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A RARE CASE OF BATTEN DISEASE FROM A TERTIARY CARE CENTRE: DIAGNOSTIC AND MANAGEMENT CHALLENGES

Ophthalomology

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ABSTRACT

Background: Batten's Disease also known as Neuronal Ceroid Lipofuscinosis. Juvenile onset form, i.e. Juvenile Neuronal Ceroid Lipofuscinosis (JNCL) is most common neurodegenerative disease in childhood. **Case History:** We report a case of a 9 year young female who presented with complain of both eye Diminution of vision since 2 yrs. Patient complained of Night Blindness, loss of Peripheral vision and difficulty in identifying colours initially followed by which there was gradual and preogressive worsening of vision in both eyes. Patient also had rotatory nystagmus. She had history of seizure episodes. On clinical examination there was marked visual impairment with disc pallor and macular thinning on fundus examination. MRI was done which was suggestive of Cerebral and cerebellar Leukoencephalopathy. Genetic evaluation showed homozygous nonsense variation in Exon12 of CLN3 gene located on chromosome 16, confirming diagnosis of Batten's Disease a Neurodegenerative Disorder. **Conclusion:** This case of Batten's disease type 3 (CLN3) highlights the progressive nature of juvenile neuronal ceroid lipofuscinosis and underscores the diagnostic complexity associated with early neurodegenerative symptoms. The patient's gradual vision loss, cognitive decline, and motor dysfunction, combined with confirmatory genetic testing, emphasized the importance of multidisciplinary evaluation and early suspicion in paediatric neurodegenerative presentations. The rarity of CLN3 disease and its overlapping features with other conditions make timely diagnosis challenging. This report contributes to the limited body of literature on CLN3 and reinforces the need for increased clinical awareness, earlier genetic screening, and ongoing research into disease-modifying therapies. Clinicians should maintain a high index of suspicion when encountering similar symptom clusters, as early diagnosis can aid in family counseling, supportive care planning, and potential inclusion in clinical trials.

KEYWORDS

Batten's Disease, Neuronal Ceroid Lipofuscinosis, Neurodegenetaion, CLN gene mutation, vision loss.

INTRODUCTION:

Batten's disease, formally known as neuronal ceroid lipofuscinosis (NCL), represents a group of rare, inherited neurodegenerative disorders characterized by lysosomal accumulation of autofluorescent lipopigments such as ceroid and lipofuscin. These disorders result from mutations in at least 13 identified CLN genes, each encoding proteins involved in lysosomal function and intracellular trafficking. Among the various subtypes, the juvenile-onset form, also known as juvenile neuronal ceroid lipofuscinosis (JNCL), is the most prevalent and severe neurodegenerative condition of childhood.

JNCL is inherited in an autosomal recessive manner and is primarily caused by mutations in the CLN3 gene, located on chromosome 16p12.1. The most common mutation—a 1.02 kb deletion—results in a truncated form of the battenin protein, which retains partial function but ultimately leads to lysosomal dysfunction. This impairment causes progressive accumulation of autofluorescent ceroid material within neuronal lysosomes, leading to neurotoxicity and widespread neuronal degeneration.

Clinically, JNCL typically manifests between 4 and 8 years of age, with early symptoms including progressive vision loss due to retinal degeneration. As the disease advances, affected individuals experience cognitive decline, motor dysfunction, seizures, and eventual premature death. Despite its rarity, JNCL remains a critical diagnosis in paediatric neurology due to its progressive nature and lack of curative treatment.

This case report aims to contribute to the limited literature on JNCL by presenting a clinically and genetically confirmed case of CLN3 disease. It underscores the importance of early recognition of hallmark features and the role of genetic testing in guiding diagnosis and counseling, thereby enhancing clinical understanding and supporting timely interventions.

Case History:

A young 9 year old female presented to ophthalmology OPD at G.G.G. hospital, with complain of both eye gradual and progressive Diminution of vision since 2 yrs.

History Of Presenting Illness:

The patient began experiencing night blindness approximately two years ago, which her parents initially attributed to fear of the dark. Over time, she developed noticeable peripheral vision loss, leading to frequent bumping into objects, difficulty in navigating familiar surroundings, and challenges while reading or recognizing distant faces.

Additionally, the child reported difficulty in identifying and distinguishing colors. The visual symptoms were gradually progressive, with a marked decline in overall clarity of vision in both eyes. The patient developed involuntary eye movements described as rotatory nystagmus. Patient also had previous seizure episodes. Patient was a baby of a consanguineous parentage, with no other significant birth history like trauma or asphyxia. There was no other relevant past ocular history or family history.

