AANP Diagnostic Slide Session 2019 – Case #6

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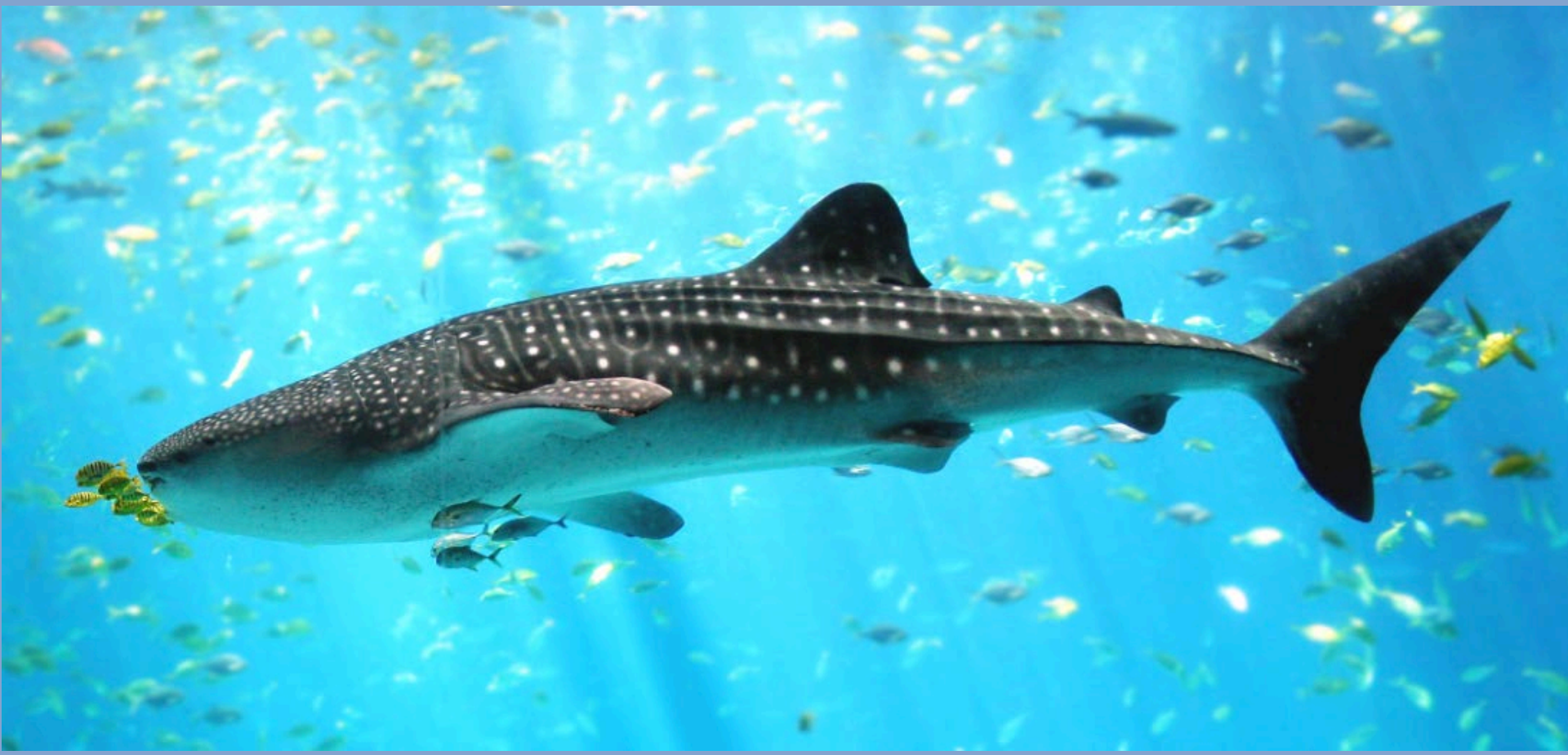
University of California San Francisco



Atlanta, Georgia
June 8, 2019

The authors have nothing to disclose.

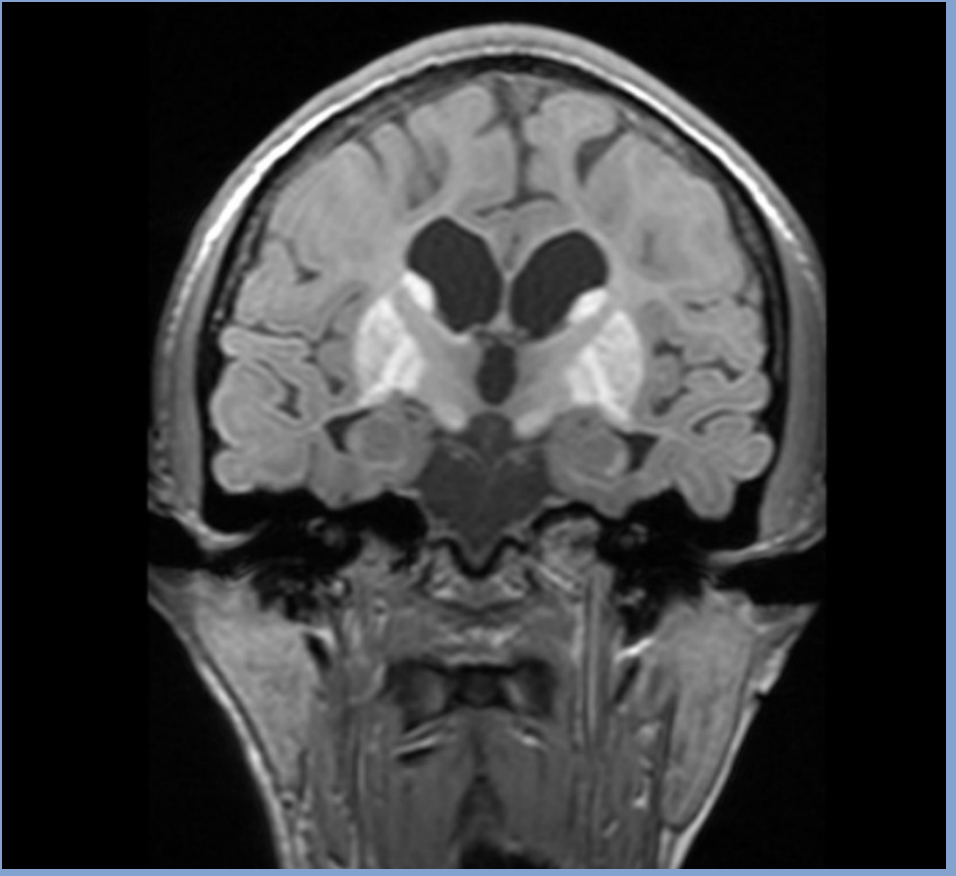
The decedent was a 23-year-old woman.

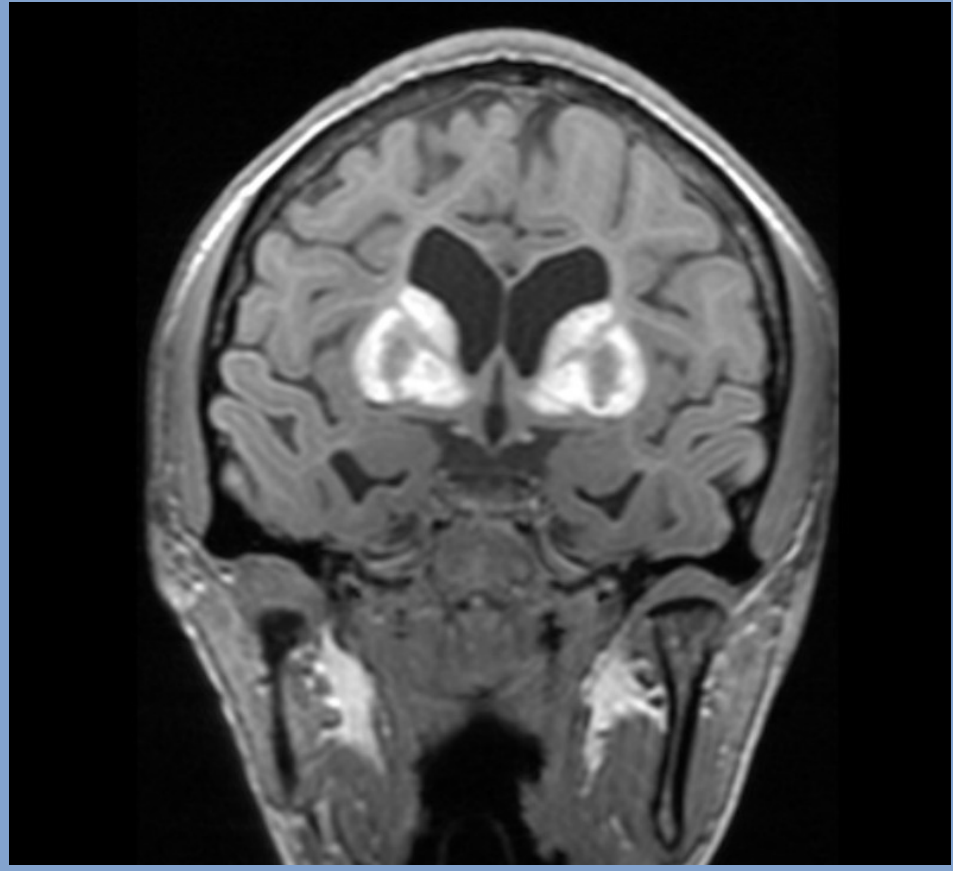
There were early developmental delays.

Progressive motor regression began at age 10.

