MAYO CLINIC

64th Annual Diagnostic Slide Session 2023

Case 10

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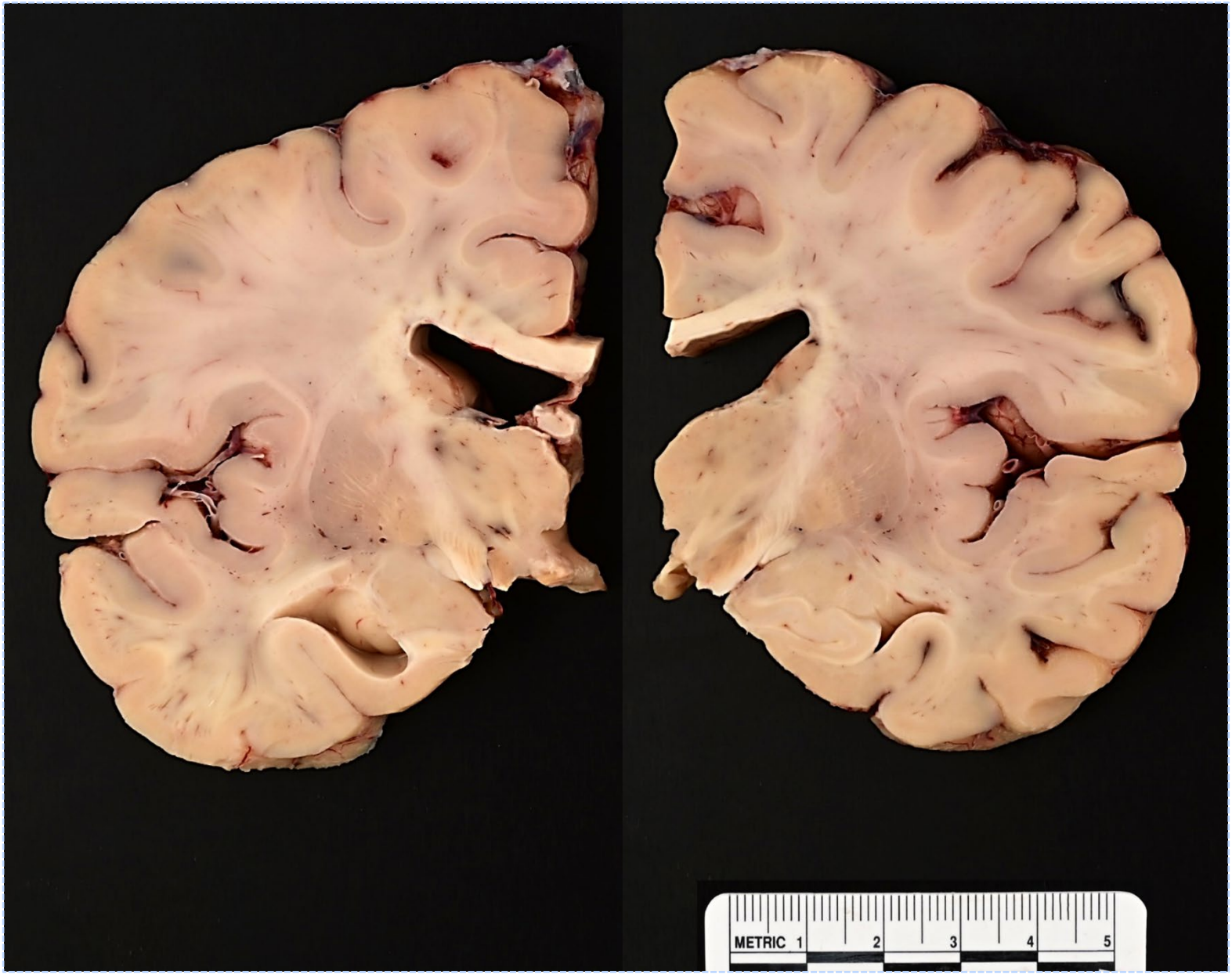
No financial disclosures

