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A rare cause of variant late-infantile neuronal ceroid lipofuscinosis: CLN8-related disease

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Abstract

Neuronal Ceroid Lipofuscinosis (NCL) is a rare, inherited lysosomal storage disorder characterized by the accumulation of lipofuscin within neuronal cells, leading to progressive neurodegeneration. It is caused by pathogenic variants in at least 14 known genes, resulting in distinct clinical phenotypes. Neuronal ceroid lipofuscinosis presents with varying phenotypes depending on the age of onset and the underlying pathogenic gene variant. This case report highlights a 7-year-old boy with a variant form of late-infantile NCL, caused by a pathogenic variant in the CLN8 gene, who developed developmental regression, seizures, motor dysfunction, and vision loss. This case emphasizes the importance of early recognition, genetic testing, and MRI evaluation for timely diagnosis and management of NCL. It also underscores the need for interdisciplinary collaboration involving neurologists, geneticists, and radiologists in managing patients with neurodegenerative disorders like NCL. Early diagnosis can aid in genetic counseling, family planning, and potential intervention strategies.

INTRODUCTION

Neuronal Ceroid Lipofuscinosis (NCL) is characterized by the abnormal accumulation of lipofuscin pigment within neuronal cells. It is a rare lysosomal storage disorder caused by the toxic accumulation of metabolites within cells of brain, skin, skeletal muscles leading to neuronal damage. NCL is inherited in an autosomal recessive manner and is associated with pathogenic variant in 14 known genes, CLN1 to CLN14 which result in distinct disease phenotypes.[1]

The disease onset is usually in childhood. This disorder is classified into four groups based on the age of onset: congenital, infantile, late infantile, and juvenile forms. The clinical manifestations vary depending on the underlying pathogenic variant but commonly include cognitive decline, behavioral changes, vision loss, and epilepsy.[2] In this case report Magnetic resonance imaging (MRI) of the brain typically reveals cortical and cerebellar atrophy, which are hallmark findings in NCL. The definitive diagnosis is established through genetic testing.[3] This case underscores the importance of considering NCL in patients presenting with developmental regression, cognitive decline, and epilepsy. Early diagnosis is crucial for appropriate management and genetic counseling.

CASE REPORT

A 7-year-old boy, born to consanguineous parents, presented with progressive neurodevelopmental regression. Perinatal history was unremarkable, and early developmental milestones were achieved appropriately. At 4 years of age, he developed tremulousness of the lower limbs, gait instability, and frequent falls, followed by progressive loss of ambulation. Over the subsequent two years, he became bedridden with neck weakness, progressive visual impairment, and marked reduction in verbal output, eventually becoming mute. He developed generalized tonic–clonic seizures and frequent myoclonic jerks.

Family history

The pedigree revealed parental consanguinity. The proband was the only affected individual in the family. Both parents and two sisters were clinically unaffected. No other family members had similar neurological illness (Figure 1).

On physical examination, length, weight, and head circumference were normal for age.

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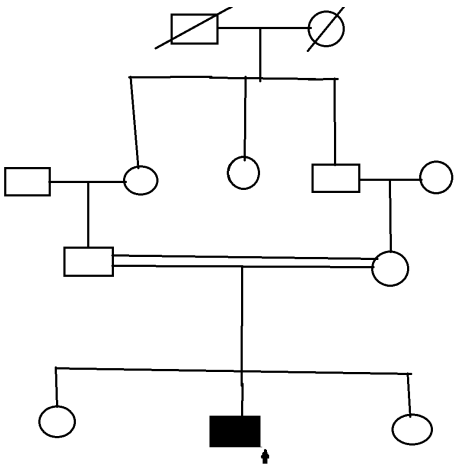

Figure 1. Pedigree of the family.

Neurological examination revealed impaired higher mental functions, increased tone in the lower limbs, brisk deep tendon reflexes, and bilateral extensor plantar responses. Both pupils were equally reactive to light, and fundoscopy is normal. Routine laboratory investigations, including renal and thyroid function tests, ammonia, and lactate levels, were normal. EEG demonstrated generalized epileptiform discharges.