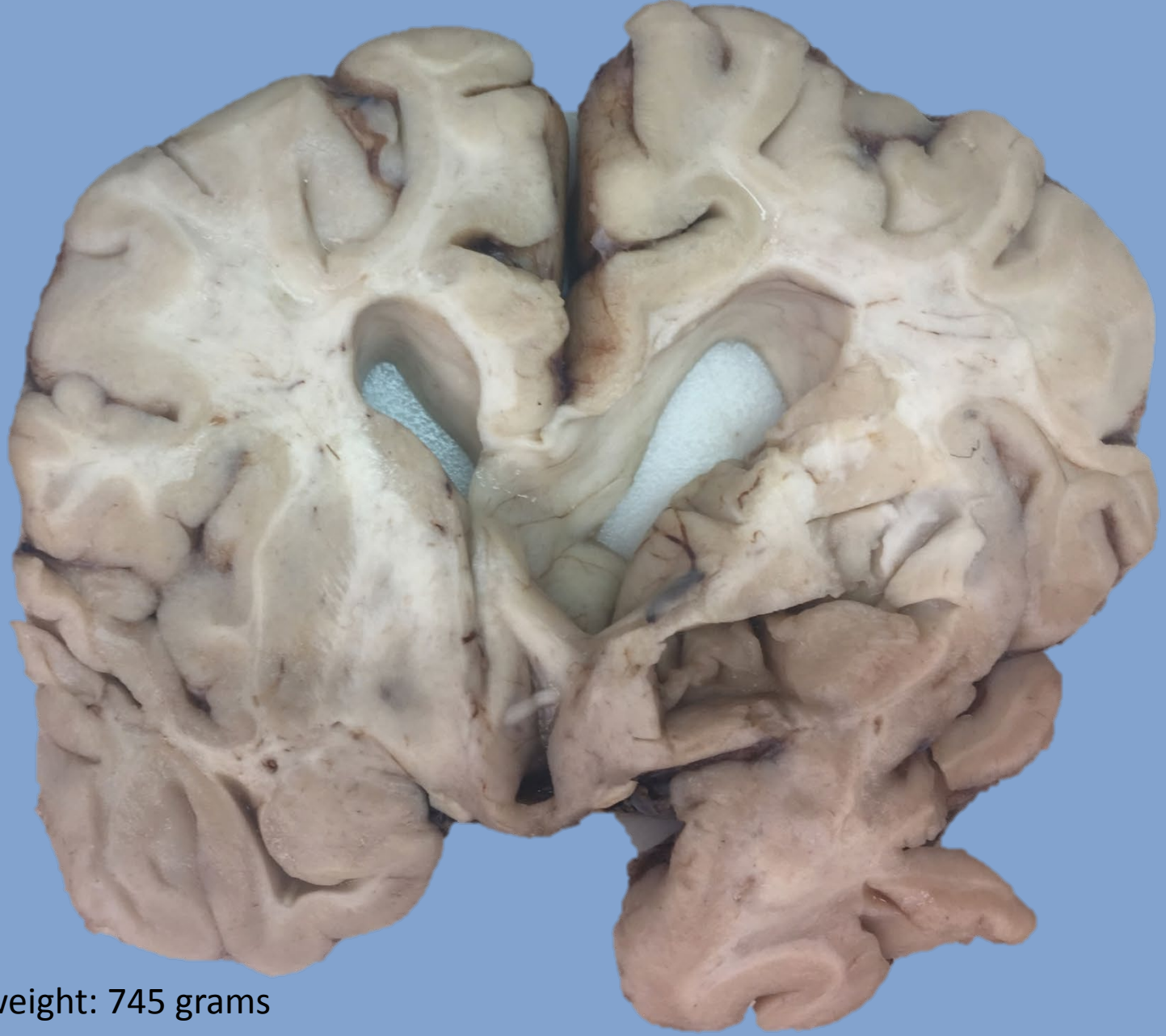
By her late teens she was almost entirely wheelchair bound, and fed primarily by a gastric tube.

She became increasingly nonverbal,
with dystonia and ballistic movements.



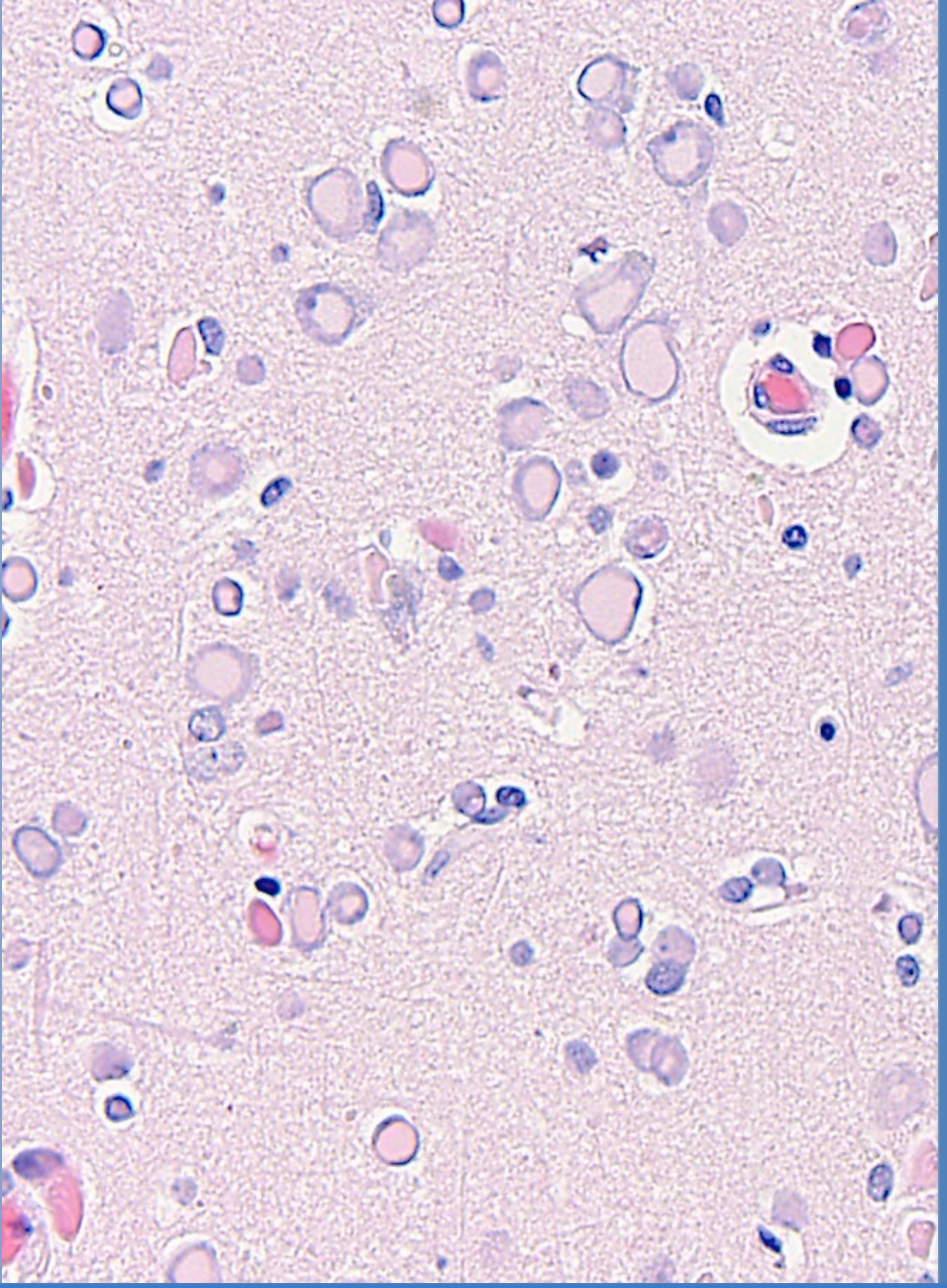


Bilateral T1 hyperintense signal abnormalities within the caudate, putamen, globus pallidus, thalamus, hippocampus, red nucleus, and cortical spinal tract