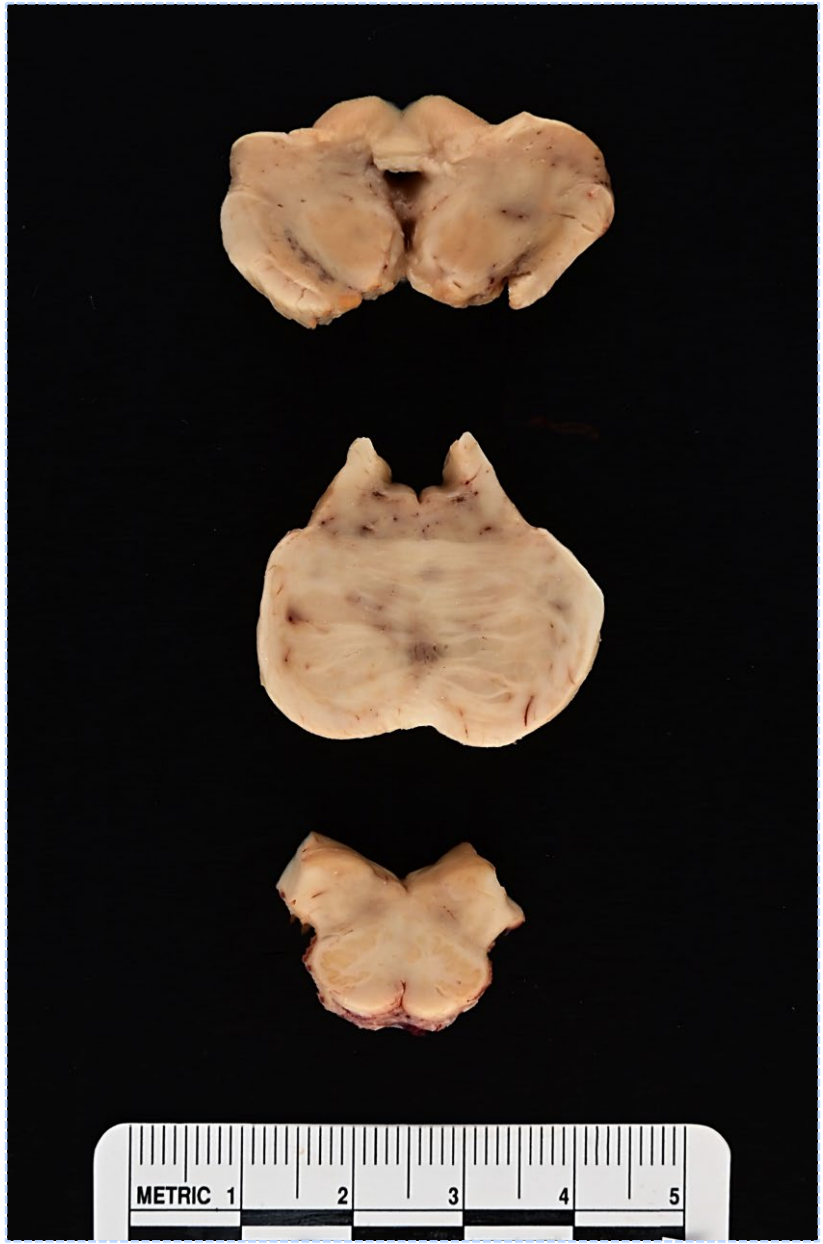
Clinical summary

- 76-year-old woman with gradually progressive symptoms for over 10 years

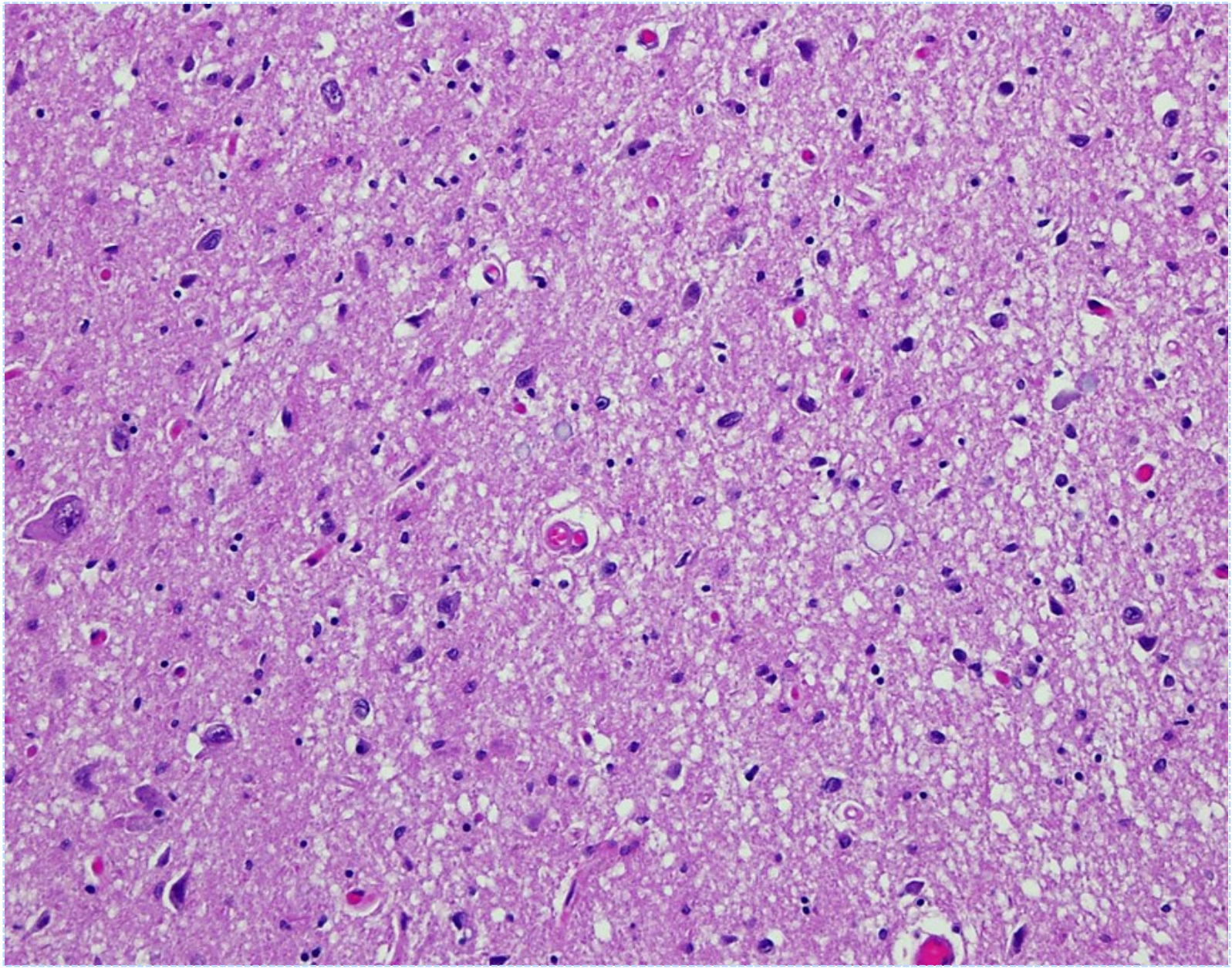
Symptoms	Laboratory tests	Electrophysiology	Serial brain MRIs
• Facial tightening • Throat pulsations • Sleep disorder • Bulbar dysfunction • Ophthalmoplegia • Ataxia • Hyperkinesia	• CK, copper, ceruloplasmin, ESR and TSH: normal • Myasthenia gravis panel, NMDA and TPO antibodies: negative	• Consistent with choreiform movements • Normal EEG and EMG	• Minimal, chronic microvascular ischemic change

