Improving Diagnosis of CLN3 Batten Disease

Earlier recognition. Earlier diagnosis. Better outcomes.

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BDFA
BATTEN DISEASE FAMILY ASSOCIATION

Aim

To decrease the diagnostic odyssey faced by families of children with CLN3 Batten disease.

Batten Disease

- Batten disease is the common name for a devastating group of genetically inherited disorders causing a progressive, terminal neurodegenerative condition.
- Batten disease is caused by mutations in one of 13 different CLN genes with CLN2 and CLN3 being the most common in the UK.
- Classified as a lysosomal storage disorder (LSD), each mutation affects a key component of the endolysosomal system
- Presenting clinical features are a combination of epilepsy, psychomotor regression on previously age-appropriate milestones, cognitive decline and loss of vision.
- There is no cure, and treatment is mostly palliative.
- Families face a long diagnostic odyssey and an everchanging caregiving burden.

CLN3 Natural History

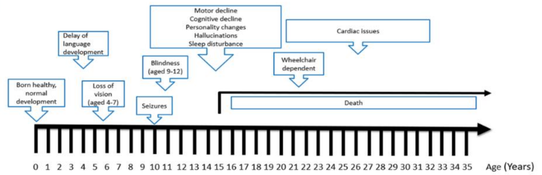

Figure 1. CLN3 natural history timeline

CLN3

- Caused by biallelic pathogenic variants in the CLN3 gene.
- CLN3 is a 48 kDa lysosomal transmembrane protein.
- Around 80% of affected individuals have the common 1kb deletion.
- Vision loss is usually the first presenting symptom occurring around 5-6 years of age
- Initial loss of central vision
- Rapid progress to total blindness over approximately three to five years
- Symptoms emerge and worsen over the next 15 – 20 years
- Life expectancy is between mid teens to mid thirties

Diagnosis

BDFA have recently published a study investigating the impact of CLN2 and CLN3 Batten disease on families in the United Kingdom.

- Thematic analysis of data resulted in 6 main themes
- Failure to recognise significance of early symptoms
- The shock of a Batten disease diagnosis
- The demands of caring for complex and ever-changing needs
- Constant battle to access appropriate and timely support services
- The extensive impact on the unaffected sibling
- The all-encompassing impact on the family

As parents felt there was a failure to recognise the early symptoms we asked them about their experiences of receiving a CLN3 Batten disease diagnosis in the UK.

- All parents cited changes in vision as an initial symptom.
- Other early symptoms were
- Clumsiness
- Behaviour changes
- Learning difficulties

Initial symptoms were first noticed by

- Primary school - 60%
- Family members - 30%
- Other - 10%

Although initial symptoms are subtle our parents said:

- They instinctually knew something was wrong
- They often felt symptoms were dismissed by healthcare professionals
- They experienced a cyclical pattern of visiting doctors and misdiagnoses

80% of children were referred to Ophthalmology as the first speciality. Differential diagnoses received included:

- Macular dystrophy
- Stargardt
- Cone rod dystrophy
- Retinitis pigmentosa
- Astigmatism

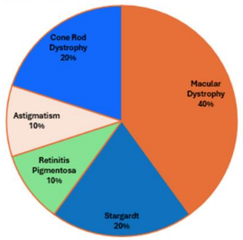

Figure 2. Graph to show differential diagnoses

CLN3 Batten Disease Clinical Presentation

- Initial presentation is usually visual impairment
  - Rapid best-corrected bilateral visual loss
  - With or without photophobia and night blindness
- Early ocular symptoms can be non-specific
- ERG may be electronegative with a diminished b-wave amplitude or no recordable rod-mediated activity
- Clinically evident maculopathies on fundoscopy and optical coherence tomography (OCT) may be present around the time of diagnosis.

