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

Fresh brain weight: 745 grams
Differential diagnosis?

Additional immunohistochemical or molecular evaluation?
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.
**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”

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Hereditary Neuroferritinopathies

Inclusions can be seen within neurons and glia

Both cytoplasmic and nuclear inclusions occur

Extracellular deposits are also found

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.

Eosinophilic nuclear inclusions are also present in other organs. “Hereditary ferritinopathy” is not exclusively a neuroferritinopathy.
Neurodegeneration with brain iron accumulation (NBIA)

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

NBIA-type 1
*PANK2* mutation

NBIA-type 2
*PLA2G6* mutation

NBIA-type 3
*FTL* mutation

Phenotype-Gene Relationships

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<thead>
<tr>
<th>Location</th>
<th>Phenotype</th>
<th>Phenotype MIM number</th>
<th>Inheritance</th>
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▼ 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).
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)