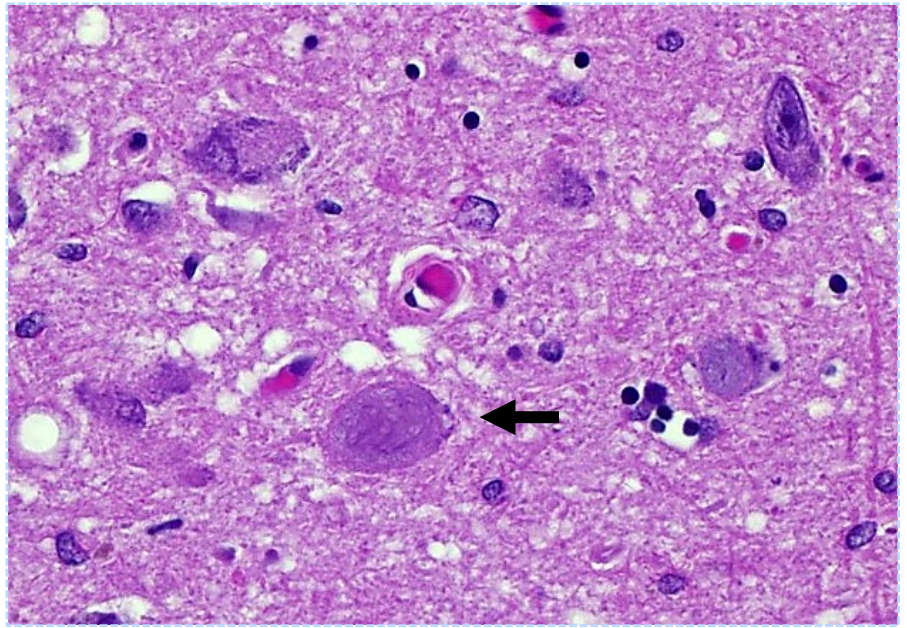
- She died of pneumonia

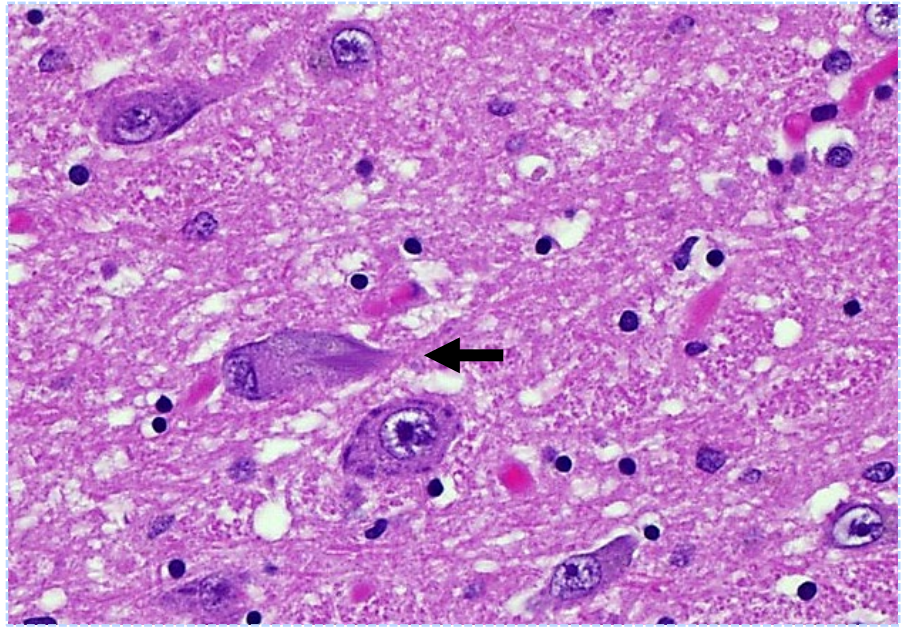




Thalamus

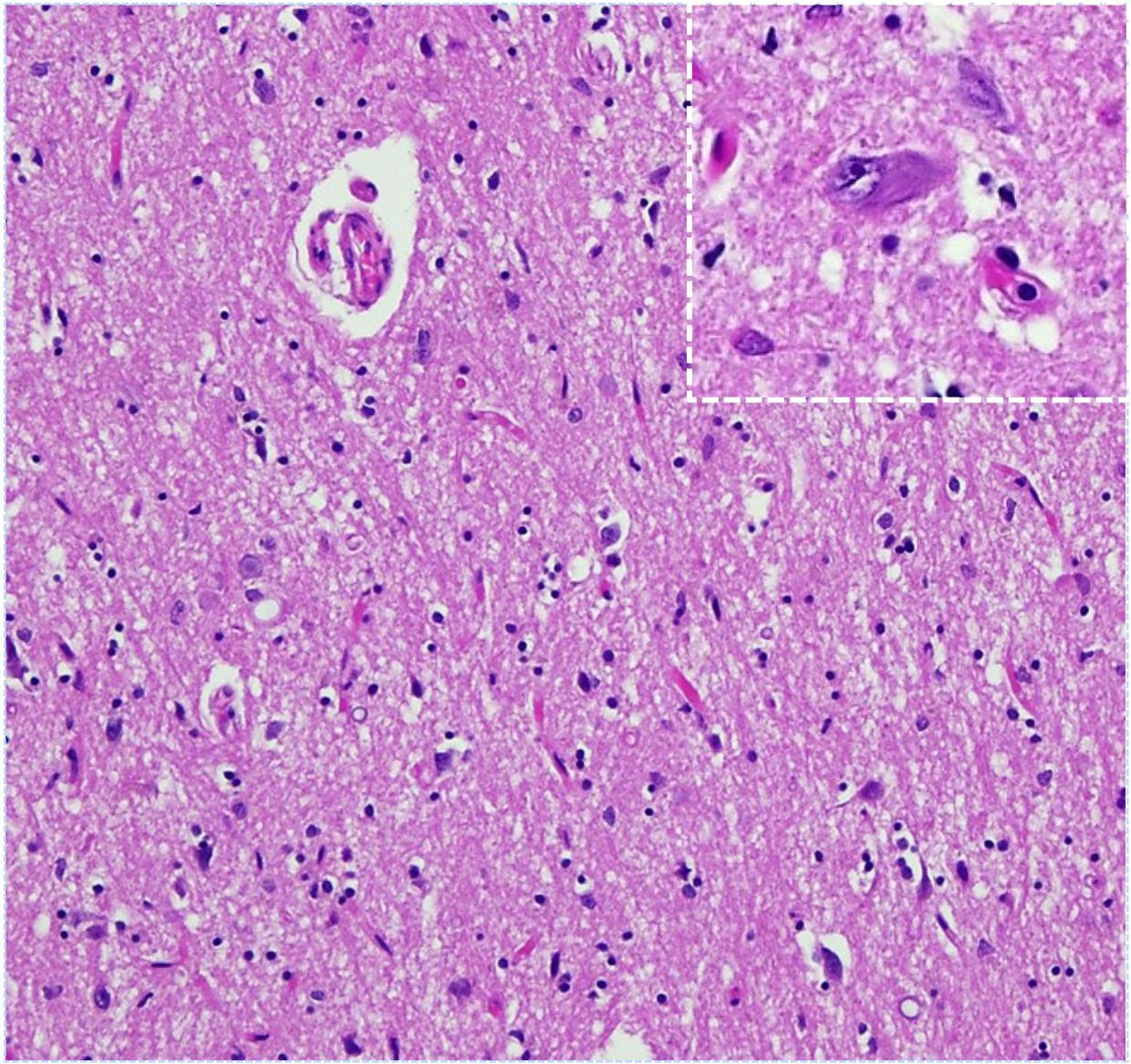




