

Natural History of JNCL and other NCLs

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Neuronal Ceroid Lipofuscinosis - History

First description of juvenile-onset form probably by Stengel in 1826

Initial report with pathology by Batten in 1903 as juvenile-onset of a familial form of 'cerebral degeneration with macular changes'

Also reported Vogt (1905) and by Speilmeyer (1905)

A seemingly similar disorder with late-infantile onset was reported by Jansky (1908) and Bielschowsky (1913)

A similar disease with adult onset (but without vision loss) was described by Kufs (1925)

An infantile-onset form was described by Haltia and Santavuori (1973)

NCL Classification

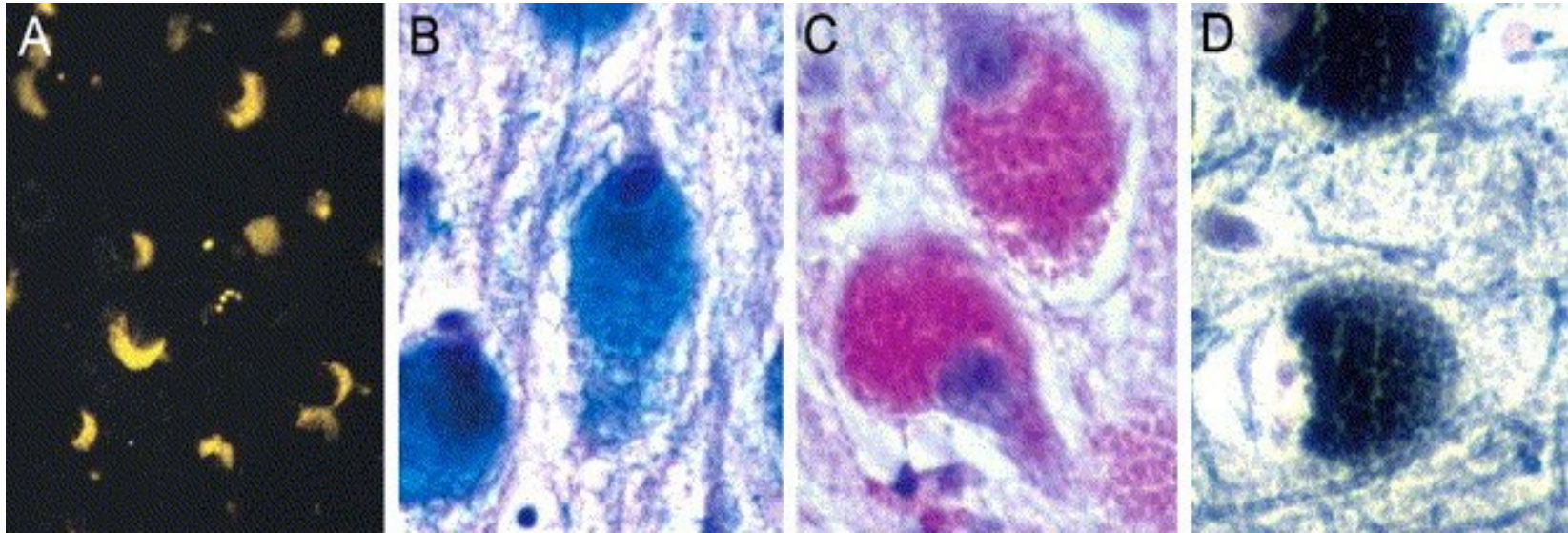
Disorders of cerebral degeneration with accumulation of autofluorescent lipopigment (ceroid lipofuscin) starting at different ages

Classified by age at onset

- Infantile NCL (Haltia-Santavuori disease)
- Late-Infantile NCL (Jansky-Bielschowsky disease)
- Juvenile NCL (Batten-Spielmeyer-Vogt disease)
- Adult NCL (Kufs disease)

Support for distinction came from ultrastructural abnormalities that were initially thought to be specific for each form