His visual evoked potentials (VEP) for both eyes showed prolonged latency; while brainstem evoked response audiometry (BERA) was non-recordable in both ears. Magnetic resonance imaging (MRI) of the brain demonstrated bilateral periventricular T2 hyperintensities adjacent to the posterior horns of the lateral ventricles along with diffuse cerebral and cerebellar atrophy (Figure 2).

The patient, who was experiencing motor regression, vision loss, and seizures, was suspected to have NCL. Whole-exome sequencing identified a homozygous pathogenic missense variant in the *CLN8* gene (NM_018941.4:c.509C>T; p.(Thr170Met)) located in exon 2. This variant has been previously reported in association with variant late-infantile neuronal ceroid lipofuscinosis and was classified as pathogenic according to ACMG guidelines, based on prior reports, predicted deleterious effect, and phenotypic concordance.

DISCUSSION

NCL (Neuronal Ceroid Lipofuscinoses) diseases can be classified in various ways. They can be categorized based on genotype (CLN1 to CLN14), phenotype (congenital, infantile, late-infantile, and juvenile forms), or by the names of authors who described them, such as Haltia-Santavuori, Jansky-Bielschowsky, Batten, Spielmeyer-Vogt, and Kufs.[1]

CLN2 (Batten Disease) and CLN3 are the most common variants of NCL. Seizures, dementia,

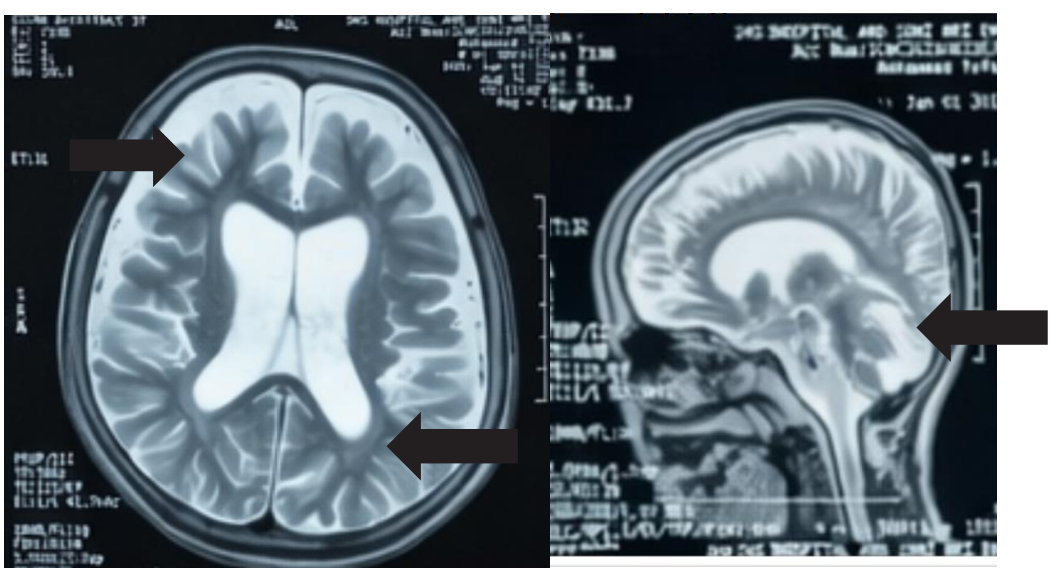

Figure 2. MRI Brain scan suggestive of hyperintensities adjacent to the bilateral posterior horns of the lateral ventricles on T2-weighted images and extensive cerebral and cerebellar degeneration.

and visual loss form a common triad observed in most types. Our patient exhibits these symptoms and has been identified as having the CLN8 type. The presentation of our case, occurring between the ages of 2 and 5, fits into the category of late-infantile NCL. The associated genes for this category include CLN1, CLN5, CLN6, CLN7, and CLN8.[5] There is two categories in late-infantile NCL: classical and variant. They both share common features, such as seizures and visual loss, but ataxia is found in the classical type, whereas motor and cognitive regression are predominant in the variant type.[5] The prevalence of NCL is 1 in 100,000 to 1 in 1,000,000 live births worldwide.[6] Our case highlights the importance of early recognition and diagnosis, particularly because the variant late-infantile form of this disease exhibits variability in its presentation. Several studies have focused on NCL8 cases. To place the clinical and molecular features of the present case in context, a comparative summary of previously reported variant late-infantile neuronal ceroid lipofuscinosis cases, including CLN7 and CLN8 subtypes, is presented in Table 1. Imaging studies, particularly MRI, play a pivotal role in early recognition. Studies conducted on patients with the NCL8 genotype consistently demonstrate that cerebellar atrophy is a common MRI finding observed across all reported cases.[7] These findings underscore the importance of early MRI evaluation and genetic testing in patients with suspected NCL. Early identification can facilitate timely intervention and improve management strategies for affected individuals.