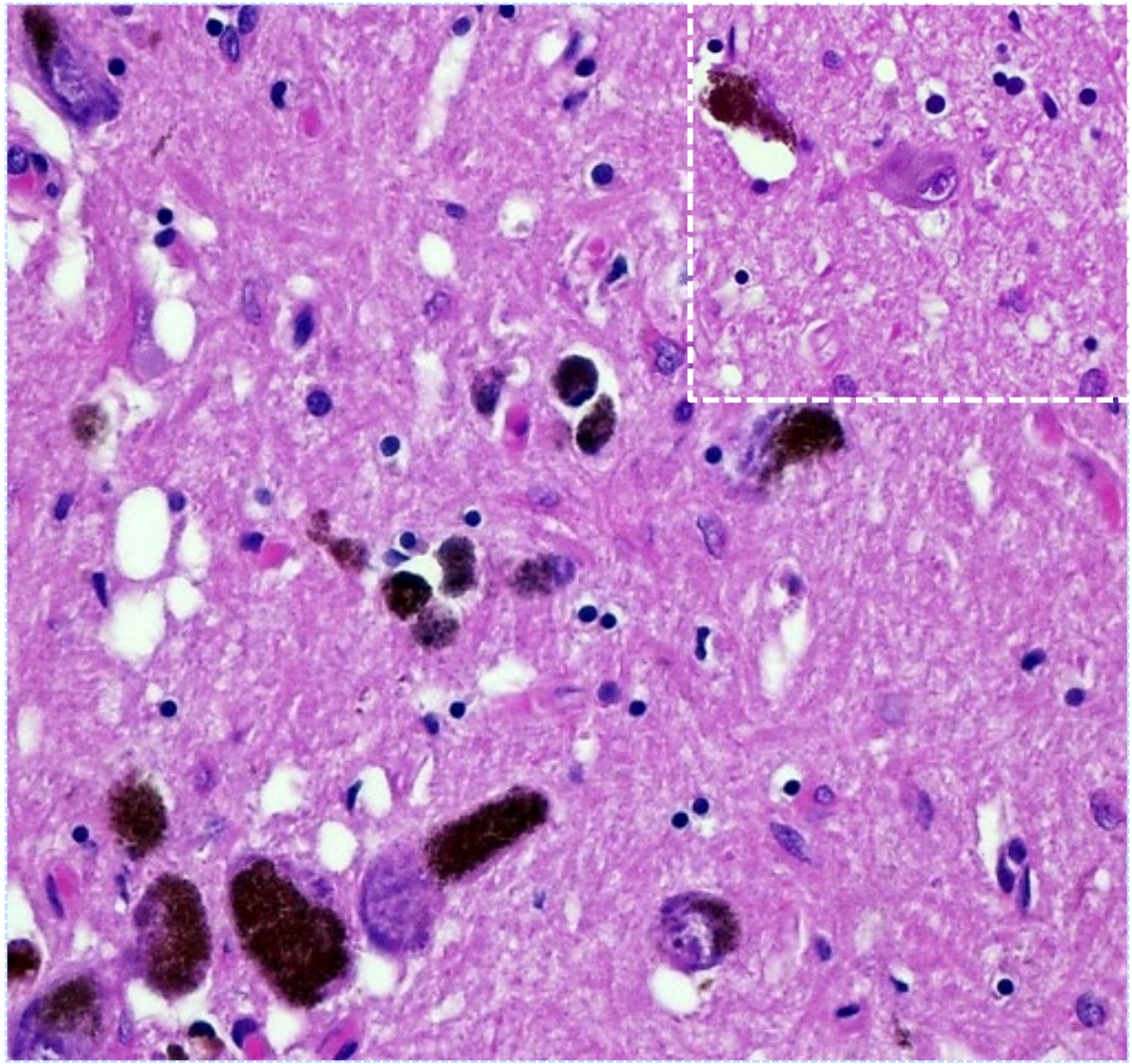


Midbrain

Periaqueductal gray matter

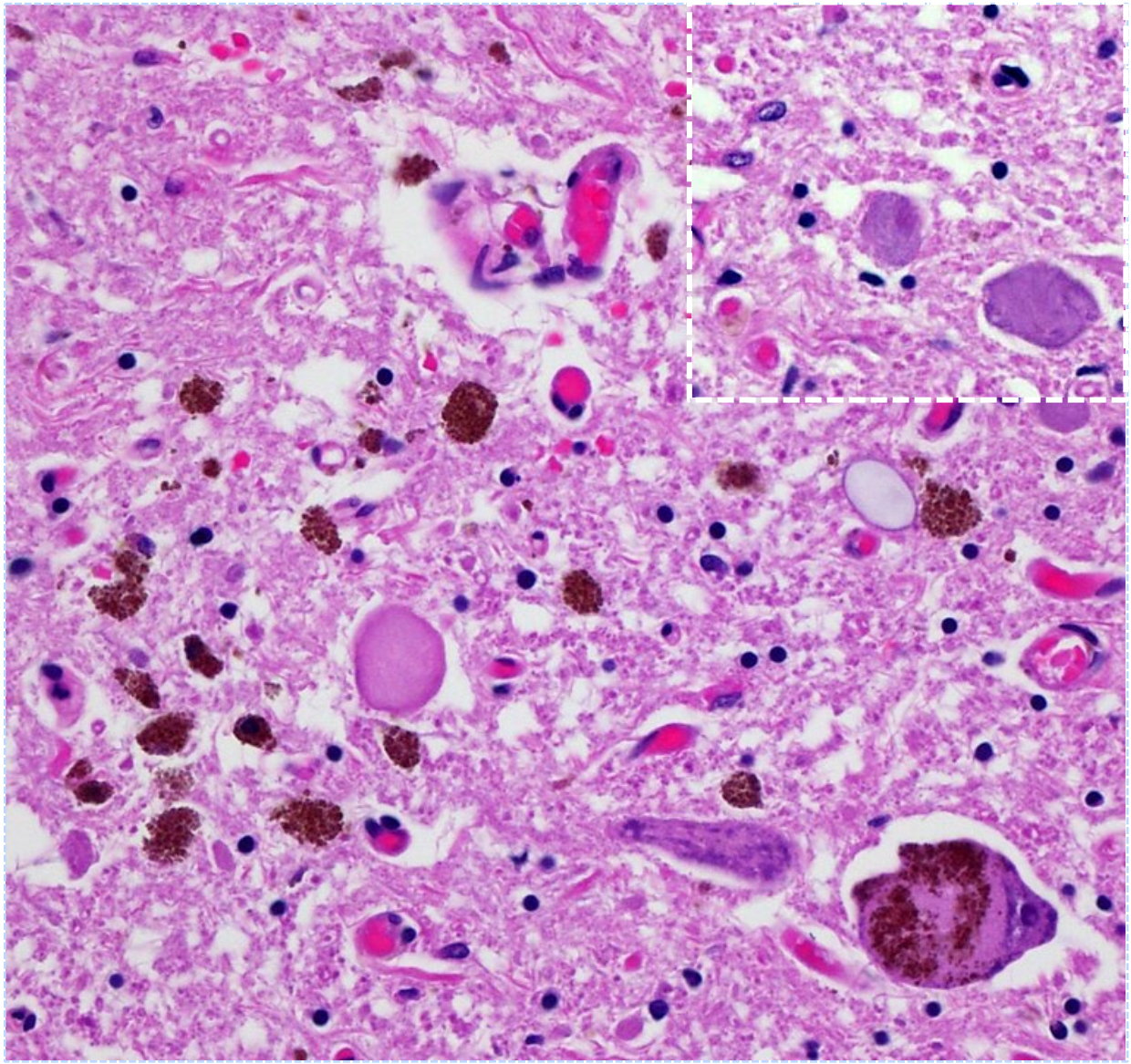


Substantia nigra

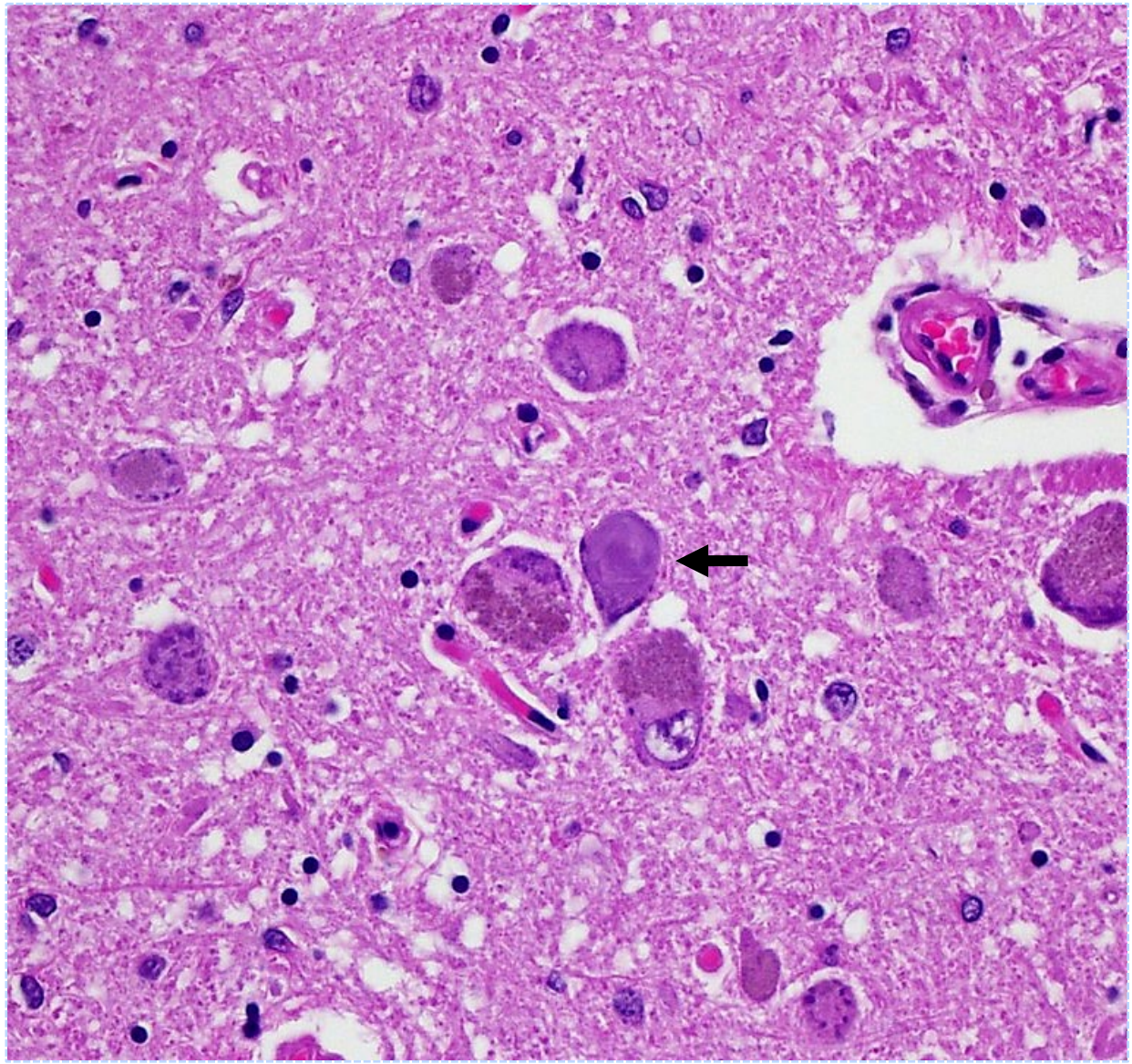


Pons

Locus ceruleus