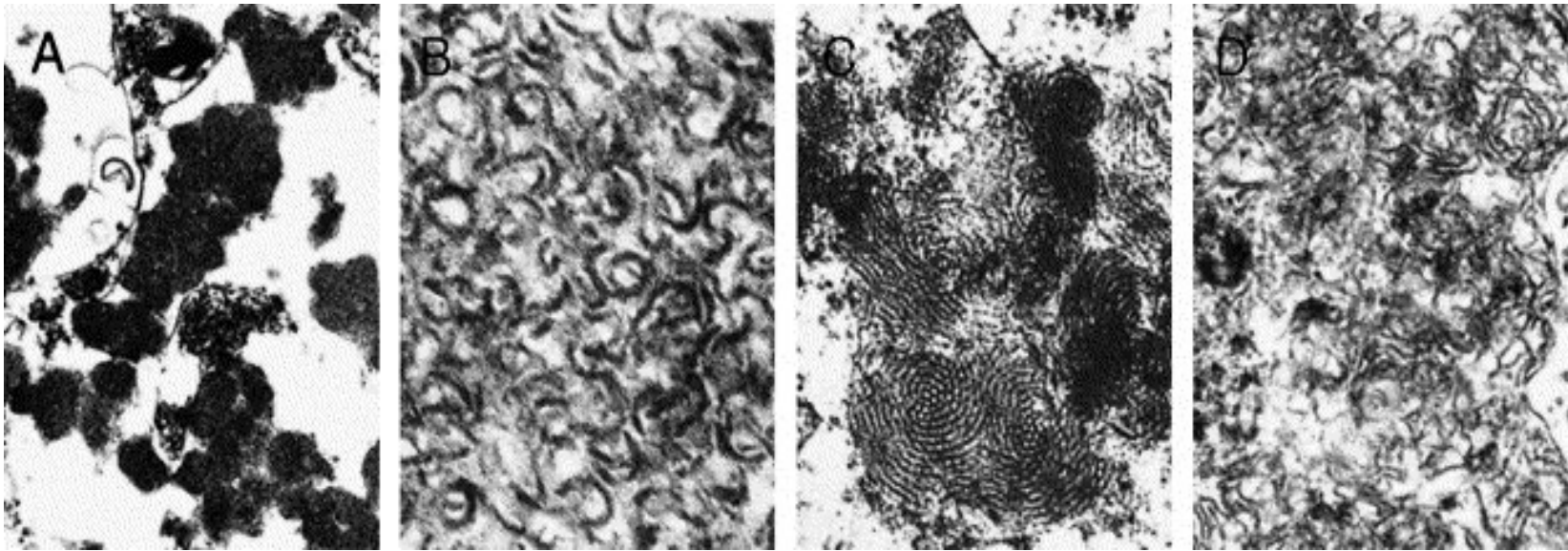
Neuronal Ceroid Lipofuscin



- (A) Autofluorescent intraneuronal storage material (CLN5)
- (B) Luxol fast blue (CLN8)
- (C) Periodic acid-Schiff (CLN8)
- (D) Sudan black B (CLN8)

From Haltia, 2003

Ultrastructural Patterns in NCLs



- (A) granular osmiophilic deposits (GRODs) (CLN1)
- (B) curvilinear profiles (CLN2)
- (C) fingerprint patterns (CLN3)
- (D) rectilinear profiles (LINCL variants)

From Haltia (2003)

Classification of NCLs

Over 10 different NCL genes have now been identified

Age of onset does not necessarily predict NCL type

Now classified by presumed genetic locus

Genotype does not reliably predict phenotype

- Spectrum of phenotypes for associated with certain genes with genotype-phenotype associations in some cases
- Phenotypic homogeneity for others

Phenotypic, including age at onset, can guide rational diagnostic testing

| Gene | Age at Onset | Chromosome | Protein | Ultrastructure |
|---------------|---|------------|-----------------------------------|--|
| CLN1 | Infantile, but also late infantile, juvenile, and adult | 1p32 | PPT1 | Granular Osmiophilic deposits (GRODS) |
| CLN2 | Late infantile, but also juvenile | 11p15 | TPP1 | Curvilinear profiles |
| CLN3 | Juvenile | 16p12 | lysosomal transmembrane protein | Fingerprint profiles |
| CLN4 (DNAJC5) | Adult (AD) (Parry) | 20q13.33 | Cysteine string protein | Rectilinear profiles |
| CLN5 | Late infantile (Finnish variant) | 13q22 | soluble lysosomal protein | Rectilinear profiles, Curvilinear profiles, Fingerprint profiles |
| CLN6 | Late Infantile Adult (Kufs) | 15q21 | transmembrane protein of ER | Rectilinear profiles, Curvilinear profiles, Fingerprint profiles |
| CLN7 | Late Infantile, Turkish variant | 4q28 | MFSD8, lysosomal membrane protein | Fingerprint profiles |
| CLN8 | Late infantile, Northern epilepsy | 8q23 | transmembrane protein of ER | Curvilinear profiles |
| CLN10 | Congenital ? Later onset ? | 11p15 | Cathepsin D | GRODS? |

