Neuronal Ceroid Lipofuscinosis (NCL)
A practical approach
Disclosures

None
Neuronal Ceroid Lipofuscinosis

- Genetically inherited neuro-degenerative lysosomal storage diseases mainly characterized by
  - Progressive intellectual deterioration
  - Seizures
  - Vision loss

- Incidence (1.3 – 7 in 100,000 live births). Most common hereditary progressive neurodegenerative disease

- Autosomal recessive (except adult which can be autosomal dominant)

- Clinically characterized by the age of onset:
  - Congenital, Infantile, Late infantile, Juvenile, Adult
Brief history

- **1826**: Stengel reported the clinical features of juvenile NCL in 4 Norwegian siblings with progressive blindness, epilepsy, cognitive decline, and motor dysfunction.

- **1903 and 1923**: Batten, Spielmeyer, and Vogt independently showed intraneuronal storage accumulation in juvenile patients that had clinical resemblance to those reported by Stengel.

- **1969**: Zeman and Dyken introduced the term neuronal ceroid-lipofuscinosis referring to the common pathologic feature of these disorders.
Objectives

Clinical overview of Neuronal Ceroid Lipofuscinosis (NCL)

- Suspecting NCL
- Current Nomenclature
- Pathologic inclusions and Electron Microscopy findings
- Biology of the NCL proteins

The most common NCL disorders

- CLN1
- CLN2 and variant Late Infantile NCL
- CLN3
- Adult NCL

Diagnostic approach

Treatment

Resources
When to suspect a NCL disorder?

- Seizures
- Regression, cognitive decline or failing to reach developmental milestones
- Vision loss (except adult and Northern Epilepsy)
- Motor function impairment (involuntary movements, myoclonus, ataxia, spasticity)

*Initial symptoms vary among NCL phenotypes*
## Current Nomenclature

<table>
<thead>
<tr>
<th>NCL type</th>
<th>Prior designation</th>
<th>Genes</th>
</tr>
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<tbody>
<tr>
<td><strong>CLN1</strong></td>
<td>Infantile NCL (Santovouri-Haltia)</td>
<td><em>PPT1</em></td>
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<tr>
<td><strong>CLN2</strong></td>
<td>Late Infantile NCL (Jansky-Bielschowsky)</td>
<td><em>TPP1</em></td>
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<td><strong>CLN3</strong></td>
<td>Juvenile NCL (Spielmeyer-Sjogren)</td>
<td><em>CLN3</em></td>
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<td>CLN4</td>
<td>Kufs [Parry type]</td>
<td><em>DNAJC5</em></td>
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<td>CLN5</td>
<td>variant LINCL</td>
<td><em>CLN5</em></td>
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<tr>
<td>CLN6</td>
<td>variant LINCL, Kufs type A</td>
<td><em>CLN6</em></td>
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<tr>
<td>CLN7</td>
<td>variant LINCL</td>
<td><em>MFSD8</em></td>
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<td>Kufor-Rakeb PARK9</td>
<td><em>ATP13A2</em></td>
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<td>Kufs Type B</td>
<td><em>CTSF</em></td>
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<td>EPM3</td>
<td><em>KCTD7</em></td>
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<td>Phenotype</td>
<td>Phenotype by Gene and Onset</td>
<td>Presenting Findings</td>
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<td>Proportion</td>
<td>Gene Symbol</td>
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<td>Rare</td>
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<td></td>
<td>Major in Finland; minor</td>
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<tr>
<td></td>
<td>elsewhere</td>
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<tr>
<td>Juvenile (JNCL)</td>
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<td></td>
<td>Minor</td>
<td>PPT1</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>TPP1</td>
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<tr>
<td>Northern epilepsy (NE) (progressive epilepsy with mental retardation [EPMR])</td>
<td>Major in Finland, rare elsewhere</td>
<td>CLN8</td>
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<tr>
<td>Adult (ANCL) (Kufs disease)</td>
<td>Rare</td>
<td>CTSD, PPT1, CLN3, CLN5, CLN6, CTSF, GRN</td>
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<td>Adult (ANCL) (Parry disease); autosomal dominant</td>
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<td>DNAJC5</td>
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</tbody>
</table>
Storage material in NCL

Auto-fluorescent, waxy, dusky lipid accumulation reminiscent of aging pigment lipofuscin (lysosomal inclusions)

Secondary markers:

- Lysosomal storage of Saposins A and D in CLN1, CLN10, Parry disease (associated with GRODs)
- Subunit c of the mitochondrial ATP synthase in CLN2, CLN3 and adult-onset forms (associated with FP, CL and rectilinear bodies)
Granular osmophilic deposits (GROD) in CLN1 and CLN10 forms

Predominantly curvilinear profiles (CV) in CLN2

Fingerprint profiles (FP) in CLN3

Rectilinear complex (RL) in CLN3, CLN5, CLN6, CLN7, CLN8

Mixed-type inclusions (CV, FP, and GROD) in CLN5, CLN6, MFSD8, CLN8 and other late-infantile variant forms