At presentation, the patient's visual acuity was severely impaired. The right eye had perception of light (PL+), but projection of rays (PR) was inaccurate. The left eye could appreciate hand movements. Colour vision could not be assessed in either eye due to the poor level of visual acuity at time of presentation. Intraocular pressure, measured using non-contact tonometry, was 15 mmHg in the right eye and 16 mmHg in the left.

Anterior Segment Findings:

RIGHT EYE	ANTERIOR SEGMENT	LEFT EYE
NORMAL	LIDS	NORMAL
NORMAL	CONJUCTIVA	NORMAL
NORMAL	SCLERA	NORMAL
CLEAR	CORNEA	
++	ANTERIOR CHAMBER	++
NORMAL	IRIS	NORMAL
SLUGGISHLY REACTIVE TO LIGHT	PUPIL	SLUGGISHLY REACTIVE TO LIGHT
CLEAR	LENS	CLEAR
ROTATORY NYSTAGMUS	OCM/OCP	ROTATORY NYSTAGMUS

Dilated Fundus Examination: (Fig 1 & 2)

RIGHT EYE	FUNDUS	LEFT EYE
CLEAR	MEDIA	CLEAR
DISC PALLOR	DISC	DISC PALLOR
ARTERIOLAR ATTENUATION	BLOOD VESSELS	ARTERIOLAR ATTENUATION

MACULAR THINNING	MACULA	MACULAR THINNING
PERIPHERAL PIGMENTARY CHANGES	GENERAL FUNDUS	PERIPHERAL PIGMENTARY CHANGES

Figure 1: Right Eye

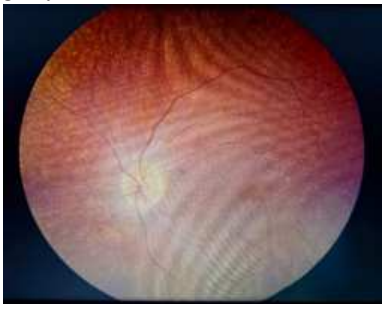

Figure 2: Left Eye

On systemic evaluation with central nervous system examination shows loss of language skills and speech. Radiological evaluation with MRI showed evidence of cerebral and cerebellar atrophy suggestive of Leukoencephalopathy.

Eletroretinogram showed evidence of Scotopic- shows flat a-wave and b-wave in left eye and very reduced amplitude in right eye, suggestive of lost cone responses. Photopic - both a-wave and b-wave shows reduced amplitude, suggestive of rods and intraretinal layers dysfunction. (figure 3 & 4).

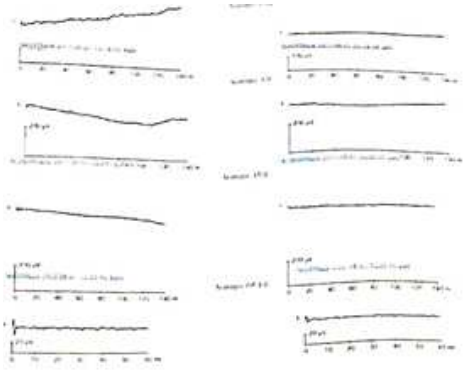

Figure: 3

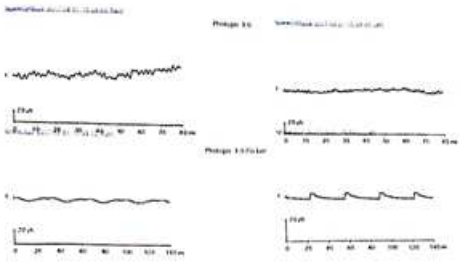

Figure: 4

Genetic Evaluation showed homozygous nonsense variation in Exon12 of CLN3 gene located on chromosome 16, confirming diagnosis of Batten's Disease a Neurodegenerative Disorder.

DISCUSSION:

Batten's disease, a subset of neuronal ceroid lipofuscinoses (NCLs), represents a group of rare, inherited neurodegenerative disorders that primarily affect children. Characterized by progressive vision loss, cognitive decline, seizures, and motor deterioration, Batten's disease leads to premature death, typically in the second decade of life.

Pathophysiology And Genetic Basis:

Batten's disease, formally known as neuronal ceroid lipofuscinosis (NCL), represents a group of rare, inherited neurodegenerative disorders characterized by lysosomal accumulation of autofluorescent lipopigments such as ceroid and lipofuscin. These disorders result from mutations in at least 13 identified CLN genes, each encoding proteins involved in lysosomal function and intracellular trafficking. These deficiencies result in the accumulation of auto fluorescent storage material within neurons and other cells, causing cellular dysfunction and neurodegeneration. The mode of inheritance is typically autosomal recessive, meaning both parents must be carriers of the defective gene. The most common form of Batten's disease is juvenile NCL (CLN3), caused by mutations in the CLN3 gene, which encodes a protein known as battenin. Other forms include CLN1 (infantile NCL), CLN2 (late infantile NCL), and CLN5, each associated with different genetic mutations and clinical presentations. Among the various subtypes, the juvenile-onset form, also known as juvenile neuronal ceroid lipofuscinosis (JNCL), is the most prevalent and severe neurodegenerative condition of childhood.

