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Atypical Batten Disease (CLN3); a case report and brief review of the literature

Kalogeropoulos D.[1], Khandhadia S. [1], Shawkat F.[1], Lotery A.J.[1,2]

[1] *Southampton Eye Unit, University Hospital Southampton, Southampton, United Kingdom*

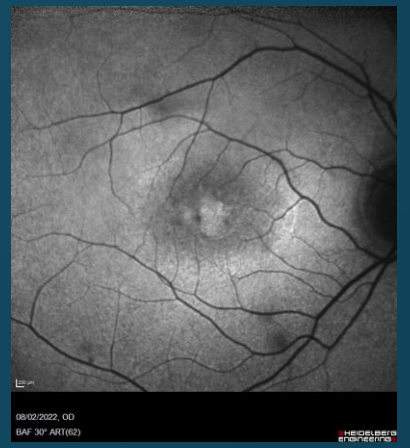
[2] *Faculty of Medicine, University of Southampton, Southampton, United Kingdom*

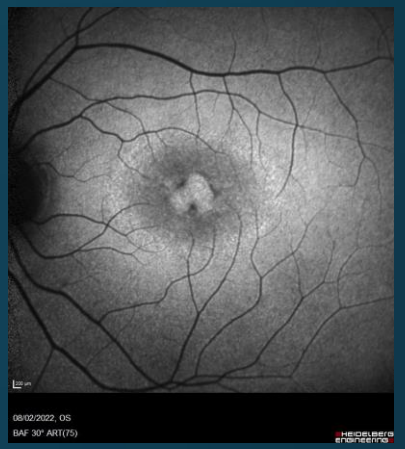
Neuronal ceroid lipofuscinoses (NCLs) are hereditary neurodegenerative disorders with a 1 in 100,000 live births prevalence, linked to 13 genes. Genetic testing is vital for diagnosis. CLN3 mutations cause juvenile NCL (JNCL), marked by childhood symptoms and premature death. A prevalent CLN3 mutation, a homozygous 1 kb deletion, constitutes 85% of JNCL cases. This case highlights CLN3 mutation's potential for an isolated retinal phenotype, suggesting consideration in atypical CMO diagnoses.

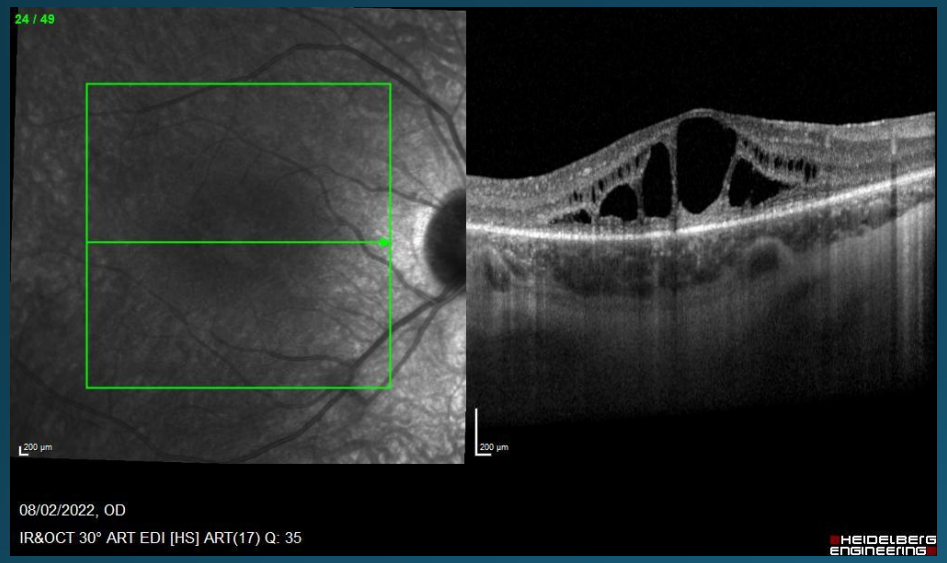
A 19-year-old white female was referred to our clinic for further evaluation and management of chronic cystoid macular oedema following an otherwise normal pregnancy a few months ago. Her vision had steadily been deteriorating from 6/18 to 6/60 in the right eye, and from 6/12 to 6/24 in the left eye. Various treatments including topical dexamethasone and ketorolac, oral acetazolamide, as well as orbital floor and intraocular steroids (in the form of a dexamethasone implant) were previously attempted with no beneficial effect. Moreover, fluorescein and indocyanine green angiography (performed prior to her referral) had shown only minor macular leakage.