Mixed-type inclusions (CV, FP, and GROD) in Adult NCL forms

Glykys and Sims, 2017. In: Swaiman’s Pediatric Neurology
Preferential cellular localization of NCL proteins

*Intracellular pathways involve:*

- Endosomal-lysosomal autophagy degradation pathways
- The synaptic trafficking and function pathways
- The neuro-inflammation/immune regulation pathways
- Mitochondrial function abnormalities

Specific protein deficiencies, pathway blockades and metabolic substrate accumulation, as well as downstream functional deficiencies

Glyks and Sims, 2017. In: Swaiman's Pediatric Neurology
A pathogenesis model

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Diagnostic approach

Treatment

Resources
CLN1 (Classic infantile, INCL, Santavuori-Haltia)

- **Most common.** Presents between 6 - 24 months. Live expectancy: ~10 years

- **Gene:** *PPT1* (palmitoyl-protein thioesterase). Lysosomal housekeeping enzyme. Removes long-chain fatty acids, usually palmitate from cysteine residues.

- **Initial presentation:** developmental failure, myoclonic jerks or seizures
  - Hand stereotypies as Rett syndrome; speech problems; loss of interest in toys
  - Retinal blindness and myoclonic jerks by 1 year of age

- **MRI:** variable cerebral/cerebellar atrophy, hypointensity in thalami; leukoencephalopathy.

- **EEG:** Lack of sleep spindles. Absence of attenuation in amplitude when opening eyes by 16–24 months. Gradual loss of amplitude, isoelectric by around 3 years.

- **Inclusions:** GRODs

- **Other presentations:** variant late-infantile onset, Juvenile and Adult
**CLN2** (Classic late infantile, LINCL, Jansky – Bielschowsky disease)

- Presents at 2-4 years. Bedridden by 6 years of age. Live expectancy: 6 years - adolescent

- **Gene:** *TPP1* (tripeptidyl peptidase 1). Removes N-terminal tripeptides from small peptides

- **Initial presentation:** Epilepsy (GTC, absence, focal seizures, myoclonus)
  - Loss of acquired motor/language and cognitive skills
  - Visual impairment at 4-6 years
  - Early hypotonia is replaced with severe spasticity with flexion contractures
  - Autoregulation of vascular tone is lost, resulting in mottled cold hands and feet and hypothalamic involvement leads to temperature instability

- **MRI:** Cerebellar and cerebral atrophy ± thalamic hypodensity

- **EEG:** Characteristic giant occipital poly-spike discharges in response to a single flash of light or to low-frequency, repetitive stimulation

- **Inclusions:** CL

- **Other presentations:** Infantile, juvenile
Variants of late infantile NCL (vLINCL)

- **CLN5 disease**: (onset 3 - 7 years). Motor clumsiness, learning problems, visual failure. Seizures by 9 years of age. [Juvenile, Adult and congenital forms]

- **CLN6 disease**: (onset 2-5 years). Motor delay and cerebellar findings. Seizures before 5 years. Visual loss occurs early. Rapidly progressive. [Juvenile with progressive myoclonus, adult forms]

- **CLN7 disease**: (onset 2-7 years). Aggressive behavior and severe epilepsy in association with developmental regression. More severe seizure phenotype. [Pure visual, Juvenile]

- **CLN8 disease**: (onset 2-7 years). Developmental delay and then myoclonic seizures and ataxia. Rapidly progressive. By 10 years of age, most of the children are wheelchair-bound [Progressive Epilepsy with Mental Retardation 5-10 years]
CLN3 (Classic Juvenile NCL, JNCL, Spielmeyer-Vogt disease)

- Presents at 3-8 years. Live expectancy late teens early 20s
- **Gene: CLN3.** Endosomal/lysosomal transmembrane protein that seems to play a pivotal role in the late endosomal/lysosomal membrane transport system
- **Initial presentation:** rapidly progressing vision loss. Maybe only sign for 2-5 years
  - Macular changes, pan-retinal degeneration; pigmentary changes in retinal periphery; optic pallor (retinitis pigmentosa)
  - Behavioral problems and sleep disturbance, cognitive decline by 10 years of age
  - Epilepsy (GTC, focal onset) starts around 12-14 years
  - Extrapyramidal signs (shuffling gait, rigidity). Speech disturbances (stuttering).
  - Cardiac involvement with conduction dysfunction
- **MRI:** cerebral, and to a lesser degree, cerebellar atrophy in the later stages
- **EEG:** Large-amplitude spike and slow-wave complexes by around 9 years.
- **Inclusions:** FP, CL and RL
- **Other presentations:** slower disease, retinitis pigmentosa and cone-rod dystrophy.
Adult NCL - Kufs disease