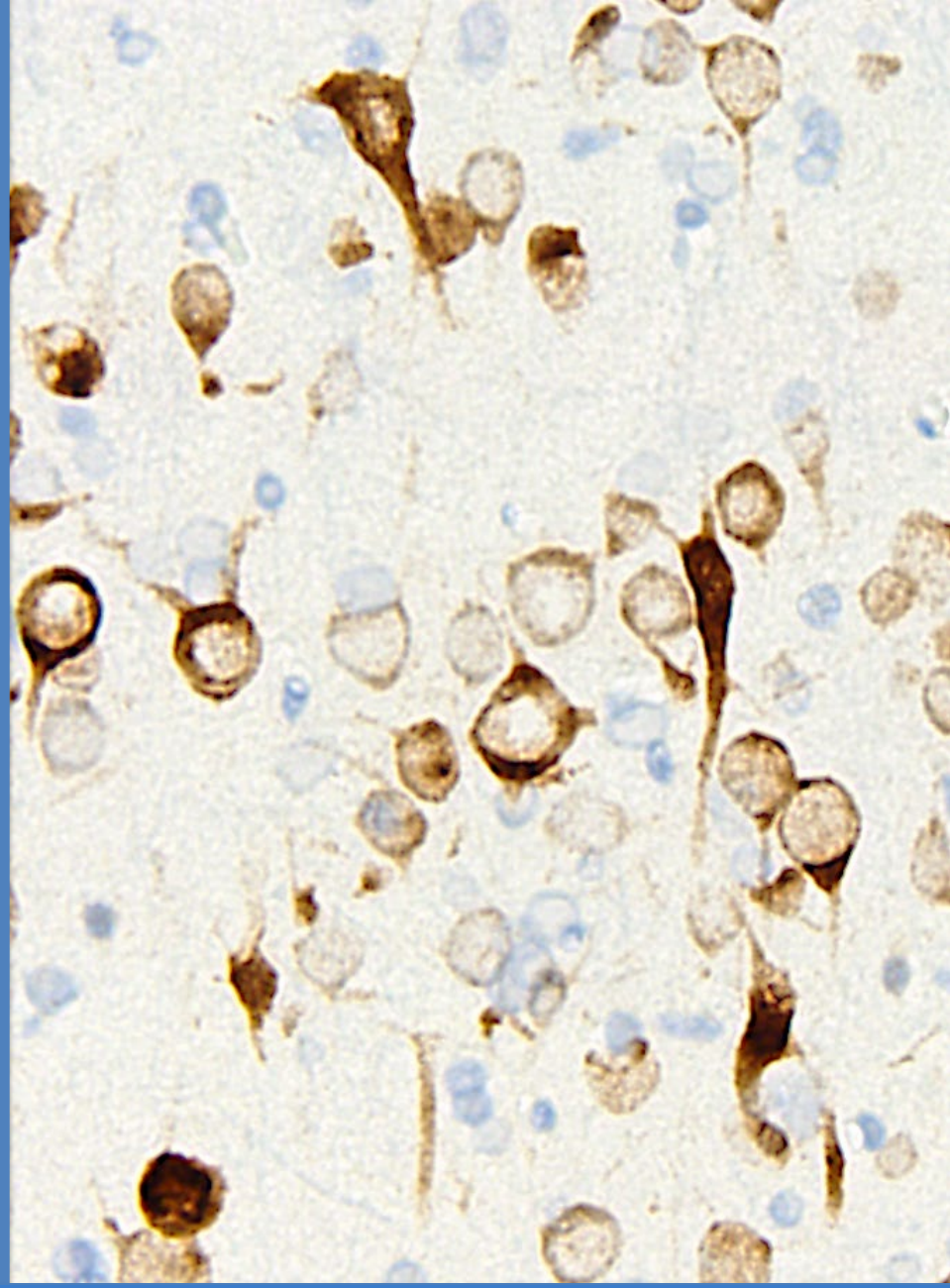


Fresh brain weight: 745 grams

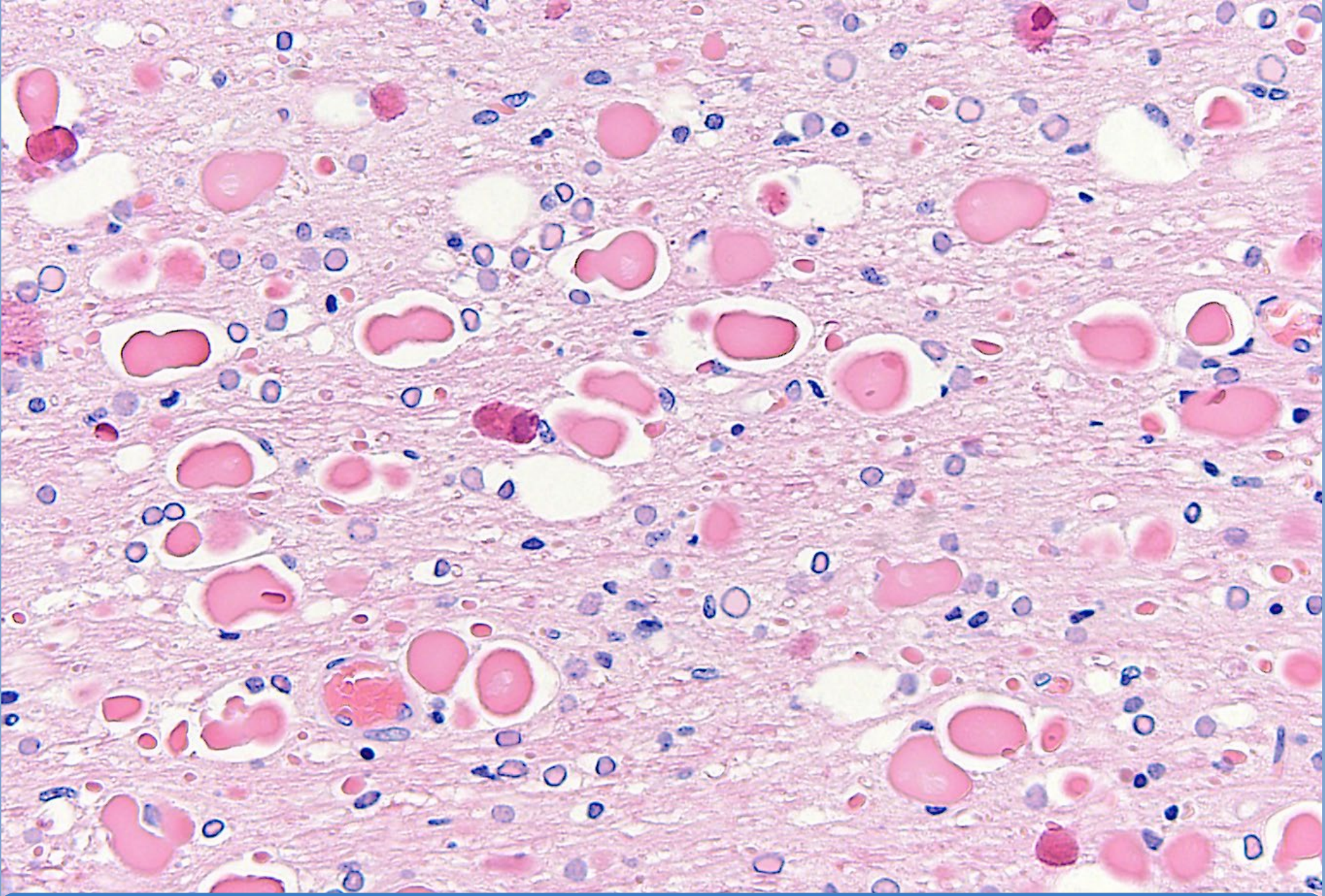
Coronal section with decreased bulk and coloration of globus pallidus
Severely reduced volume of the corpus callosum and cerebral white matter