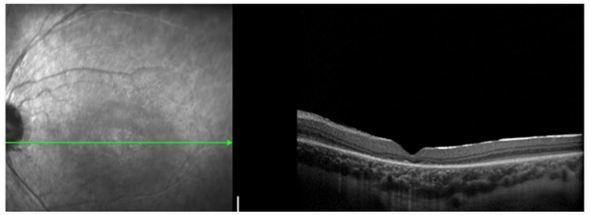

Figure 3a. 6-year child showing some signs of deterioration at this stage as seen by loss of the retinal layers in the central area

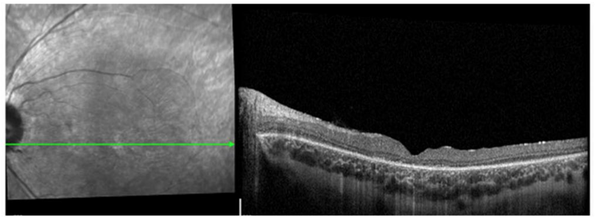

Figure 3b. Same child 6 months later showing deterioration progressing outwards over time.

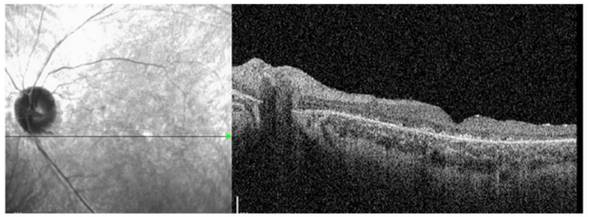

Figure 3c. Same child 18 months after first scan. The quality of the final scan is poor because of the rapid deterioration in vision and the child not being able to fixate for higher quality scans.

Potential Treatments

As CLN3 disease is progressive, early diagnosis is crucial to enable patients to benefit from treatments likely to be trialed in the UK soon.

- **Small molecule therapy**
- Miglustat
  - Substrate reduction therapy in Gaucher and NPC
  - Reduces build up of harmful products in the
  - lysosomes
  - Phase III trial due in 2026

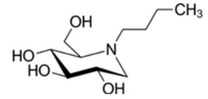

Figure 4. Skeletal formula of Miglustat.

- Gemfibrozil
  - PPARα agonistic properties that boost lysosome biogenesis via TFEB upregulation
  - Shown to reduce inflammation in the brain and promote neuronal survival in murine Batten disease models
  - IND opened with the FDA for a Phase 2, open-label basket trial
- **Gene therapy**
  - Gene therapy has been used in clinical trials for CLN2, CLN3, CLN5, CLN6 and CLN7 (all based on AAV, mainly AAV9)
  - Many potential gene therapies have not progressed beyond Phase I/II (funding)
- **ASOs**
- Milasen (CLN7)
  - Developed for an unusual mutation
  - Concept to clinic in 10 months
- **Zebronkysen (Project Butterfly)**
  - Splice-switching ASO developed for an unusual CLN3 mutation
  - First administered in June 2024
    - Objectives
    - Safety
    - Efficacy
    - Biomarkers
- Shown improvements in autonomic nervous system, effects of dystonia and QoL

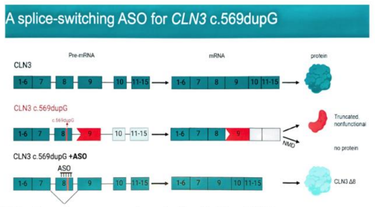

Figure 5. Using a splice-switching ASO to target an unusual mutation in the CLN3 gene.

Conclusions

- CLN3 Batten disease is a devastating and progressive condition.
- Diagnostic delays are common for children with both CLN2 and CLN3 disease; this leads to delayed access to symptomatic and supportive care that could improve their quality of life and enable parents to put in place anticipatory measures to allow them to best adjust to the degenerative impact of the condition.
- New treatments being develop will be most effective earlier in the disease
  - Therefore, require earlier diagnosis is essential
- **A CLN3 disease diagnosis should be considered in all children under the age of 10 years presenting with rapid best-corrected bilateral visual loss.**

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