Clinical Presentation:

The clinical manifestations of Batten's disease vary depending on the specific subtype but generally include Vision loss, Often the first symptom, due to retinal degeneration. Seizures which typically begin in early childhood and may be refractory to treatment. Cognitive decline i.e. Progressive developmental regression leading to intellectual disability. Motor deterioration like Ataxia, spasticity, and loss of ambulation and Behavioural changes like Personality changes, irritability, and psychiatric symptoms. The onset of symptoms usually occurs between ages 4 to 8 years, with disease progression leading to premature death in the second decade of life.

Diagnostic Challenges:

Diagnosing Batten's disease can be challenging due to its rarity and the overlap of symptoms with other neurodegenerative disorders. Early stages may present with nonspecific symptoms, leading to delays in diagnosis. Key diagnostic tools are Genetic testing for Identification of mutations in genes associated with NCLs. Enzyme activity assays to measure specific lysosomal enzyme activities. Electroretinography (ERG) used to Assess retinal function. Brain imaging like Magnetic resonance imaging (MRI) to detect neurodegenerative changes. Early and accurate diagnosis is crucial for initiating appropriate management and providing genetic counseling to affected families.

Current Management Strategies:

Currently, there is no cure for Batten's disease, and treatment is primarily supportive. Management strategies aim to alleviate symptoms and improve quality of life:

- **Antiepileptic Drugs:** To control seizures.
- **Physical And Occupational Therapy:** To maintain mobility and independence.
- **Speech Therapy:** To address communication difficulties.
- **Nutritional Support:** To manage feeding difficulties and ensure adequate nutrition.

In 2017, the U.S. FDA approved cerliponase alfa (Brineura), the first enzyme replacement therapy (ERT) for CLN2 Batten disease. Cerliponase alfa is a recombinant form of the TPP1 enzyme, administered via intraventricular infusion, and has been shown to slow the decline in motor and language function in pediatric patients with CLN2 disease.

Recent Advancements in Treatment:

Recent research has focused on developing disease-modifying therapies for Batten's disease:

- **Gene Therapy:** Clinical trials are exploring the use of adeno-associated virus (AAV)-mediated gene delivery to restore functional gene expression in affected neurons. For example, a clinical trial for CLN5 Batten disease is underway at the University of Rochester Medical Centre, aiming to evaluate the safety and efficacy of gene therapy for this subtype.

- **Antisense oligonucleotides:** A customized antisense oligonucleotide, milasen, was developed for a single patient with a rare mutation in the CLN7 gene. This personalized approach represents a novel strategy in treating genetic disorders.
- **Extracellular vesicle-mediated delivery:** Research is investigating the use of extracellular vesicles as carriers for enzyme replacement therapy, aiming to improve the delivery of therapeutic enzymes to the central nervous system.

These advancements hold promise for altering the course of the disease and improving outcomes for affected individuals.

Importance Of Early Diagnosis And Multidisciplinary Care:
Early diagnosis is critical for initiating potential disease-modifying therapies and providing timely supportive care. Multidisciplinary care involving neurologists, ophthalmologists, geneticists, therapists, and palliative care specialists is essential in managing the complex needs of individuals with Batten's disease. Genetic counseling is also vital for families, especially in regions with high rates of consanguinity, to understand inheritance patterns and make informed reproductive decisions.

CONCLUSIONS:

This case of Batten's disease type 3 (CLN3) highlights the progressive nature of juvenile neuronal ceroid lipofuscinosis and underscores the diagnostic complexity associated with early neurodegenerative symptoms. The patient's gradual vision loss, cognitive decline, and motor dysfunction, combined with confirmatory genetic testing, emphasized the importance of multidisciplinary evaluation and early suspicion in paediatric neurodegenerative presentations. The rarity of CLN3 disease and its overlapping features with other conditions make timely diagnosis challenging. This report contributes to the limited body of literature on CLN3 and reinforces the need for increased clinical awareness, earlier genetic screening, and ongoing research into disease-modifying therapies.

Batten's disease remains a challenging condition with significant morbidity and mortality. However, recent advancements in genetic and enzyme-based therapies offer hope for altering the disease trajectory. Early diagnosis and a comprehensive, multidisciplinary approach to care are essential in improving the quality of life and outcomes for affected individuals. Clinicians should maintain a high index of suspicion when encountering similar symptom clusters, as early diagnosis can aid in family counseling, supportive care planning, and potential inclusion in clinical trials.

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