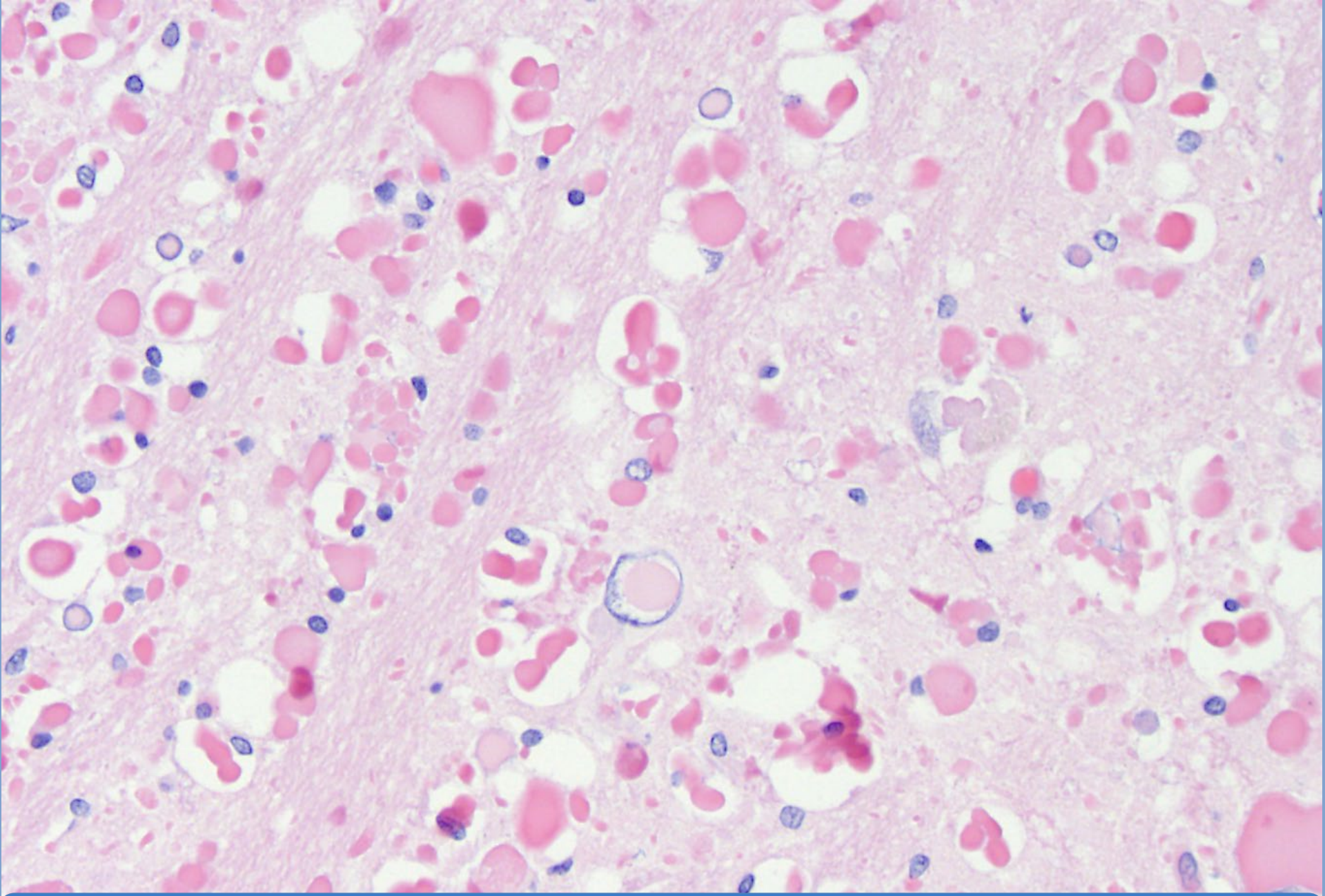
Cortex 200x



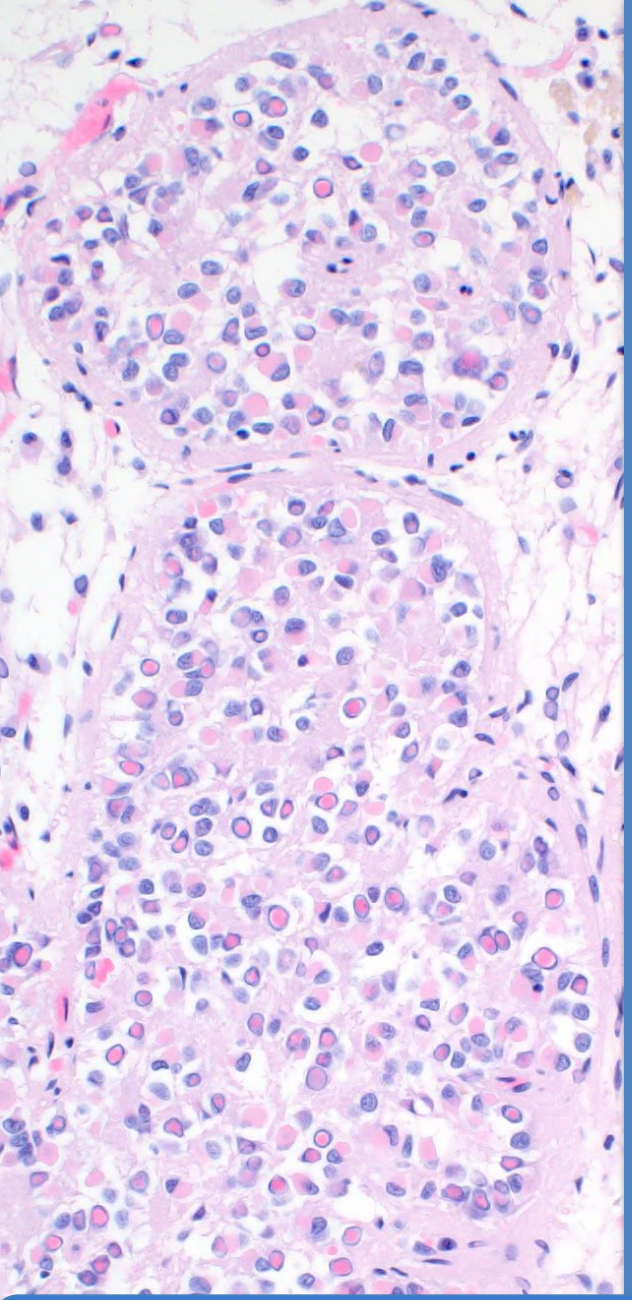
NeuN 200x



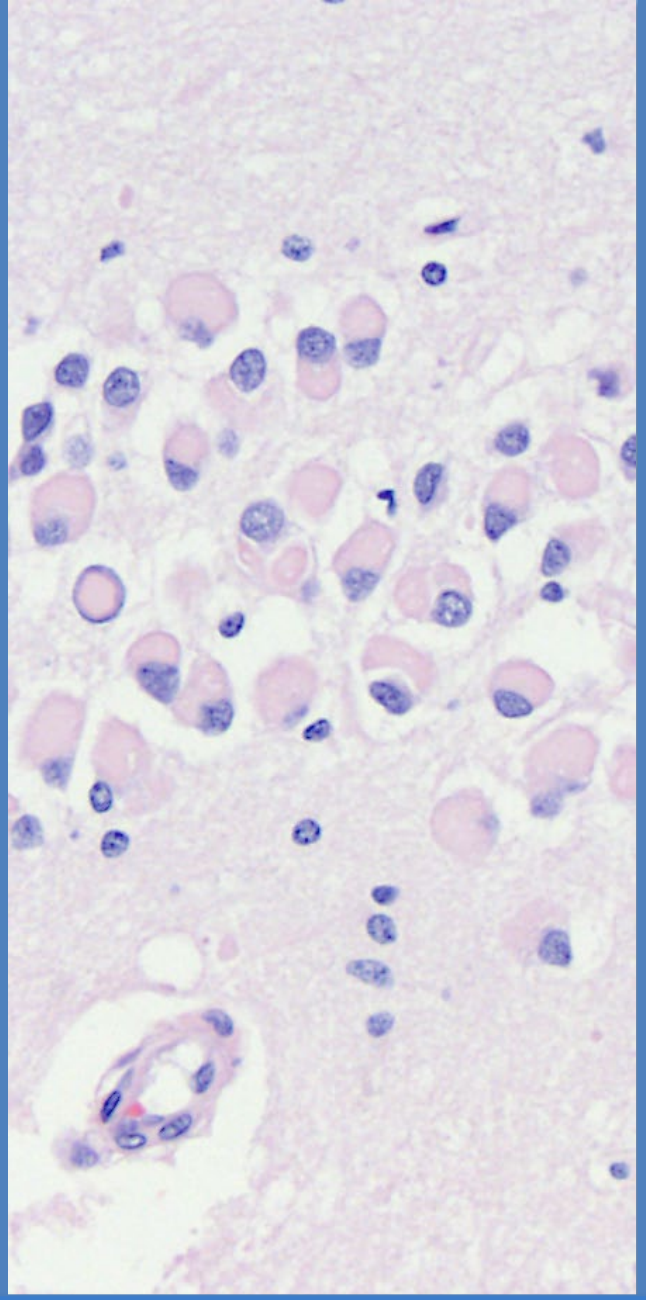
White matter, 100x



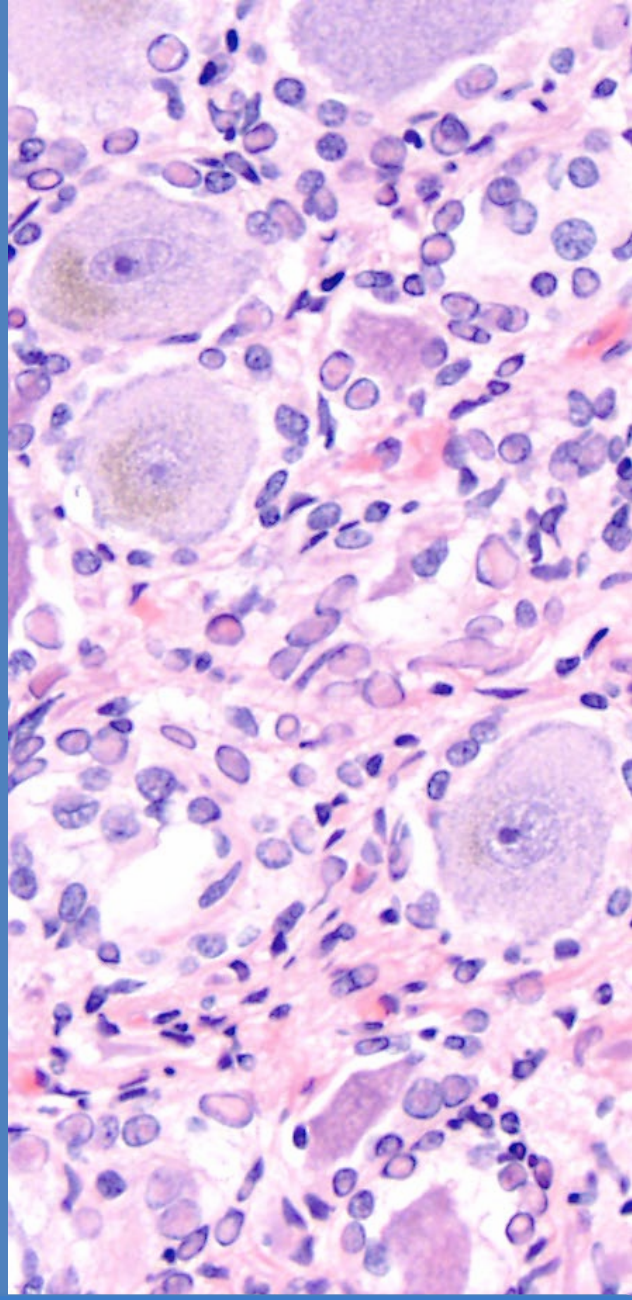
Globus pallidus, 200x