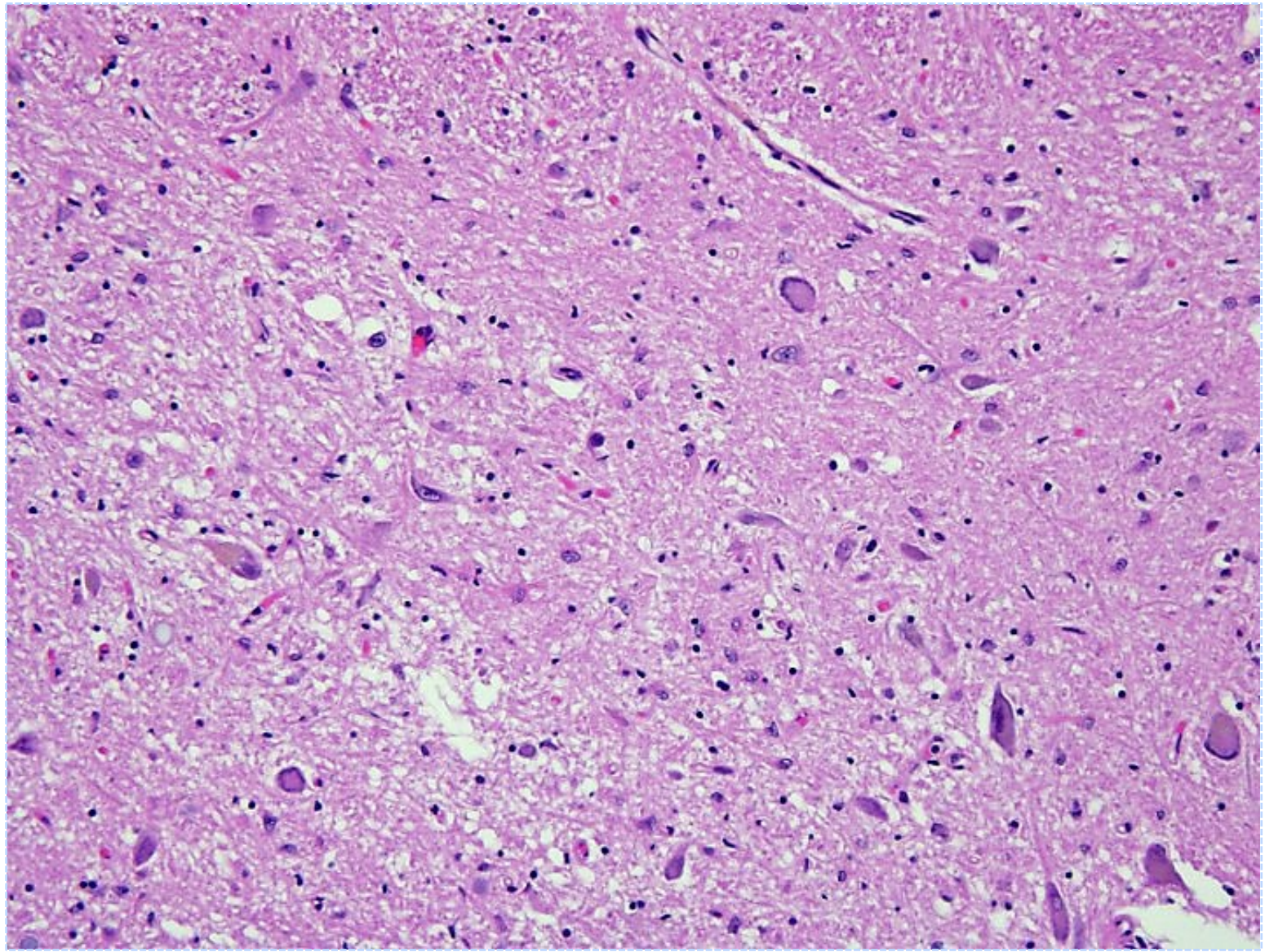


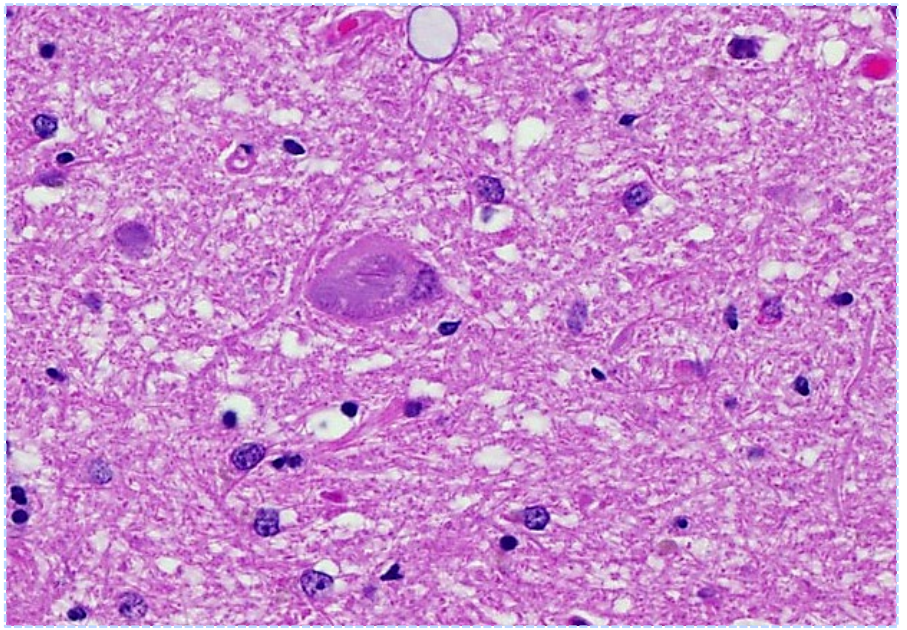
Raphe nucleus

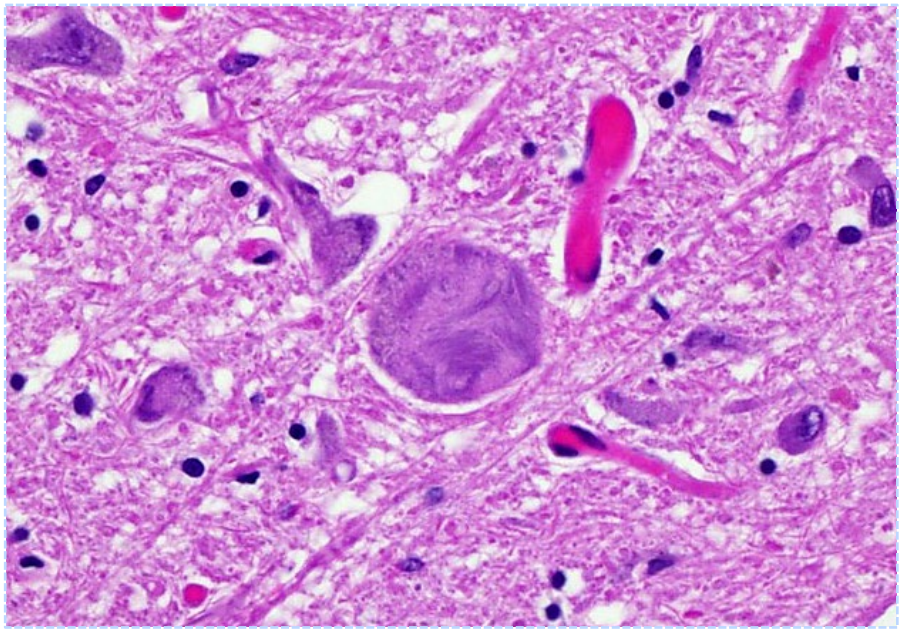


Medulla

Tegmentum