- Presents at around 30 years; death around 10 years later
- Symptoms may appear as early as age 11 years
  - **Type A:** progressive myoclonus epilepsy, dementia, ataxia, late pyramidal/extrapyramidal signs. Seizures often uncontrollable
  - Found to have *CLN6, GRN* (CLN11) mutations
  - **Type B:** behavior abnormalities/dementia, motor dysfunction, ataxia, extrapyramidal signs (no vision loss)
  - Found to have mutations in *CTSF* (CLN13)
- **CLN4 (DNAJC5; autosomal dominant)**
  - Present at ~40 years of age with myoclonic seizures, dementia and movement abnormalities. *Visual function preserved*
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Diagnostic approach (Pre-genetic panel)

- Age of Symptoms
- Enzymatic Testing
- Skin Biopsy

Directed Gene Testing
Proposed approach to diagnosis in NCL

Newborn with encephalopathy ± microcephaly

- Enzyme testing for CTSD, PPT1, TPP1
  - (+) Test appropriate gene CTSD, PPT1, TPP1
  - (-) Consider alternative diagnosis

6 mo - 4 yo with developmental delay or regression ± seizures

- Epilepsy panel (including NCL genes)
- Enzyme testing for PPT1, TPP1, CTSD
  - (+) Test appropriate gene PPT1, TPP1, CTSD
  - (-) Skin biopsy and/or eye exam/ERG
    - (+) Test for CLN5, CLN6, MFSD8, CLN8, KCTD7 or NCL panel/Epilepsy panel
    - (-) Consider alternative diagnosis

Whole Exome or Whole Genome test

Glykys and Sims, 2017. In: Swaiman's Pediatric Neurology
Proposed approach to diagnosis in NCL

4 - 12 yo with visual loss and/or epilepsy and mental deterioration

Test for CLN3 common deletion
  - if heterozygous
    - Full CLN3 gene sequence
      - Enzyme testing for PPT1, TPP1
      - Test appropriate gene PPT1, TPP1
        - Test for CLN5, CLN6, MFSD8, CLN8, ATP13A2, CTSD, full CLN3 sequence or NCL Panel/Epilepsy panel
          - Consider alternative diagnosis
            - Skin biopsy
              - Whole Exome or Whole Genome test

Glykys and Sims, 2017. In: Swaiman's Pediatric Neurology
Proposed approach to diagnosis in NCL

12 - 30 yo with mental, motor or behavioral abnormalities ± seizures

Enzyme testing for CTSD, PPT1, TTP1

AR: CLN6, GRN, CTSF, CLN5, MFSD8

AD: DNAJC5

NCL panel

Skin biopsy

Test appropriate gene CTSD, PPT1, TPP1

Whole Exome or Whole Genome test

Consider alternative diagnosis

Glykys and Sims, 2017. In: Swaiman's Pediatric Neurology
Treatment of NCL disorders

- Mainly supportive

- **Seizures**: valproate (VPA) and lamotrigine (LTG) appear equally effective, with 80% of the patients responding (Aberg LE, et al, 2000)

- Benzodiazepines may benefit seizures, anxiety, spasticity, and sleep disorders

- Antidepressants and antipsychotic agents are sometimes indicated for those with behavioral disturbances (CLN3 disease)

- School attendance, augmentative therapies

- Genetic counseling

- **CLN2**: Cerliponase alfa (Intra-ventricular administration) to slow the loss of ambulation in symptomatic patients 3 years of age and older with CLN2 (Approval by FDA and EU). [ClinicalTrials.gov identifier: NCT01907087](https://clinicaltrials.gov/ct2/show/NCT01907087)
Therapies under investigation

CLN1
Oral cysteamine bitartrate and N-acetylcysteine: Produced complete depletion of GRODs. Average time to isoelectric EEG was longer than natural history (36 vs. 52 months). Less irritability

ClinicalTrials.gov identifier: NCT00028262

CLN2
A TPP1 gene transfer safety study using an adeno-associated virus (AAV) vector injected directly into the brain.

ClinicalTrials.gov identifier: NCT01414985 and NCT01161576

CLN3
Mycophenolate mofetil for Treatment of Juvenile Neuronal Ceroid Lipofuscinosis (JUMP) trial.

ClinicalTrials.gov identifier: NCT01399047
Resources

Our Promise to Nicholas Foundation
www.ourpromisetonicholas.com

NCL Resource - A Gateway for Batten Disease
www.ucl.ac.uk/ncl

Neuronal Ceroid-Lipofuscinosis (Batten Disease)
Gene Reviews Mole SE, Williams RE. Neuronal Ceroid-Lipofuscinosis.
http://www.ncbi.nlm.nih.gov/books/NBK1428/

Batten Disease Fact Sheet
National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov/disorders/batten/detail_batten.htm

NCL Resource—A Gateway for Batten Disease
www.ucl.ac.uk/ncl
Selected references


At MGH

MGH-CHGR Joint Program in the NCL Disorders

Neurogenetics Program

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Thank you