The NCLs Represent Different Diseases

Common Features

- Neurodegeneration with onset in childhood
- Clinical Features
 - Retinopathy
 - Epilepsy
 - Dementia
 - Movement Disorder
- Intracellular storage material

Differences

- Clinical features
- Age at Onset
- Cell biology and biochemistry
- Rate and characteristics of progression

CLN1 Disease (classic Infantile NCL)

Early development appears normal

Onset between 6 and 24 months of age

Rapid psychomotor regression, ataxia, myoclonus, seizures and visual failure. Seizures not as prominent as in CLN2 disease

Ultimately vegetative with spasticity

Blindness by age 2 years with optic atrophy and macular and retinal changes but no pigment aggregation – early extinction on ERG

In the early stages there is generalized cerebral atrophy, and hypointensity on T2-weighted images of thalamus and basal ganglia

CLN1 Disease (later-onset variants)

Late-infantile – onset between ages 2 and 4 years

- Visual and cognitive decline followed by ataxia and myoclonus

Juvenile – onset between ages 5 and 10 years

- Cognitive decline (5 – 10 years)
- Seizures (7 – 17 years)
- Motor decline (7 – 15 years)
- Vision loss (10 – 14 years) – late compared to CLN3

Adult – onset after age 18 years

- Cognitive decline and depression
- Ataxia, parkinsonism, vision loss later

CLN1 Disease

All forms have GRODs

Presence of GRODs correlates highly with presence of PPT1 deficiency

Rough association between age at onset and genotype with mutations predicted to cause severe truncation or loss of protein are more likely to be seen in infantile-onset cases

CLN2 Disease

Age at onset 1 – 4 years typically

Psychomotor regression (usually 2nd year of life)

Refractory epilepsy (onset 2 -4 years) – multiple types

Ataxia, myoclonus (may be severe), ultimately spastic quadriparesis

Vision loss – abnormal ERG, VEP, retinal degeneration most visible in the macula. No cherry red spot.

Children with later onset (after 4 years) tend to have milder course with more prominent ataxia and less prominent epilepsy