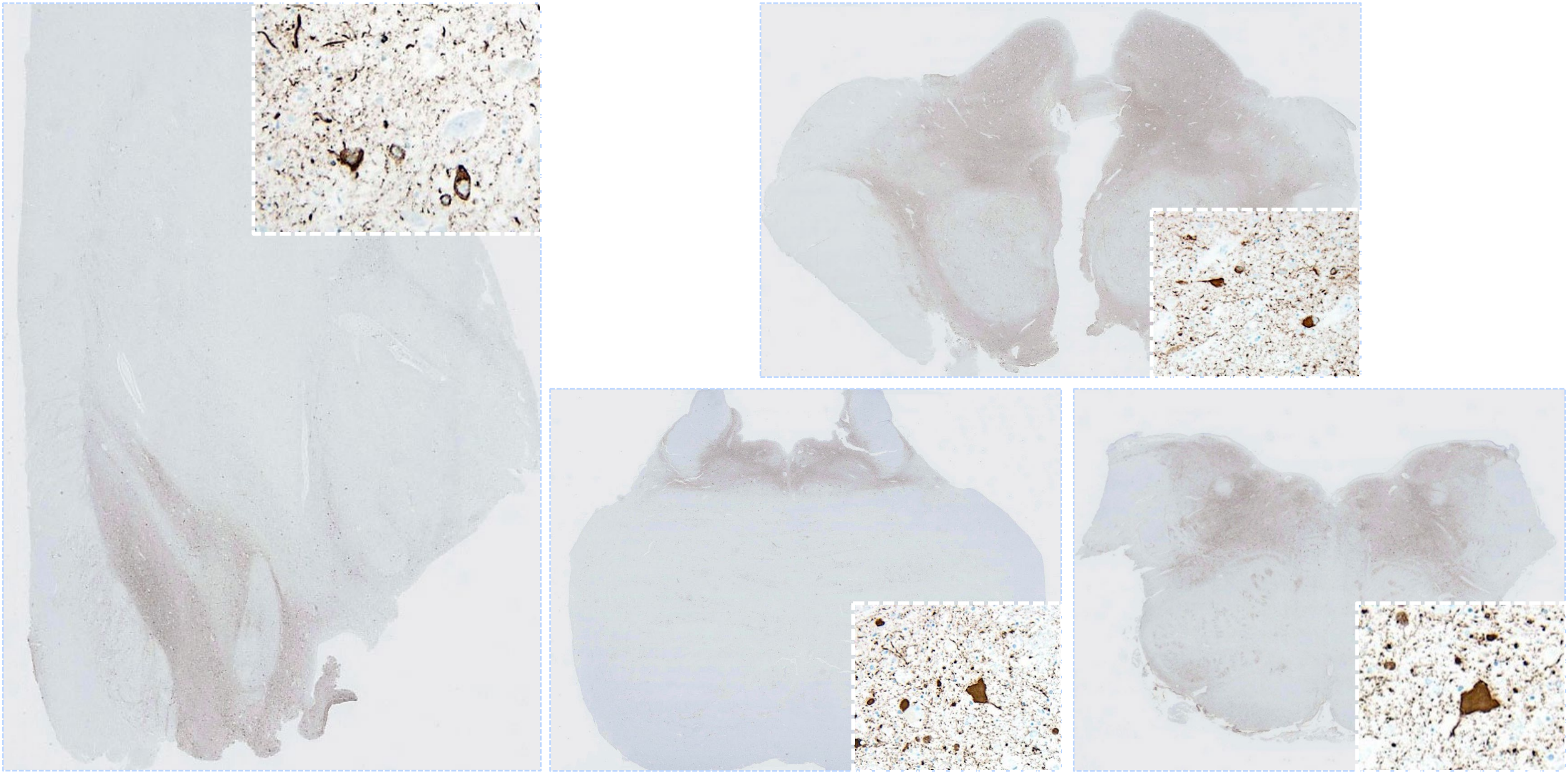






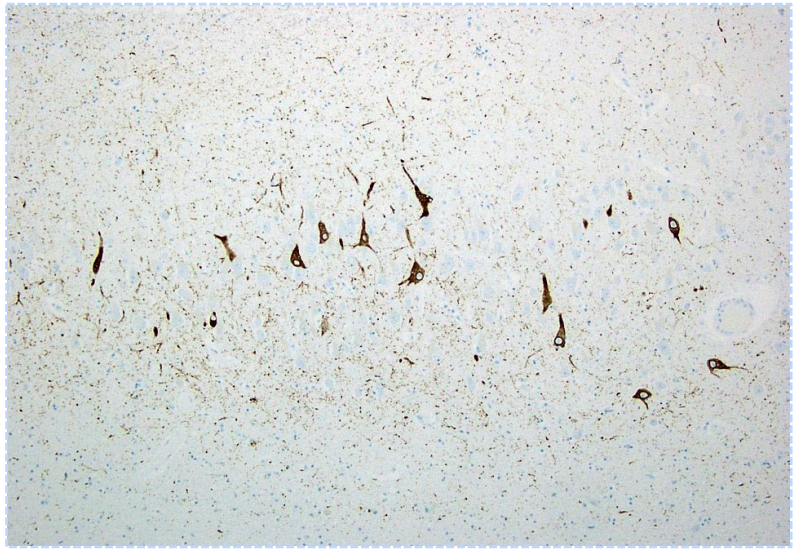
Differential diagnosis?

Phosphorylated Tau (AT8)

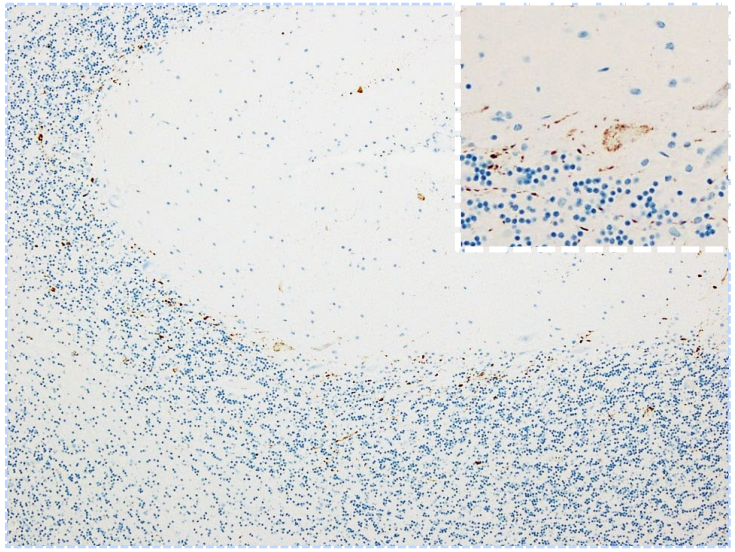


Phosphorylated Tau (AT8)

