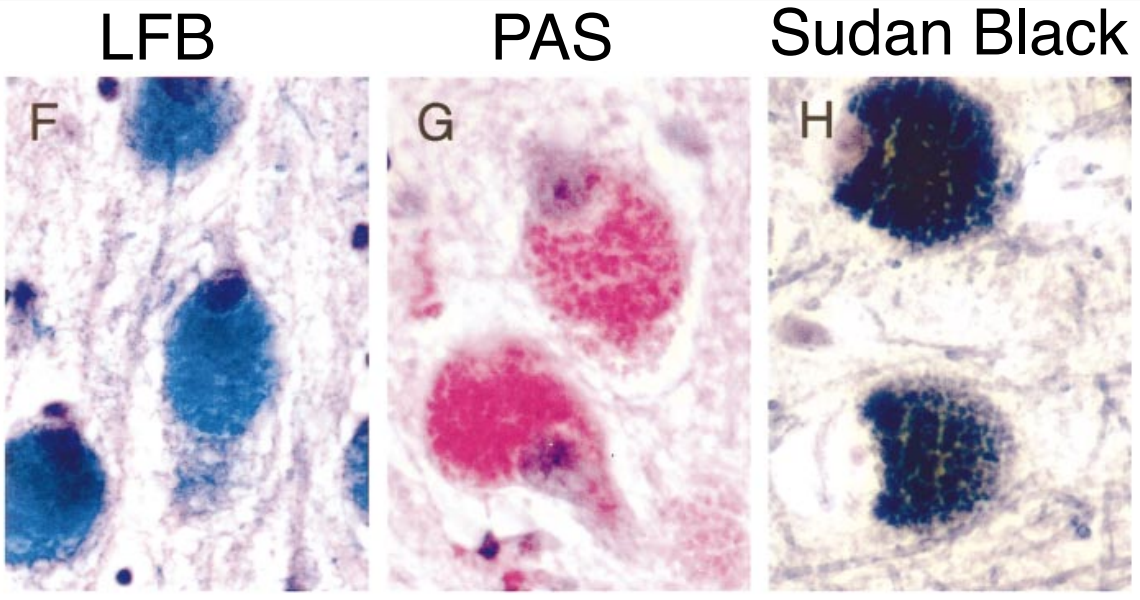

- Characteristic ultrastructural finding:
  - Fingerprint bodies

Haltia, *J Neuropathol Exp Neurol*, 2003

Summary

JNCL/CLN3 disease

- Genetic testing: homozygous deletion in *CLN3 (most common)*
- Generalized cortical atrophy
- ASM/lipopigment in neurons throughout the brain
- Retinal degeneration
- Fingerprint body inclusions on EM

References

1. Haltia, M. The neuronal ceroid-lipofuscinoses. J Neuropathol Exp Neurol. 2003 Jan;62(1):1-13.

2. Johnson TB, Cain JT, White KA, Ramirez-Montealegre D, Pearce DA, Weimer JM. Therapeutic landscape for Batten disease: current treatments and future prospects. Nat Rev Neurol. 2019 Mar;15(3):161-78.

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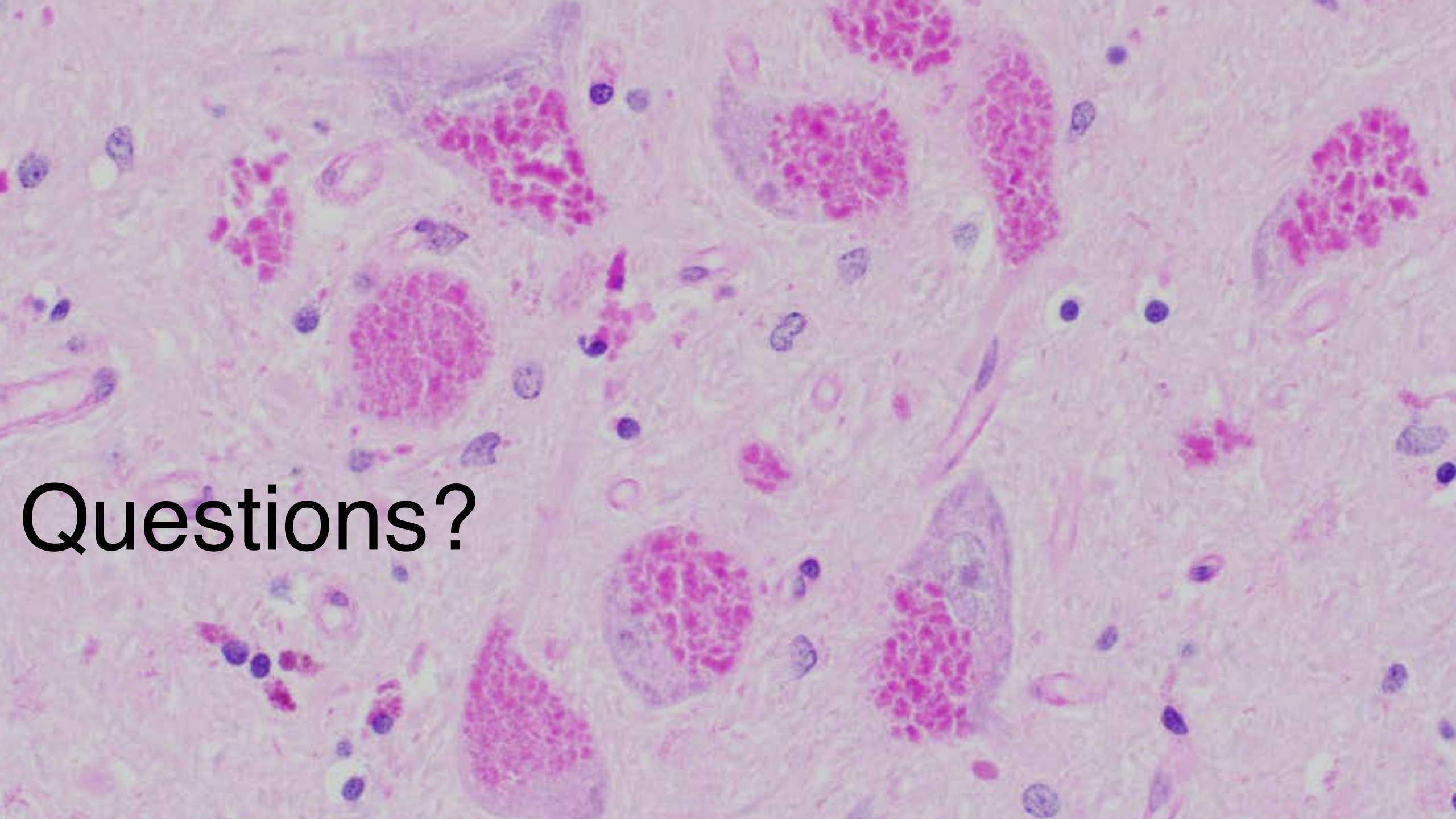
4. Wright GA, Georgiou M, Robson AG, et al. Juvenile Batten Disease (CLN3): Detailed Ocular Phenotype, Novel Observations, Delayed Diagnosis, Masquerades, and Prospects for Therapy. Ophthalmol Retina. 2019 Nov 13.


Questions?