Pineal gland



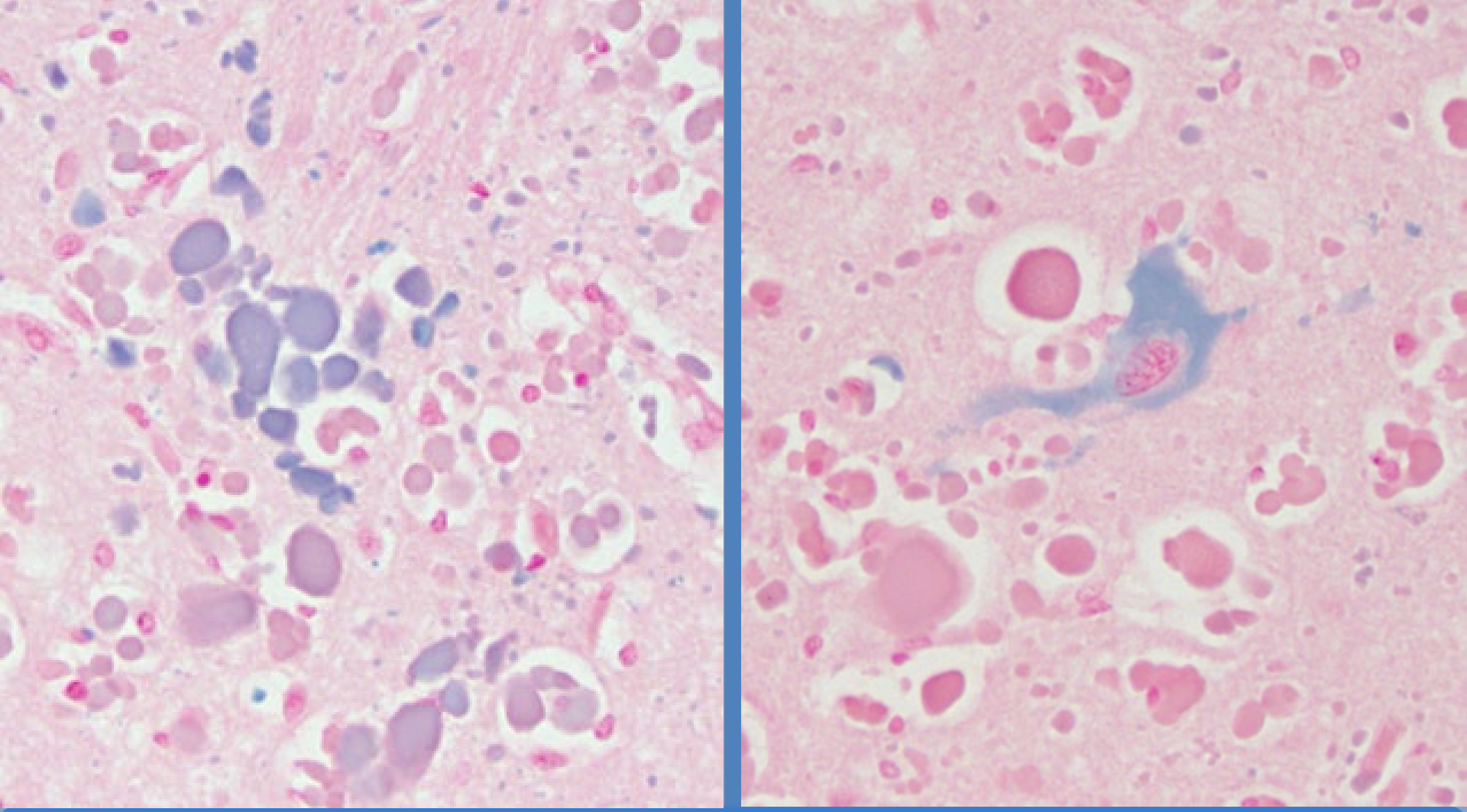
Dentate gyrus



DRG

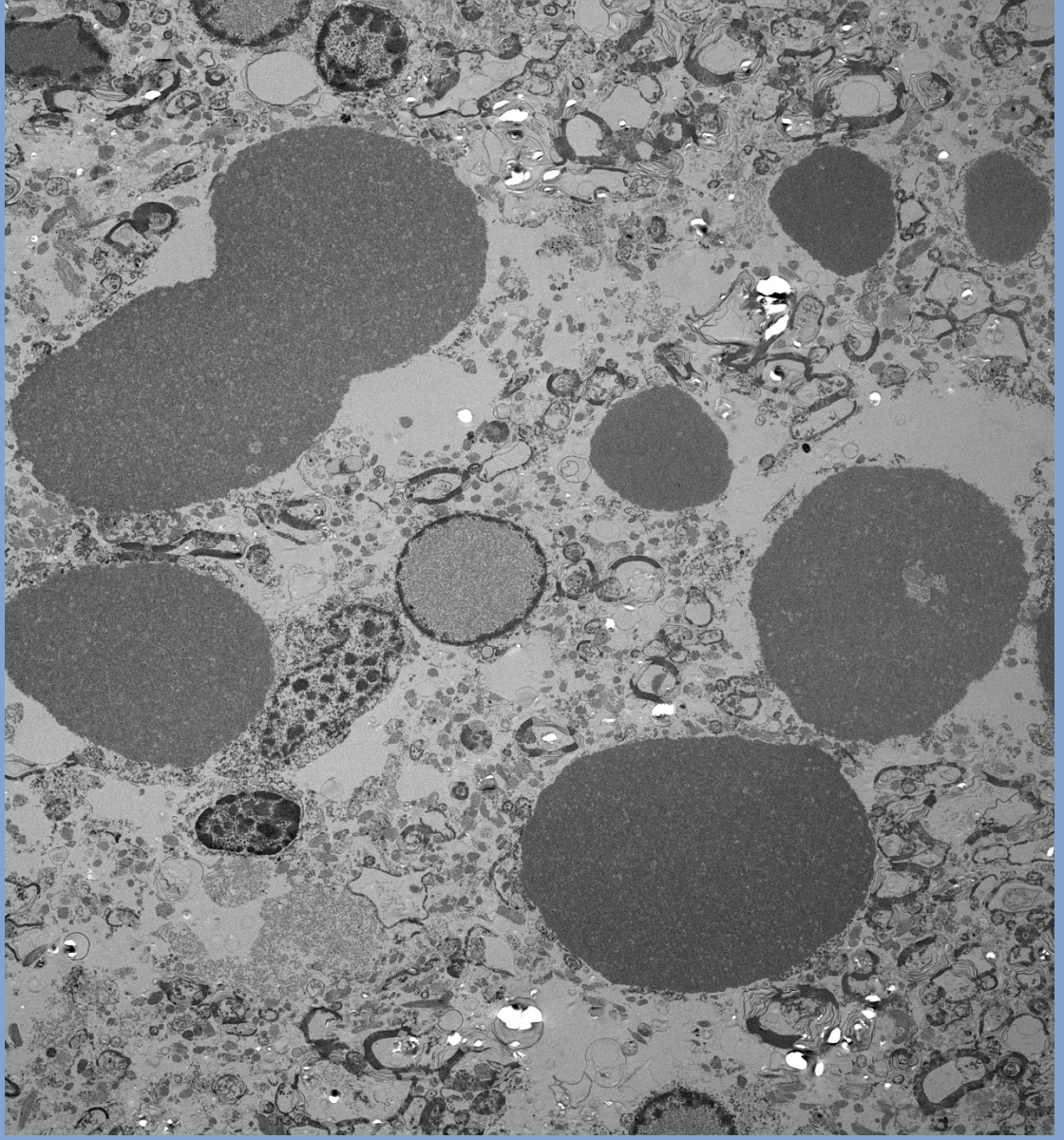
Differential diagnosis?

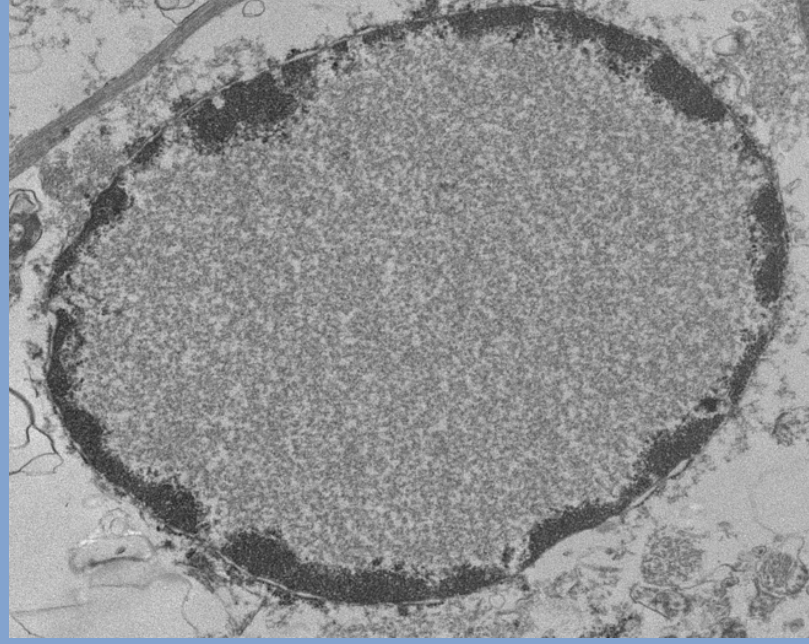
Additional immunohistochemical or molecular evaluation?

