DSS Case 2020-4

Lucy Evans BS
Edwin Stone MD, PhD
Robert Mullins PhD
Budd Tucker PhD
Katherine Gibson-Corley DVM, PhD
Karra Jones MD, PhD

The University of Iowa

June 13th, 2020
Disclosures

We have no relevant financial disclosures.
Clinical history

27-year-old female
27-year-old female

- Initially presented in childhood with visual problems
Clinical history

27-year-old female

- Initially presented in childhood with visual problems
- Diagnosed with retinitis pigmentosa (RP)
  - Progressed to clinical blindness
Clinical history

27-year-old female

• Initially presented in childhood with visual problems
• Diagnosed with retinitis pigmentosa (RP)
  • Progressed to clinical blindness
• CNS symptoms in her 20s
  • Word finding difficulties
  • Memory loss
  • Generalized tonic-clonic seizures
Clinical history

27-year-old female

• Initially presented in childhood with visual problems

• Diagnosed with retinitis pigmentosa (RP)
  • Progressed to clinical blindness

• CNS symptoms in her 20s
  • Word finding difficulties
  • Memory loss
  • Generalized tonic-clonic seizures

• Brain MRI showed generalized cortical atrophy of unknown etiology
Clinical history

27-year-old female

- Initially presented in childhood with visual problems
- Diagnosed with retinitis pigmentosa (RP)
  - Progressed to clinical blindness
- CNS symptoms in her 20s
  - Word finding difficulties
  - Memory loss
  - Generalized tonic-clonic seizures
- Brain MRI showed generalized cortical atrophy of unknown etiology
- 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
• Mildly thin cortical ribbon
Autopsy

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

Hippocampus
Microscopy

Hippocampus
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
• Neurons filled with PAS and LFB positive granular storage material
Microscopy

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

Retina
Microscopy

Retina

- Severe degeneration of retinal layers → glial scar
Microscopy

Retina

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

Brain
Electron Microscopy

- Neuronal cytoplasmic inclusions
Electron Microscopy

Brain

- Neuronal cytoplasmic inclusions including fingerprint bodies
Electron Microscopy

- Neuronal cytoplasmic inclusions including fingerprint bodies
Electron Microscopy

Brain

- Neuronal cytoplasmic inclusions including fingerprint bodies
Genetic testing and Neuropathological Diagnosis

• Genetic testing: homozygous deletion in \textit{CLN3}
Genetic testing and Neuropathological Diagnosis

- Genetic testing: homozygous deletion in CLN3

- Juvenile neuronal ceroid lipofuscinosis/CLN3 disease (Batten Disease)
Neuronal Ceroid Lipofuscinoses (NCLs)

- Class of genetic lysosomal storage disorders
Neuronal Ceroid Lipofuscinoses (NCLs)

- Class of genetic lysosomal storage disorders
- Mutations in at least 14 genes
Neuronal Ceroid Lipofuscinoses (NCLs)

- Class of genetic lysosomal storage disorders
- Mutations in at least 14 genes
- Variable age of onset, symptoms, pathological findings
Neuronal Ceroid Lipofuscinoses (NCLs)

• Class of genetic lysosomal storage disorders
• Mutations in at least 14 genes
• Variable age of onset, symptoms, pathological findings
• Principle features: visual impairment, cognitive/motor decline, seizures, premature death
Neuronal Ceroid Lipofuscinoses (NCLs)

- Class of genetic lysosomal storage disorders
- 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
Juvenile NCL/CLN3 Disease

- Autosomal recessive mutation in ceroid-lipofuscinosi, neuronal 3 gene (CLN3)
  - Encodes BATTENIN: ubiquitously expressed, transmembrane protein, unknown function
  - 85% have homozygous 1kb deletion → truncated, nonfunctional protein
- Vision loss followed by cognitive/motor decline, speech problems, seizures, death in 2\textsuperscript{nd}/3rd decade
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

• 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
Juvenile NCL/CLN3 Disease

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

- Characteristic ultrastructural finding:
  - Fingerprint bodies

Haltia, J Neuropathol Exp Neurol, 2003
Summary

JNCL/CLN3 disease

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


Questions?