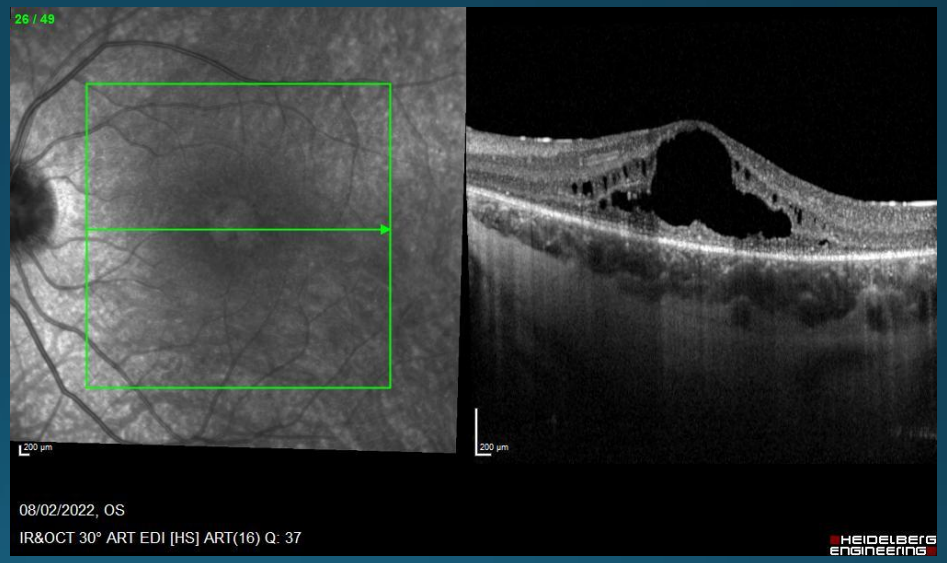
Her POH was otherwise unremarkable, while her PMH included hypothyroidism and mild asthma. The patient had undergone a comprehensive cardiovascular evaluation for symptoms of arrhythmia and atypical chest pain, with findings indicating no significant abnormalities. The patient's FMH revealed a predisposition to certain health conditions. Specifically, her aunt has been diagnosed with Fuchs' endothelial dystrophy, her maternal grandfather exhibited myotonic dystrophy and arrhythmias. The family has a notable prevalence of glaucoma and cataracts. The patient's maternal grandmother suffered from heart disease, although the precise nature of this condition remains unclear. Additionally, the patient reported that her elder brother, who is 28 years old, currently has a pacemaker in situ.

During her first assessment at our clinic her BCVA was 6/24 and 6/30 in the right and left eye, respectively. The IOP was 12mmHg in both eyes. Slit-lamp examination of the anterior segment was unremarkable. Dilated fundoscopy and ophthalmic imaging confirmed chronic cystoid macular oedema. Fundus AF revealed a bull's eye pattern of alternating hyper and hypofluorescence and increased central hyperfluorescence due to central cystoid changes. Due to the presence of these persistent macular findings, it was decided to proceed with HVF testing, EDTs and genetic testing.









HVF 24-2 revealed a rather symmetric bilateral ring scotoma. Rod and cone flash ERGs were all significantly degraded and attenuated with the cone responses being marginally better preserved than rod responses. Pattern ERGs were degraded (right eye more than left). Occipital pattern VEPs were normal to all but the smallest 10' checks were somehow degraded (right eye more than left). These results were consistent with marked retinal dysfunction involving both rod and cones, whereas the degraded pattern ERGs and small check VEPs suggest macular involvement.

Testing of genes associated with retinal dystrophy was carried out by next generation sequencing. Two heterozygous variants, a deletion of exon 7-8 and c.1213C>T p. (Arg405Trp), were identified in the CLN3 gene (OMIM*607042). Deletion of CLN3 exons has been reported frequently in the published literature, as a common pathogenic mechanism in patients with **Batten disease**. Functional studies showed that this deletion disrupts protein localisation. The presence of this pathogenic deletion has been confirmed using a custom droplet digital PCR assay.

Visual impairment, the primary symptom in over 80% of JNCL cases, typically emerges around age 5, revealing distinctive retinal characteristics. Diagnosis challenges arise from overlapping features with common retinal disorders. EDTs, particularly ERG, plays a crucial role, showing abnormalities as the disease progresses, affecting cone and rod responses. Cognitive and behavioural decline appears approximately 2 years after visual symptoms. Magnetic resonance imaging may reveal cerebral atrophy. Optical coherence tomography anomalies include outer retinal lamination loss, inner retina thinning, and heightened reflectivity linked to ERMs. Early JNCL identification is challenging, emphasizing the need for comprehensive evaluations, genetic screening, and specific tests, like peripheral blood film microscopy, electron microscopy, and molecular genetic screening of CLN3, with a predominant variation involving a 1 kb deletion.

The interesting perspective of our case is that our patient did not develop any neurological deficits. Today, approximately 5 years after her initial assessment she remains systemically and neurologically stable. Compared to other cases reported in the current literature, this is quite rare as the majority of these patients tend to manifest severe neurological features and have a rather short life expectancy.

Currently, no treatments are available for juvenile CLN_3 Batten disease or other types of NCL. Research focuses on therapeutic strategies addressing neurodegeneration, including enzyme replacement therapy, gene therapy, stem cell transplantation, and pharmacological approaches.

Conclusion

While the prompt identification of JNCL is frequently difficult due to the disease's rapid progression and unfavourable prognosis, early diagnosis is crucial. Apart from genetic confirmation, it appears that electrodiagnostic testing is also helpful in diagnosis. This case illustrates that CLN3 mutation can also produce an isolated retinal phenotype presenting with cystoid macular oedema and so CLN3 mutation should also be considered as a differential diagnosis in atypical cystoid macular oedema.

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