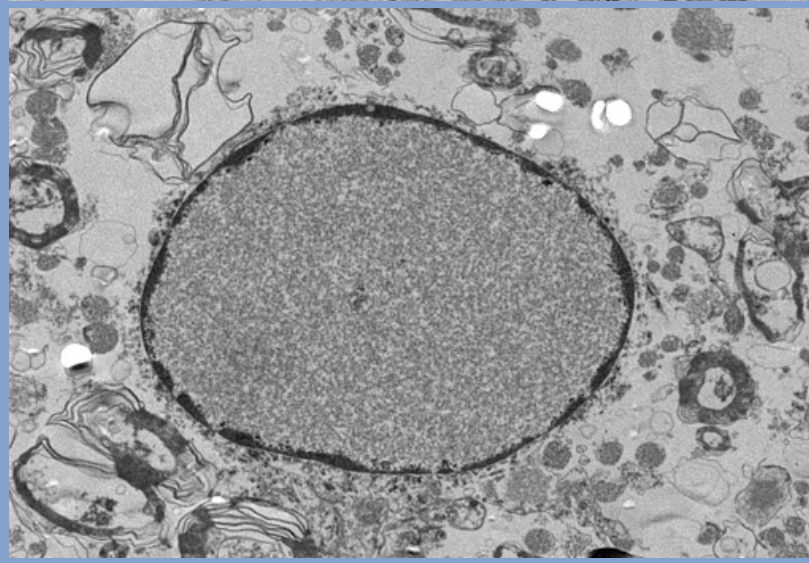


Prussian blue iron stain, basal ganglia

Special staining for iron demonstrates abnormal deposition in rare cells, and highlights a subset of the eosinophilic deposits

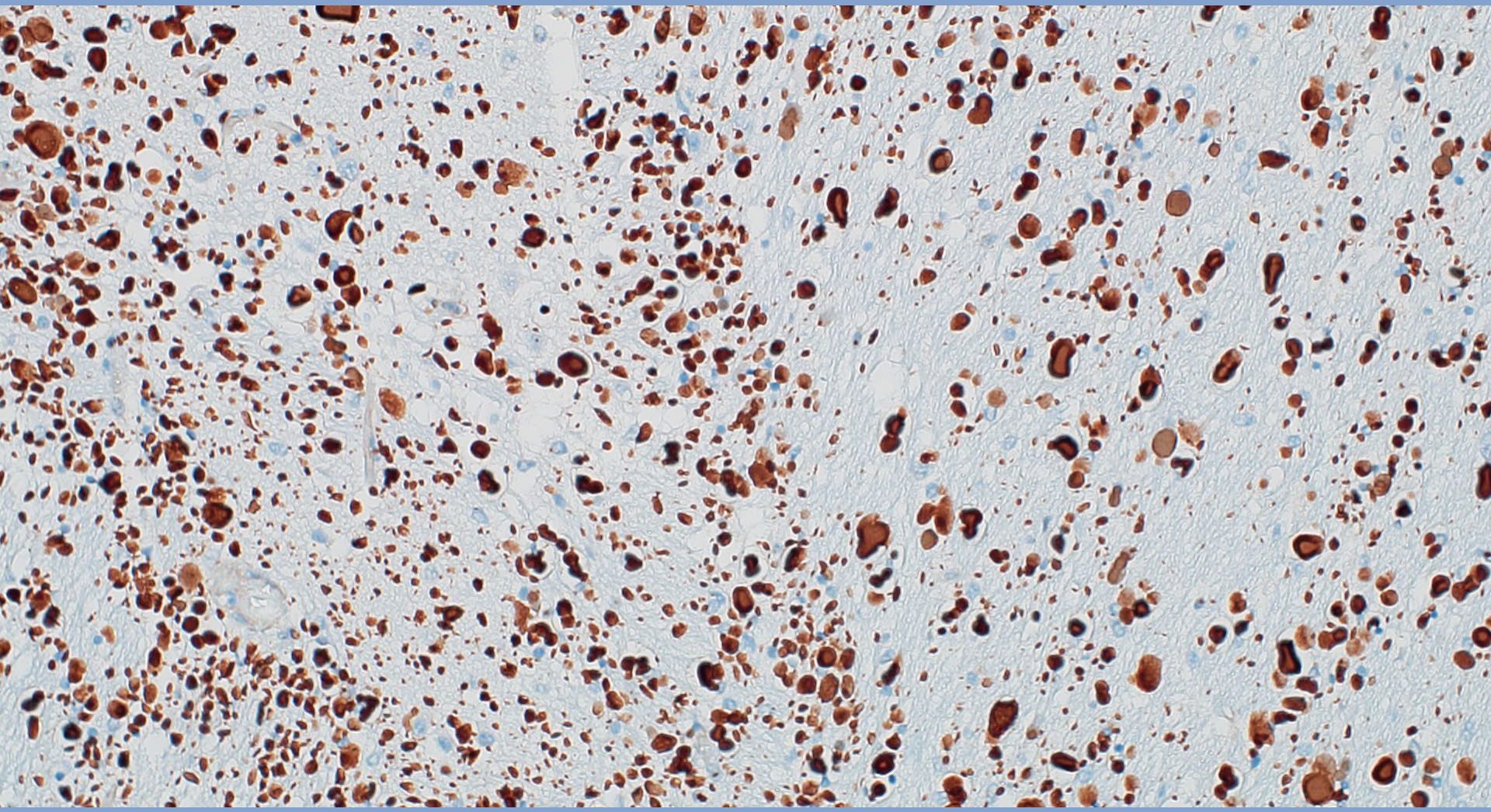






Electron microscopy of the eosinophilic inclusions and globules showed electron dense granular material, some of which was membrane bound with peripherally displaced chromatin, while other large collections were apparently not directly associated with cellular structures. The inclusions and globules contained collections of material compatible with ferritin.

The eosinophilic globules and inclusions were immunopositive for Ferritin



FINAL AUTOPSY DIAGNOSIS

Neurodegeneration with features characteristic of a neuroferritinopathy

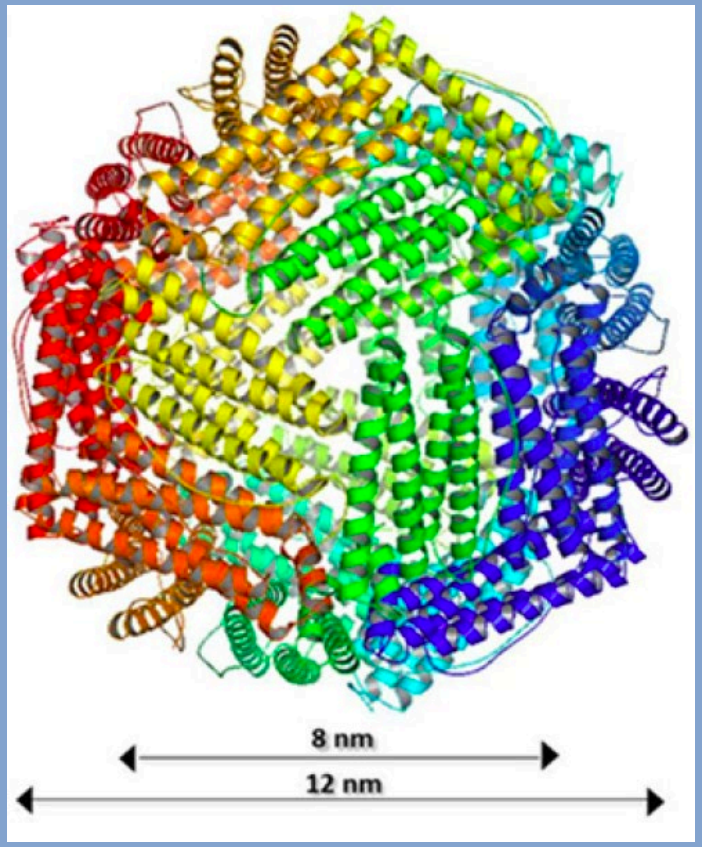
A. Eosinophilic intranuclear and intracytoplasmic inclusion bodies, apparent extracellular deposits, and patchy iron deposition.

B. Diffuse and extensive involvement of brain and spinal cord with severe involvement and patchy destruction of basal ganglia, red nucleus, substantia nigra, and white matter of cerebral cortex and cerebellum.

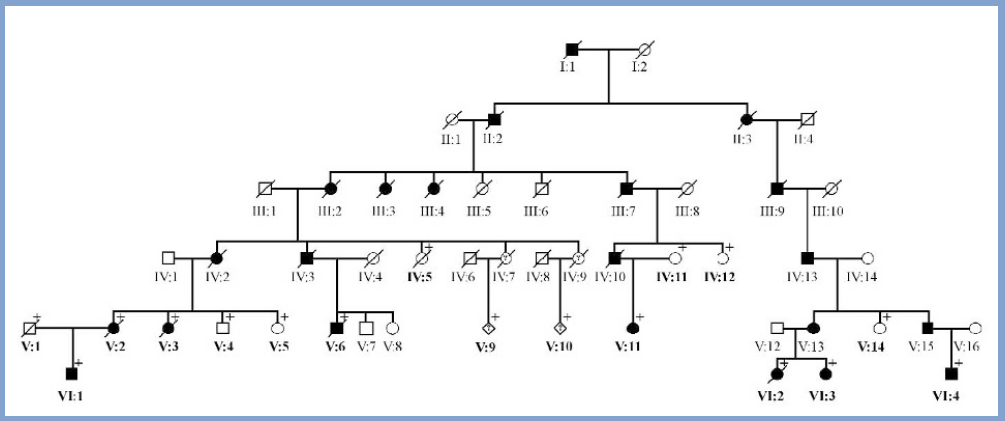
C. Severe atrophy/hypoplasia of the cerebellar vermis and brain stem.

D. Hydrocephalus ex vacuo.

D. Eosinophilic intranuclear inclusion bodies in multiple organs including skeletal muscle, Schwann cells in peripheral nerve, endothelial cells, adventitia, the mesenchyma of the heart, the adrenal cortex, occasional hepatocytes in the liver, and the collecting ducts and tubules of the kidney.



Arosio *et al.* Biochem J. 2015 Nov 15;472(1):1-15.