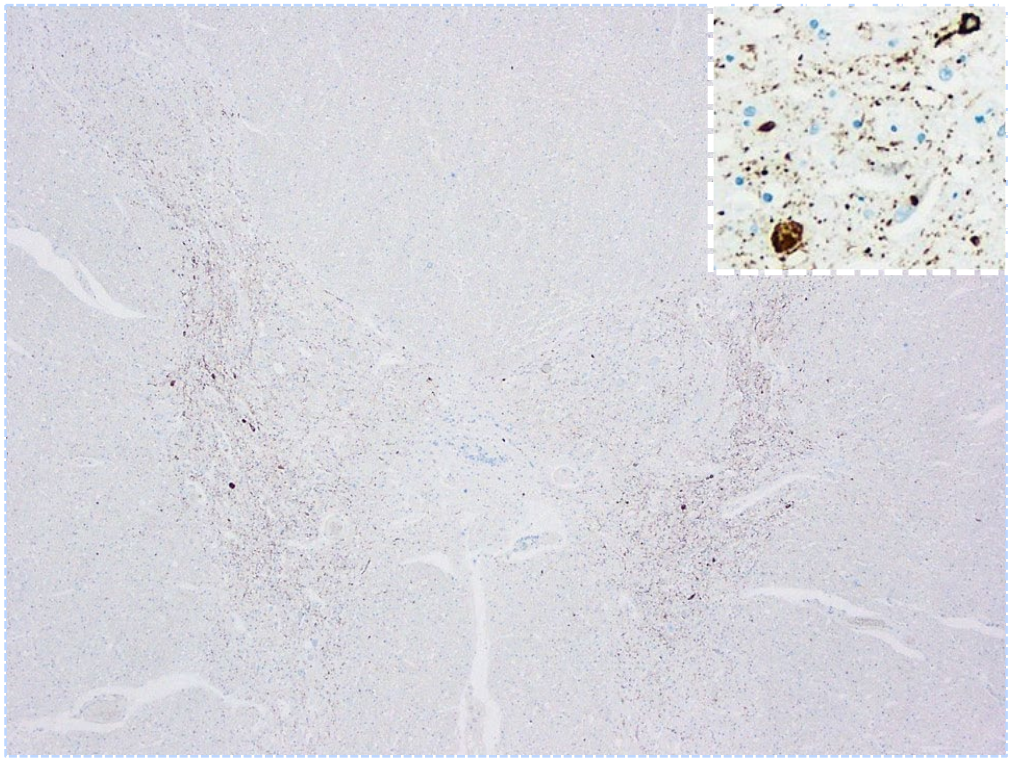
Hippocampus



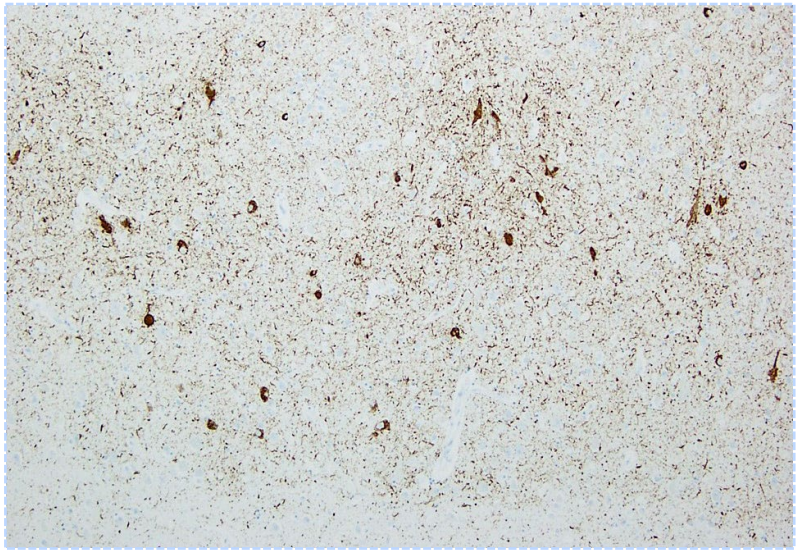
Cerebellar cortex



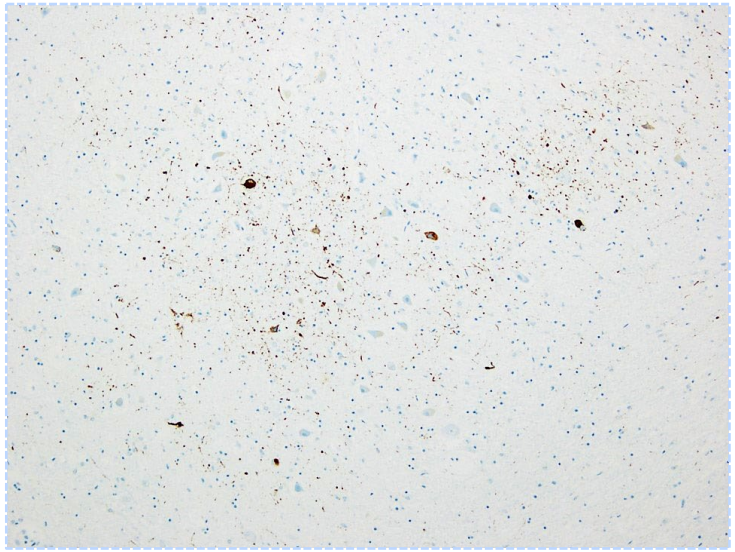
Spinal cord



Entorhinal cortex



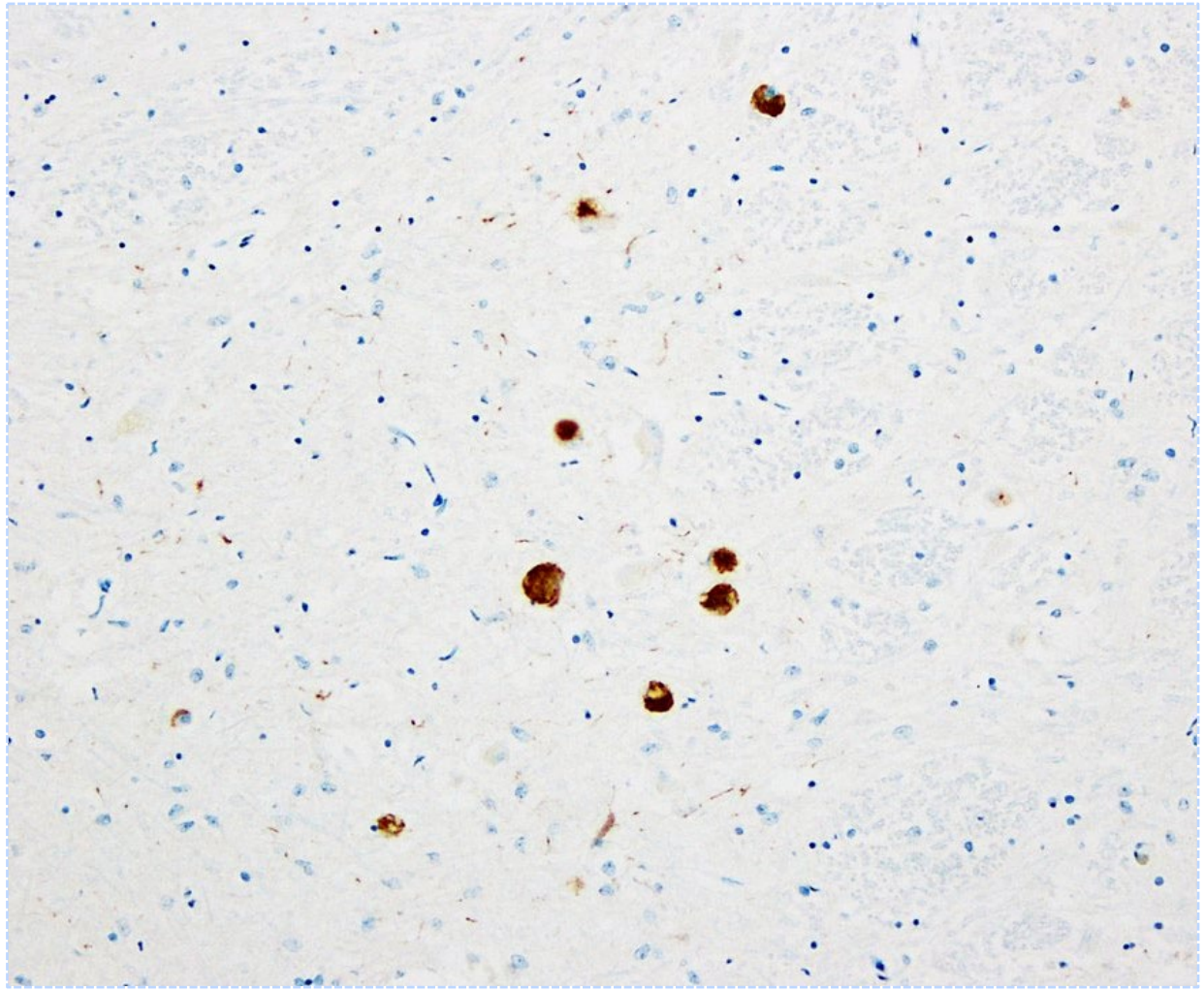
Dentate nucleus



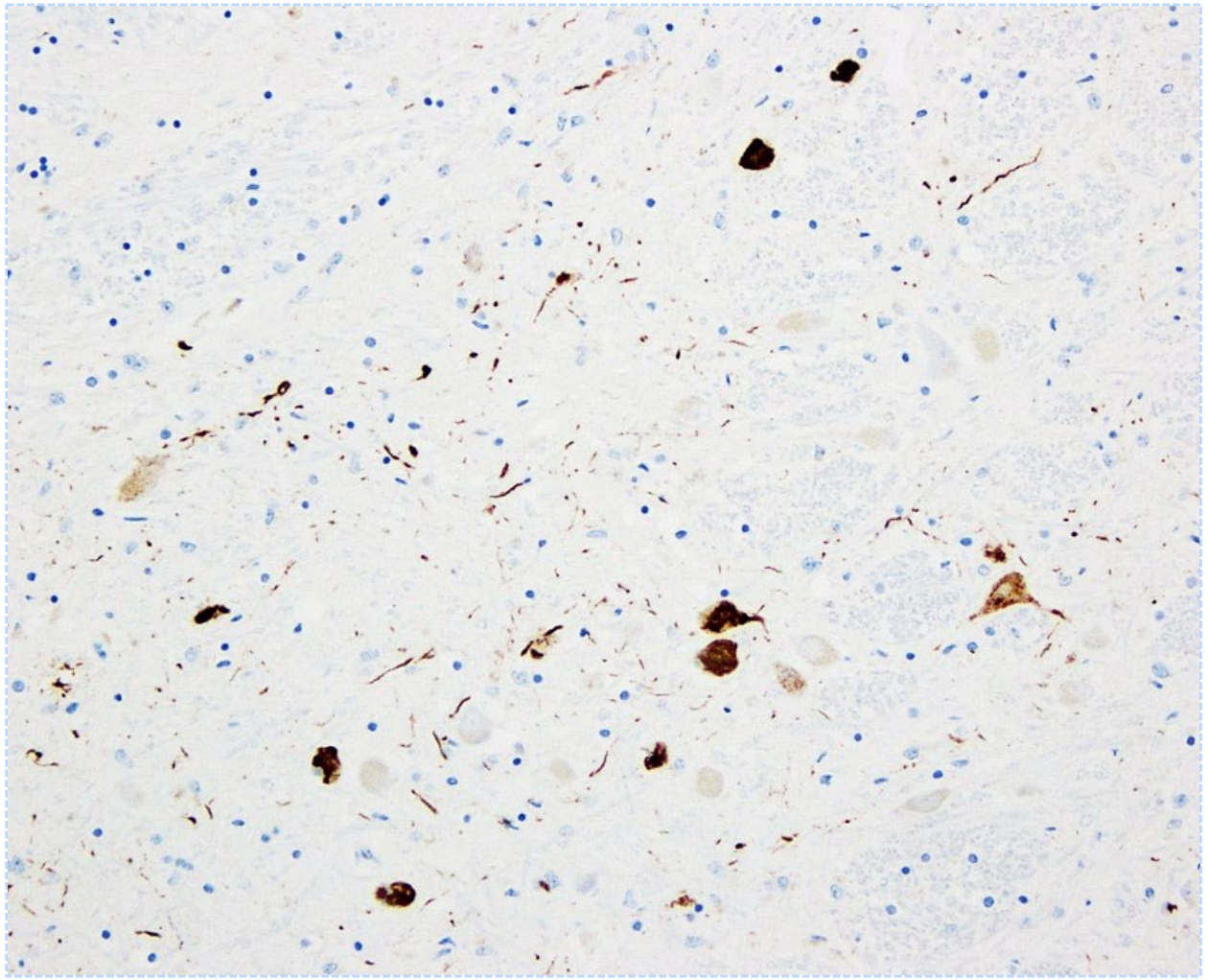
No neocortical deposits

Tau IHC

3R-Tau



4R-Tau



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No β-amyloid deposition, alpha-synuclein, or TDP-43 inclusions

Ancillary Studies

- Movement Disorder, Autoimmune/Paraneoplastic Serum Panel
  - **Positive for IgLON5 antibodies (high titer, demonstrated by indirect immunofluorescence and cell-based assay)**

Diagnosis:

Anti-IgLON5-related disease

Anti-IgLON5-related disease

- Progressive autoimmune-neurologic disease
- Average age at presentation: 60 years
- IgLON family (Lsamp, Ntm, Opcml, Negr1, and IgLON5)
  - IgLON5 suspected to maintain blood-brain barrier integrity and to be involved in neurogenesis and neuroplasticity
- Association with HLA-DRB1*1001 and HLA-DQB1*0501 haplotypes

Autoimmunity ⟷ **Neurodegeneration**

Zhang YH, et al. Neural Regen Res. 2023 May;18(5):1017-1022
Madetko, et al. Front Immunol. 2022 Mar 1;13:852215

Anti-IgLON5-related disease
Clinical manifestations

- Wide spectrum, usually longstanding
- Most patients present with
  - Sleep disorders
  - Bulbar symptoms (dysphagia, dysarthria)
  - Gait abnormality +/- cognitive impairment
  - Other: oculomotor abnormalities, movement disorders, muscle weakness, fasciculations, dysautonomia

Gaig C, et al. Neurology. 2017 May 2;88(18):1736-1743
Werner J, et al. Neurol Neuroimmunol Neuroinflamm. 2021 Feb 2;8(2):e962
Sabater L, et al. Lancet Neurol. 2014 Jun;13(6):575-86

Anti-IgLON5-related disease
Diagnosis and treatment

- Clinical features
- Polysomnography: abnormal NREM sleep initiation, REM sleep behavior disorder, motor activation, stridor, and apnea
- IgLON5 antibodies in serum and/or CSF (predominantly IgG4)
- EEG, EMG, and imaging frequently non-contributory