Genotype – phenotype correlation not definite

CLN3 disease

Onset 4 – 7 years

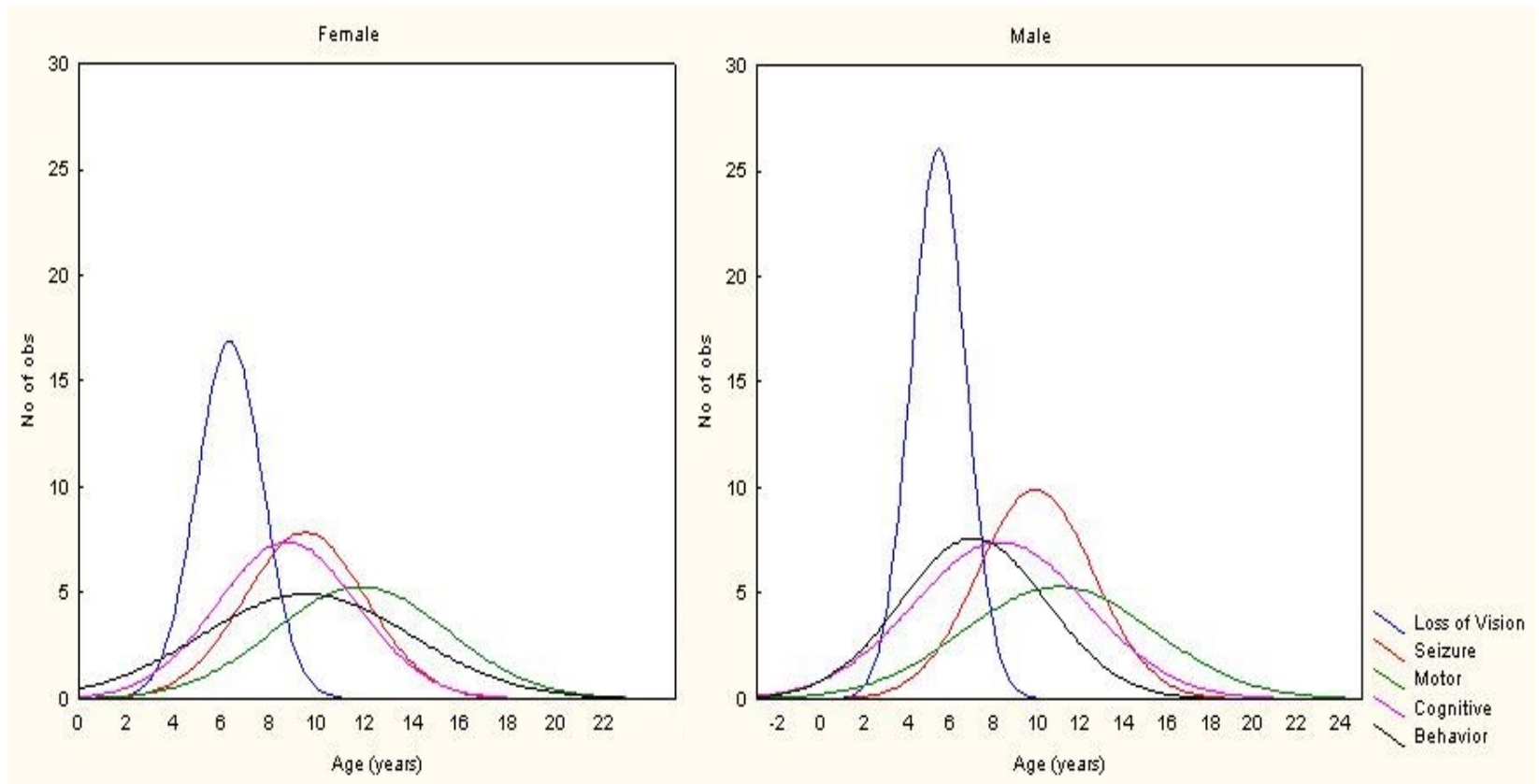
Characteristic pattern of progression

- Insidious onset of blindness (4 - 6 yrs) - earlier in males
- Progressive cognitive decline (7 – 10 yrs)
- Behavioral problems (8 – 10 yrs) – earlier in males
- Seizures (10 – 12 yrs) – GTC most common
- Parkinsonism (11 – 13 yrs)
- Severe, characteristic dysarthria usually after age 10 yrs
- Cardiac conduction abnormalities late

No variants in age at onset

No genotype – phenotype correlation

Age at Onset of Symptoms in CLN3 Disease



From Cialone et al, 2012

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CLN4 Disease

Reclassified to refer to “Parry disease” (DNAJC5) – named after a family

Only autosomal dominant NCL

Onset after age 30 years

Clinical features

- Ataxia
- Progressive dementia
- Seizures
- Myoclonic jerks

NO visual loss

CLN5 Disease

Variant late infantile NCL (vLINCL) – “Finnish variant”

Age at onset 4 – 17 years (mean 5.6 yrs) (later than CLN2 LINCL)

Clinical features

- Psychomotor regression
- Ataxia
- Myoclonic epilepsy
- Visual failure (may be presenting sign)

Not just Finnish and more common than previously thought (Xin et al., 2010)

CLN6 Disease

Variant late infantile NCL (vLINCL)

- Age at onset 18 months – 8 years
- Motor delay, dysarthria, ataxia, seizures
- Seizures an early feature (< 5 yo in > 60%)
- Early vision loss in 50%
- Rapid deterioration - death usually between 5 and 12 years of age

Recently found to be etiology of Kufs disease – Type A (formerly CLN4)

- Onset around 30 years of age
- Progressive myoclonic epilepsy with later development of dementia and ataxia
- No vision loss

CLN7 Disease

Variant LINCL (turkish) (chromosome 4q28)

Age at onset 2 – 7 years

Initial symptom typically seizures

Progressive motor decline, myoclonus, cognitive changes, and vision loss

CLN8 Disease

Two forms (chromosome 8p23)

- Northern epilepsy (Finnish) – variant of progressive myoclonus epilepsy
 - Seizures starting at age 5 – 10 years; worse with age
 - Progressive cognitive and motor decline
- Variant LINCL (Turkish, Italian, Israeli)
 - Add vision loss
 - More severe phenotype

CLN10 Disease – Cathepsin D deficiency

Earliest onset form – “Congenital NCL”

Clinical Features

- Microcephaly with brain atrophy
- Absence of neonatal reflexes
- May have neonatal seizures
- Respiratory insufficiency

Rarely live more than a few days

Cathepsin D is absent

Some mentions about later onset forms, but unable to confirm

Summary

NCLs have several features in common suggesting biological similarities or functional interactions between involved genes

Clinical manifestations of the different NCLs differ in age at onset, order of progression, and specific symptoms

Quantitative study of natural history in the NCLs can inform neurobiological investigations and development of outcome measures for clinical trials

Variability suggests either differential expression within the CNS or differential vulnerability of different neuronal populations

Clinical endpoints and other outcome measures may have important overlap across the NCLs, but the different time courses suggest that disease-specific endpoints will also be necessary