ONLINE EXCLUSIVE

Robert Henderson

Revolutionary eye treatments offer hope for children facing blindness from CLN2 batten disease. Robert Henderson discusses this, and his use of Heidelberg Engineering's Spectralis device to better combat it.

Pioneering research from Great Ormond Street Hospital (GOSH) and the University College London (UCL) Institute of Child Health is giving hope to children facing blindness caused by CLN2 Batten disease (also known as late infantile NCL or Jansky–Bielschowsky disease).

The neuronal ceroid lipofuscinoses (NCL) are a group of rare, genetic, life-limiting neurological conditions that can cause vision loss, progressive decline in motor and cognitive skills, and drug-resistant epileptic seizures. Approximately 100–150 children and adults are currently living with an NCL diagnosis in the UK. It usually begins in childhood, and can occur as early as six months, or as late as the teenage years or even adulthood. There is currently no cure for CLN2, but there are treatments available to help slow the progression of the disease and manage symptoms.

Robert Henderson, Consultant Ophthalmic Surgeon and Paediatric Ophthalmologist at Moorfields Eye Hospital and Great Ormond Street Hospital, is leading the development of pioneering eye treatments for CLN2 disease.

"CLN2 is a devastating diagnosis," says Robert [1]. "Intraventricular infusion enzyme replacement therapy (ERT), where the drug is delivered directly into the cerebrospinal fluid, is an excellent treatment for slowing the loss of cognitive and motor skills associated with CLN2 disease, however children receiving this therapy continue to rapidly go blind. With optical coherence tomography (OCT), as the disease progresses, you see changes such as retinal thinning, loss of the photoreceptor layer, ellipsoid zone degeneration, and macular and optic nerve head atrophy.

"This disease is uniquely positioned for using OCT as an outcome measure for clinical trials since the degeneration or disappearance of the ellipsoid zone is closely linked to the decline in visual function. So, it was agreed that measuring ellipsoid loss is the ideal primary clinical endpoint for the trial.

Figure 1: Robert Henderson using the Spectralis with Flex Module in theatre.

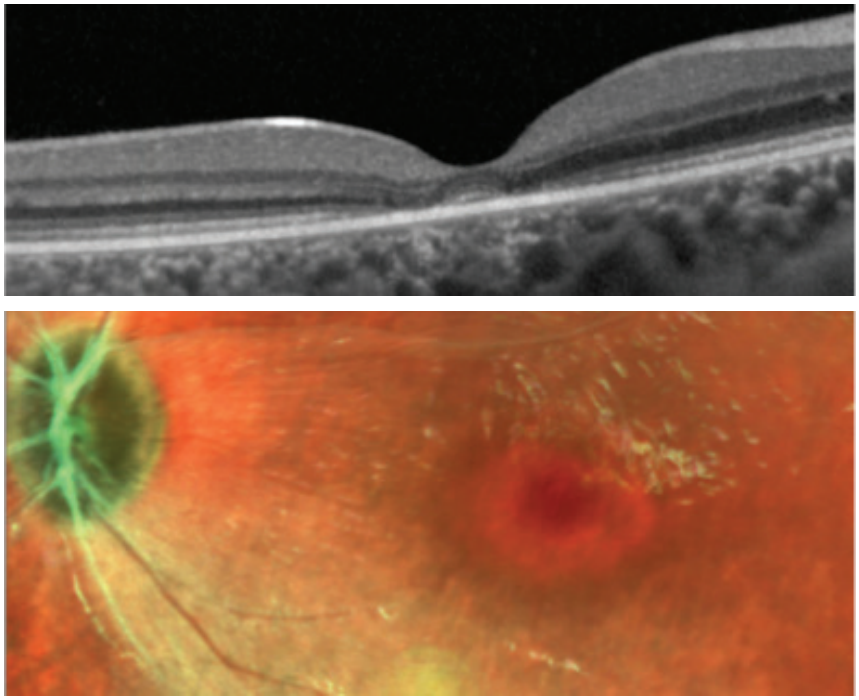
"The challenge is that we are dealing with children, and on top of that these children often have physical or cognitive impairments, which makes getting them to sit still for a detailed OCT investigation virtually impossible. This is where the Spectralis with Flex Module is invaluable."

"The Spectralis with Flex Module allows clinicians and researchers to image the eyes of patients who cannot present to a static, table-mounted headrest. With the Flex Module, Spectralis is affixed to a movable stand with an adjustable arm. It offers a degree of flexibility that goes far beyond conventional ophthalmic imaging, extending all multimodal diagnostic functionality to various positions and acquisition environments. Thereby it is possible to conduct ophthalmic examinations in supine patients, systemically unwell patients, paediatric patients, and to monitor ocular surgery outcomes.

"The reading centres for imaging from these big clinical trials have exacting standards on the quality of images we need to get," continues Robert. "We needed to capture high-resolution, dense macular OCT scans as well as a full complement of multimodal images including infrared reflectance, autofluorescence, and widefield images. The Flex is perfect for this."

Pioneering eye treatments for CLN2 disease are still in the early stages, but several promising approaches are being explored. These treatments are aimed at targeting retinal cells, which are affected in CLN2 disease but are difficult to reach with currently approved therapies.

"What we tried first was targeted drug delivery that involves delivering the TPP1 enzyme directly into the retina via intravitreal (IVT) injection," says Robert.



Figures 2 & 3: Cropped Spectralis OCT and MultiColor images showing parafoveal loss of ellipsoid and bull's-eye maculopathy in patient with CLN2 disease.

"The evidence suggests that IVT ERT may be a safe and effective treatment for CLN2 retinopathy and more research is needed to optimise the dosage and frequency of treatment to achieve the best possible outcomes" [2].

Gene therapy is also being explored for treating vision loss in CLN2 disease. Robert is also investigating ways to deliver a functional copy of the TPP1 gene to the cells in the retina, where it could help preserve or even restore vision.

"We are seeing exciting results in the gene therapy trials. Not only does it seem that vision loss in these children stops, but it also seems to restore the ellipsoid outer segments. The interim results presented at ARVO conference in 2024 suggest a rapid restoration of TPP1 levels in the treated eye, and accompanying preservation of photoreceptors [3].

"Monitoring nuanced changes in the multiple layers of the retina over time is critical to these trials. I wanted to use a Spectralis because there is currently no other OCT that you can use in theatre that has the same level of accuracy in follow-up imaging over time, or range of high-resolution imaging modalities on one device. Discovering the Flex Module for Spectralis was a blessing as it allowed us to realistically open-up these clinical trials to children. I want to raise awareness of this device among the research community as treating children early in the disease process gives investigators a unique opportunity to generate better outcomes for the families."

References

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3. Ohnsman C, Bailey AM, Huang W, et al. RGX-381: Interim results from the first-in-human clinical trial of an investigational gene therapy for the treatment of ocular manifestations of CLN2 Batten disease. *Mol Genet Metab* 2024;**141(2)**:107987.

AUTHOR

Robert Henderson,
Consultant Ophthalmic Surgeon and Paediatric Ophthalmologist, Moorfields Eye Hospital and Great Ormond Street Hospital, UK.

Declaration of competing interests:
Robert Henderson was paid a speaker's fee for participating in a Heidelberg Masterclass in February 2023. Heidelberg have loaned the use of the Spectralis Flex device mentioned in this article.

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