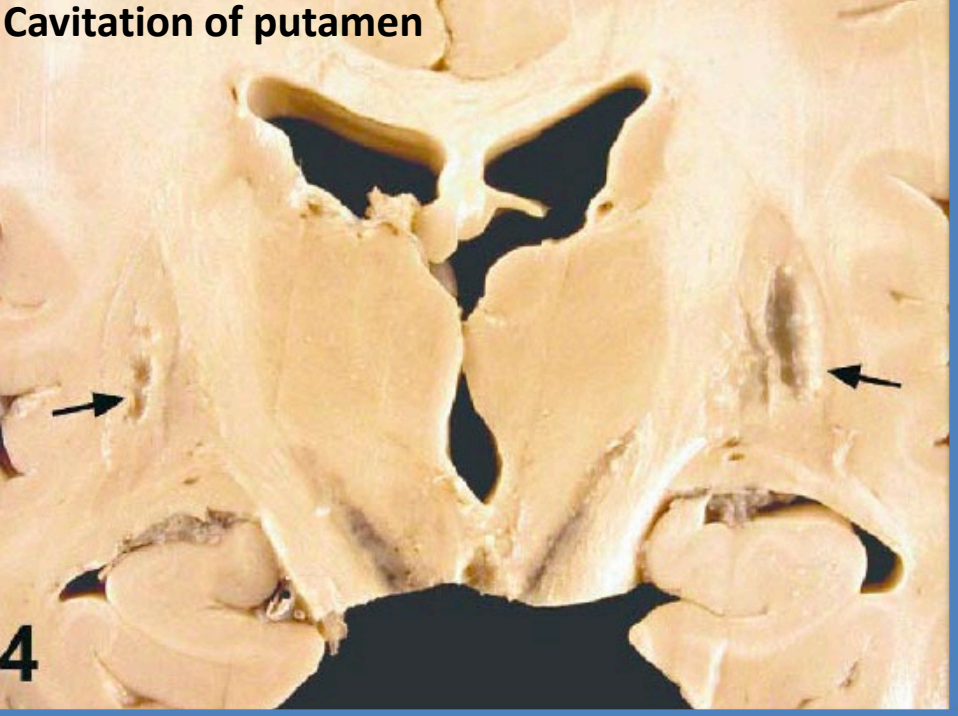


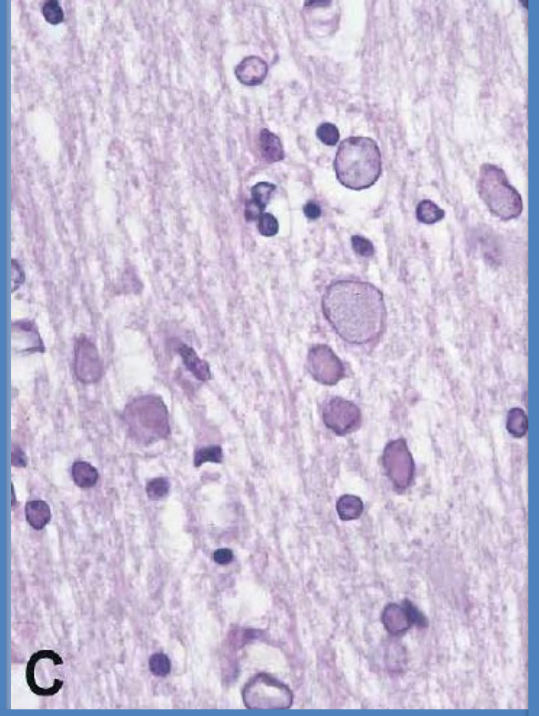
Curtis *et al.* Nat Genet. 2001 Aug;28(4):350-4.

Ferritins:
heteropolymers composed of 24 light (FTL) and heavy (FTH1) polypeptide subunits in variable proportions

Ferritins are involved in iron binding, metabolism, detoxification, and storage

Ferritin light chain *FTL* mutations cause autosomal dominant neurodegenerative disease with cellular inclusions and ferritin accumulations "Hereditary Neuroferritinopathy"





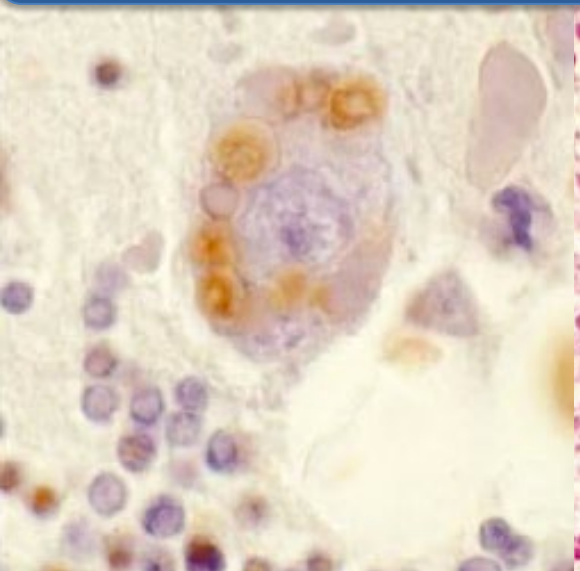
Hereditary Neuro-ferritinopathies

Inclusions can be seen within neurons and glia

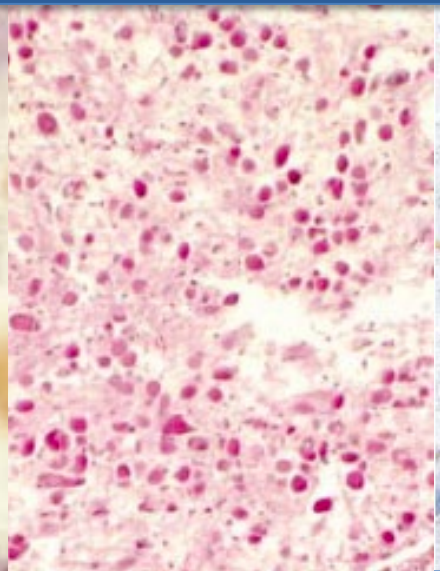
Both cytoplasmic and nuclear inclusions occur

Extracellular deposits are also found

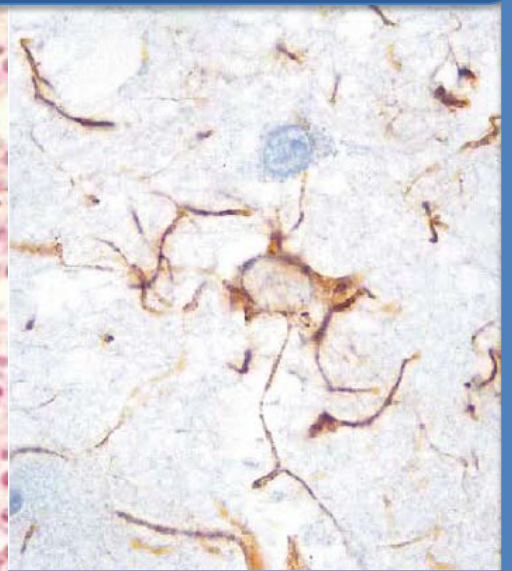
Purkinje cell with cytoplasmic ferritin + inclusions