The variability in clinical presentation

Table 1: Comparative clinical, neuroimaging, and molecular features of reported late-infantile neuronal ceroid lipofuscinosis cases (CLN7 and CLN8)

Feature	Our case (7-year-old boy)	Kentab *et al.* (2017) (Three Palestinian siblings)[6]	Alkhars *et al*. (2020) (Saudi Arabian case)[7]
Age at onset	4 years	3–5 years	4 years
Initial symptoms	Tremulousness, difficulty walking, wide-based gait, regression in motor and neurological functions	Developmental regression, seizures, visual impairment	Developmental delay, seizures, cognitive decline
Progression	Became bedridden, lost ability to walk and speak, generalized tonic-clonic seizures (GTCS), myoclonic jerks	Progressive motor and cognitive decline, blindness, epilepsy	Severe cognitive impairment, seizures, motor regression
Seizure type	GTCS, myoclonic jerks, oromandibular involvement	Myoclonic and tonic-clonic seizures	Refractory seizures
Vision loss	Present	Present	Present
Neurological findings	Increased lower limb tone, weak neck muscles, bilateral brisk reflexes, normal fundus	Hyperreflexia, spasticity, optic atrophy	Hyperreflexia, cerebellar atrophy
Genetic mutation	CLN8 gene (ENST00000311232.6), c.509C>T (p.Thr170Met), homozygous	MFSD8 gene (CLN7), variant late-infantile NCL	CLN8 gene mutation, novel variant
Mode of inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive
MRI findings	Cortical and cerebellar atrophy, periventricular signal changes	Cortical atrophy, cerebellar atrophy	Thinning of corpus callosum, cerebellar atrophy
EEG findings	Epileptic encephalopathy	Generalized epileptiform discharges	Background slowing, multifocal epileptiform activity

and progression of NCL poses challenges in timely diagnosis. Currently, there is no disease-modifying therapy for CLN8-related late-infantile neuronal ceroid lipofuscinosis. Management is primarily supportive and includes seizure control, treatment of spasticity, physiotherapy, nutritional support, and visual rehabilitation. Enzyme replacement therapy is available for CLN2 disease but is not applicable to CLN8-related NCL. Emerging therapeutic strategies, including gene therapy and substrate reduction therapy, are under investigation for various forms of NCL. Genetic counseling is essential, particularly in consanguineous families, and screening of at-risk relatives is recommended to enable early diagnosis and informed reproductive planning. If a pathogenic variant has been identified in a family, prenatal testing through chorionic villus sampling (CVS) or amniocentesis can provide early detection in subsequent pregnancies.

This case underscores the importance of maintaining a high index of suspicion for neuronal ceroid lipofuscinosis in children with progressive neurodegeneration, as early neuroimaging and molecular diagnosis not only facilitate appropriate supportive management but also enable timely genetic counseling and informed reproductive decision-making.

In conclusion, this case highlights the importance of early recognition and diagnosis of Neuronal Ceroid Lipofuscinosis (NCL), specifically the variant late-infantile form caused by the CLN8 gene variant. The patient's progressive motor and cognitive regression, vision loss, and seizures, along with characteristic MRI findings and genetic confirmation, underscore the need for timely genetic testing and imaging to ensure accurate diagnosis. Early identification facilitates genetic counseling, family planning, and better management, while an interdisciplinary approach involving neurologists, geneticists, and radiologists is crucial for optimizing care. This case emphasizes the value of early intervention in managing NCL and improving patient outcomes, despite the lack of a definitive cure.

DISCLOSURE

Conflict of interest: None

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