- Immunotherapy: variable response; early treatment appears to be associated with better long-term outcome

Autoimmunity → Neurodegeneration

Grüter T, et al. Brain. 2023 Feb 13;146(2):600-611
Shambrook P, et al. Neurol Neuroimmunol Neuroinflamm. 2021 May 13;8(4):e1009
Wang Y, et al. BMC Neurol. 2021 Mar 17;21(1):120

Anti-IgLON5-related disease
Neuropathology

1) Proposed neuropathological criteria to define the tauopathy underlying the anti-IgLON5-related disease

Possible

All of the following

- Neurodegenerative features with neuronal loss and gliosis in brain areas showing (p)Tau pathology without inflammation
- Selective neuronal involvement by deposition of pTau in the form of NFT, pretangles, and neuropil threads with both 3R and 4R-Tau isoforms
- The pTau pathology predominantly affects subcortical structures, including the hypothalamus, tegmentum, and upper spinal cord*

Probable

Criteria of "possible" AND at least one of the following

- Clinical history suggestive of a sleep disorder (NREM and REM parasomnia with sleep apnea), or brainstem, mainly bulbar dysfunction
- Presence of HLA-DRB1*1001 and HLA-DQB1*0501 alleles

Definite

Criteria for "possible" AND presence of IgLON5 antibodies in CSF or serum

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1) Modified from Gelpi E et al. Acta Neuropathol. 2016 Oct;132(4):531-43

** Erro ME, et al. Neurol Neuroimmunol Neuroinflamm. 2019 Dec 11;7(2):e651*

Conclusions

1. Anti-IgLON5-related disease is a rare entity with broad clinical manifestations and unclear pathophysiology
   - Proposed autoimmunity triggering a neurodegenerative process with neuronal Tau accumulation
2. There is significant overlap with other neuromuscular and neurodegenerative diseases: myasthenia gravis, Huntington disease, progressive supranuclear palsy, and multiple system atrophy
3. This entity should be considered in the differential diagnosis of patients presenting with longstanding neurologic symptoms in the absence of laboratory, imaging, and electrophysiologic findings

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