Extracellular putamen deposits

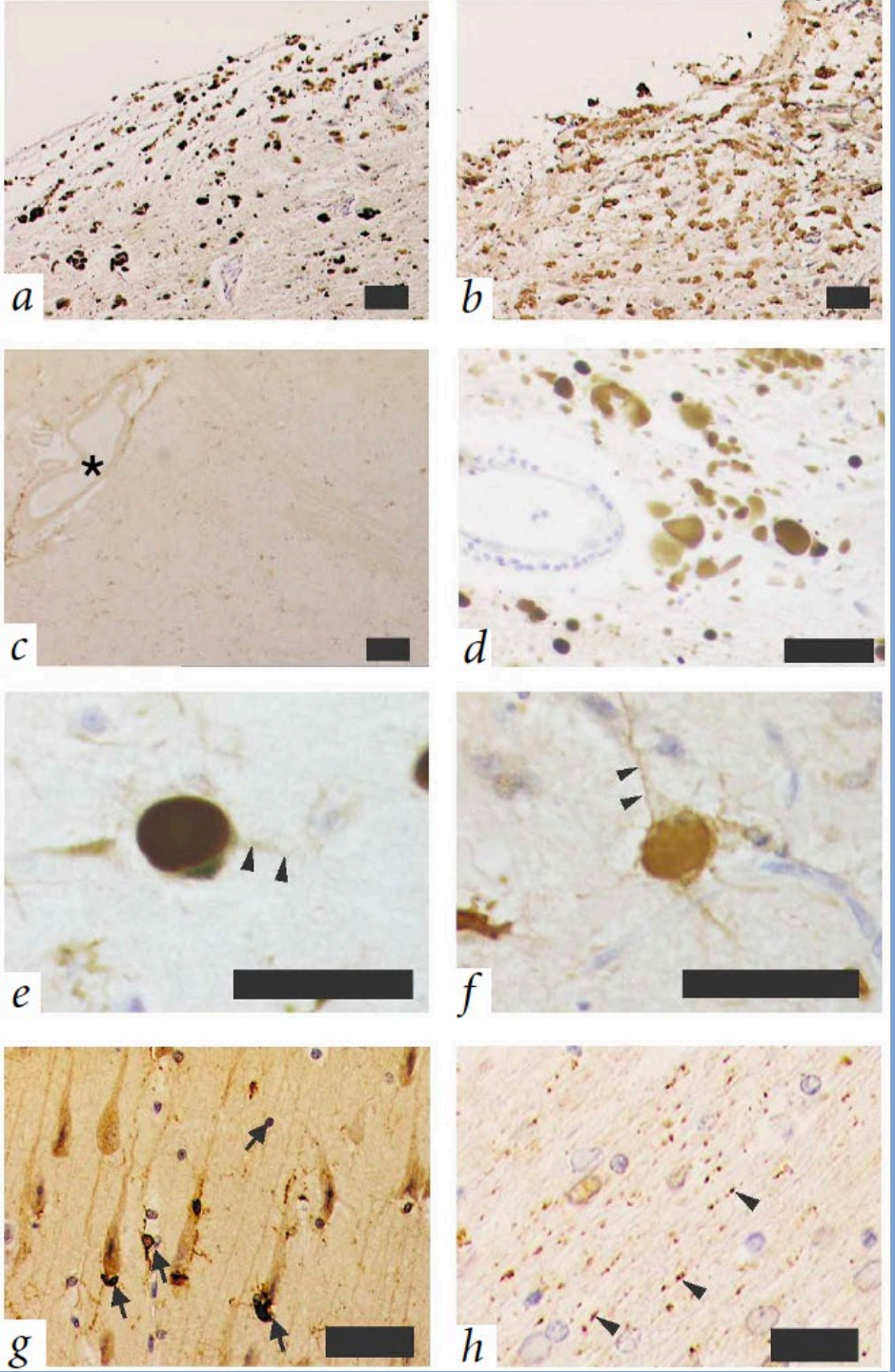


GFAP + astrocyte with vacuolated nucleus



Manusco *et al.*
J Neuropathol Exp Neurol. 2005

Vidal *et al.*,
J Neuropathol Exp Neurol 2004

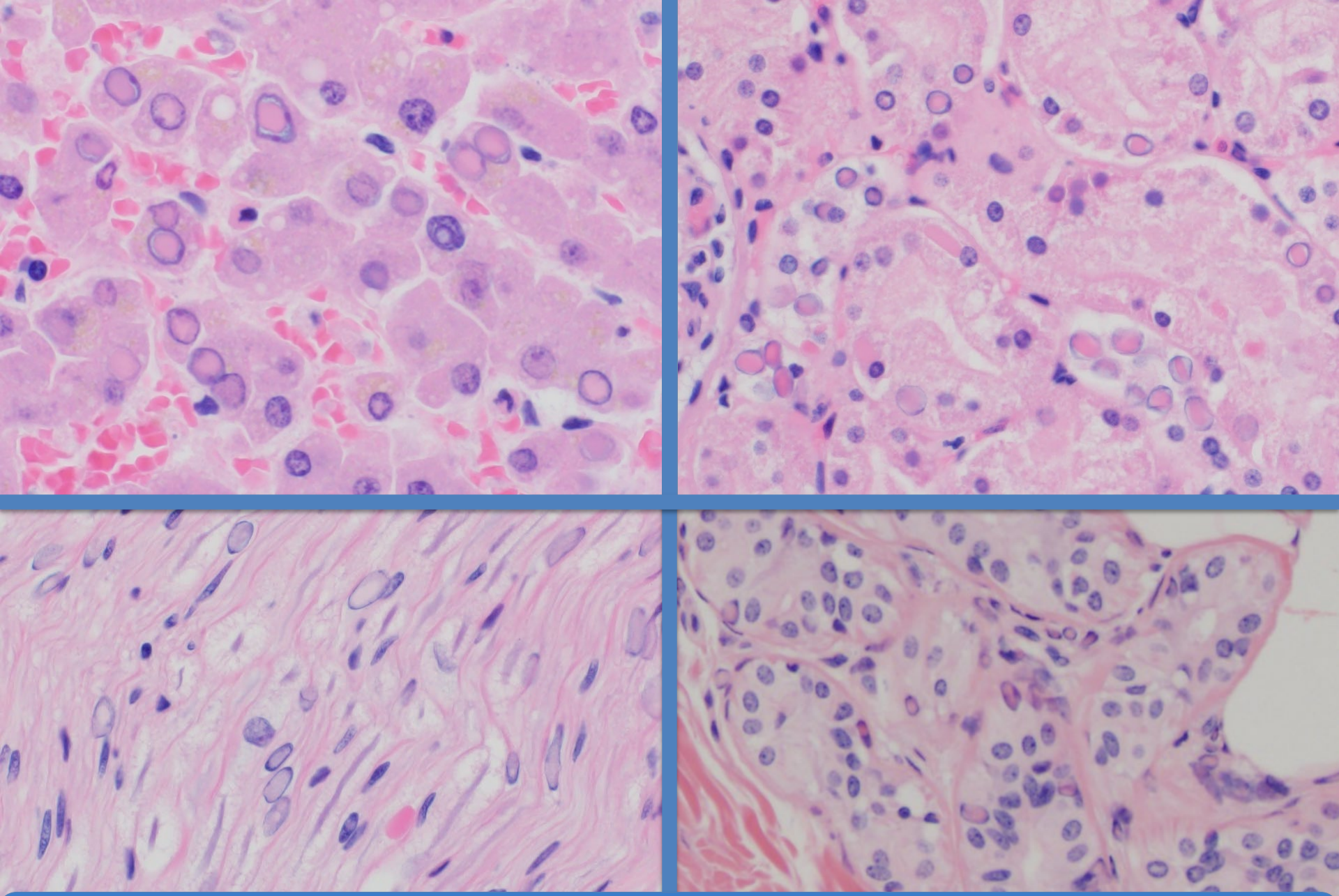


Iron- and ferritin-positive deposits
were present throughout
the forebrain and cerebellum,

these being mainly extracellular

but also showing colocalization with
microglia and oligodendrocytes
as well as with neurons,
notably in the globus pallidus.

Curtis *et al.,* Mutation in the gene encoding ferritin light polypeptide causes dominant adult-onset basal ganglia disease. Nat Genet. 2001 Aug;28(4):350-4. PMID: 11438811.



Eosinophilic nuclear inclusions are also present in other organs

“Hereditary ferritinopathy” is not exclusively a neuroferritinopathy

606159

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 3; NBIA3

Alternative titles; symbols

NEUROFERRITINOPATHY
BASAL GANGLIA DISEASE, ADULT-ONSET

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
19q13.33	Neurodegeneration with brain iron accumulation 3	606159	AD	3	FTL	134790

Clinical Synopsis | Phenotypic Series | PheneGene Graphics

TEXT

A number sign (#) is used with this entry because of evidence that this form of neurodegeneration with brain iron accumulation (NBIA), here designated 'NBIA3,' is caused by heterozygous mutation in the FTL gene (134790) on chromosome 19q13. See NOMENCLATURE section.

For a general phenotypic description and a discussion of genetic heterogeneity of NBIA, see NBIA1 (234200).

Description

Neurodegeneration with brain iron accumulation is a genetically heterogeneous disorder characterized by progressive iron accumulation in the basal ganglia and other regions of the brain, resulting in extrapyramidal movements, such as parkinsonism and dystonia. Age at onset, cognitive involvement, and mode of inheritance is variable (review by Gregory et al., 2009).

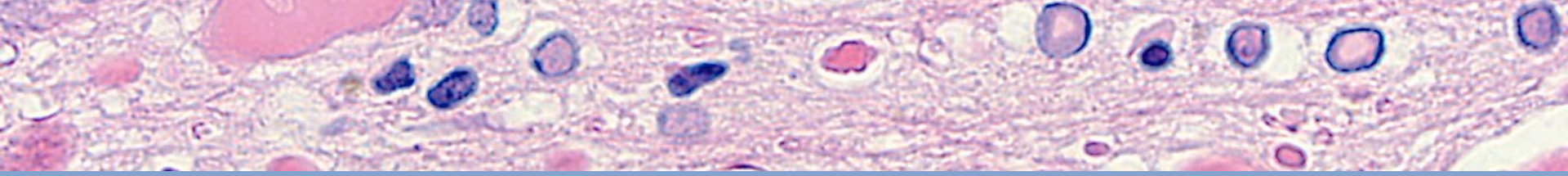
Neurodegeneration with brain iron accumulation (NBIA)

NBIA-type 1
PANK2 mutation

NBIA-type 2
PLA2G6 mutation

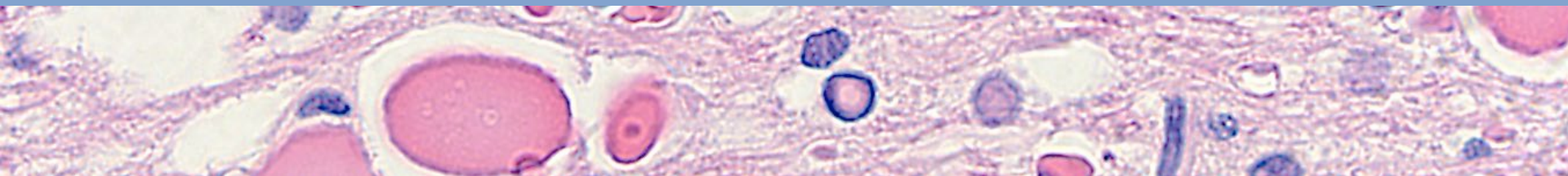
NBIA-type 3
***FTL* mutation**

Details on NBIA types 1-8 can be found at OMIM (Online Mendelian Inheritance in Man)



Hereditary Neuroferritinopathy

- Ferritin light chain *FTL* mutations cause AD neurodegenerative disease
- Inclusions within neurons and glia, and extracellular deposits
- Nuclear inclusions are also found in cells outside the CNS (ex. hepatocytes and renal tubule epithelium)
- A type of Neurodegeneration with Brain Iron Accumulation (NBIA)



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