




# NCL Disorders: Common Causes of Dementia in Children: A Case Report

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## Abstract

### Background

Dementia in children is a rare case, which results in general neurocognitive decline that is chronic and progressive in the form of loss of skills after a period of normal development. Similar to adult neurodegenerative disorders, childhood dementia also exhibits cognitive deterioration, behavioural abnormalities, and altered sleeping and feeding patterns. There were also seizures, motor problems, visual disturbances, and cognitive impairments. Dementia in children is often caused by Neuronal Ceroid Lipofuscinoses (NCL). NCL is a group of lysosomal storage disorders linked by accumulating a characteristic storage material in neurons and other cell types and progressive clinical deterioration, usually combined with visual loss, epilepsy, and motor impairment. NCL disorders result from mutations in 14 different ceroid lipofuscinosis neuronal (CLN) genes (CLN1–CLN14). Due to the large variety of NCL-causing genes and significant genotype phenotypic variability, diagnosing an NCL is difficult. However, a precise diagnosis of an NCL disease can be made in a time- and cost-effective manner using very few diagnostic steps [1], [2].

### Case Report

A 7-year-old girl with primary complaints of seizures came to the hospital with her mother. So far, she has a history of seizures at the age of 4 years. In the last two years, there have been many developmental declines. Previously, the patient could speak fluently, but now the patient can only remember the word "mother". Impaired vision and difficulty walking are also experienced.

### Conclusion

Childhood dementia has symptoms that involve cognitive impairment, motor disturbances, visual disturbances, and seizures. Dementia in children can cause a lot of worry, anxiety, and difficulties during therapy due to its complicated symptoms. It is essential to take a collective approach to childhood dementia that can influence the prognosis and efficacy of therapy. Based on the condition of the patient who experiences several symptoms such as seizures, mood changes, body movement disorders or ataxia, communication disorders, and visual disturbances. The patient's condition aligns with the theory that explains the symptoms of NCL, especially CLN2.

**Keywords:** dementia, children, childhood, neuronal ceroid lipofuscinoses (NCL)

## Introduction

Unexpected loss of cognitive abilities (dementia) in young patients presents a diagnostic challenge. It is most commonly caused by neuronal ceroid lipofuscinoses (NCL), linked by the accumulation of characteristic storage materials in neurons and other cell types, and progressive clinical deterioration, usually combined with visual loss, epilepsy, and motor impairment. Diagnosis of NCL is difficult because of the many genes that cause NCL: different NCL causative genes and significant genotype-phenotype variability. The diagnosis is made by electron microscopy of skin biopsies, enzyme tests for some types of NCL, and genetic testing, especially using next-generation sequencing (NGS) techniques. However, disease-specific diagnosis of NCL can be performed in a time- and cost-effective manner using only a few diagnostic steps. Dementia in childhood is defined as global neurocognitive decline with the loss of some developmental skills after a period of normal development. A hallmark of childhood dementia is the persistence and progressive loss of previously acquired developmental skills, as opposed to static or transient losses, for example, in cases of head injury, encephalitis, or near drowning [3] – [6].

Childhood dementia is a heterogeneous group of neurodegenerative conditions characterized by neurocognitive impairment. This decline is associated with a progressive loss of functional skills and abilities and shorter life expectancy in infants, children, and adolescents. Furthermore, childhood dementia can be differentiated from conditions such as intellectual disability or developmental delay, characterized by a loss of trajectory relative to normal development. Childhood dementia has not received much recognition or attention in the medical and scientific literature, largely because the individual conditions that comprise the childhood dementia group are most often considered separate conditions and not part of a wider scope of the disease [3], [4], [6].

## Causes of dementia in childhood

The aetiology and pathogenesis of childhood dementia are extensive and, in some cases, still undefined. This research focuses on identified childhood dementia disorders of genetic origin, most of which are caused by inherited metabolic errors, also known as inherited metabolic disorders. Most inherited metabolic disorders are enzyme defects in biochemical and metabolic pathways that affect the essential metabolism of cellular proteins, fats or carbohydrates, or organelle function disturbances [7].

Rare genetic neurodegenerative conditions such as Rett syndrome and Juvenile Huntington's disease comprise the remainder of the childhood dementia cluster. Huntington's disease is an inherited neurodegenerative proteinopathy caused by the expansion of the N-terminal polyglutamine tract in huntingtin, which can then lead to dementia. The cognitive impairment seen early in Huntington's disease tends to be mild, characterized by forgetfulness and difficulty concentrating. Over time, more severe memory decline, learning difficulties, slowed information processing, executive dysfunction, reduced language skills, and apraxia may become evident. The focus on disorders of genetic origin excludes acquired disorders, such as encephalopathies arising from infectious, viral or toxic etiologies, those associated with nutritional deficiencies and those associated with autoimmune or endocrine disorders. However, hereditary dementia constitutes a substantive burden of childhood dementia in Australia and other developed countries [3], [4], [6], [8].

The main classifications of childhood dementia include [3], [4]:

- Lysosomal disease, including mucopolysaccharides, disorders of lipid metabolism and transport, neuronal steroidal glycoproteins and lipofuscin
- Other disorders of lipid metabolism and transport
- Disturbances in the metabolism of amino acids and other organic acids
- Innate metabolic error responsive to vitamins
- Impaired absorption and transport of minerals
- Peroxisomal disease
- Mitochondrial disorders
- Leukodystrophy

- Nervous degeneration with accumulation of iron in the brain
- Other rare neurodegenerative diseases

### **Diagnosis, morbidity and mortality**

Pathways to diagnosing these conditions vary from disease to disease and usually involve a combination of early clinical symptom assessment, brain imaging, detection of biochemical markers in urine and blood, and genetic testing. Given the non-specific initial symptoms, the rarity of the individual disease and the general lack of awareness within the medical community, the diagnosis of dementia disorders in children is often delayed, sometimes for years after the first symptoms appear. Generally, children are misdiagnosed with autism, developmental or intellectual delay, attention deficit hyperactivity disorder (ADHD) and others before reaching a definitive diagnosis [3], [4].

Screening newborns for these conditions is limited, partly justified by the lack of therapeutic interventions for most disorders. Symptoms of dementia in children vary widely with clinical and phenotypic heterogeneity. However, dementia in childhood has many features in common with dementia that occurs in adults, including [3], [4], [8]:

- Decreased cognitive abilities
- Problems with attention and concentration
- Memory loss and learning difficulties
- Problems with thinking and reasoning
- Confusion and disorientation
- Uncooperative and disruptive behaviour
- Wandering and restless
- Emotional disturbances (anxiety, fear, panic attacks)
- Changes in personality and behaviour (aggression, irritability, hyperactivity)
- Sleep disturbance (often severe)
- Deterioration of social skills and socially appropriate behaviour
- Psychotic symptoms and hallucinations
- Losing the ability to speak
- Incontinence

In contrast to most dementias that occur in adults, and in addition to cognitive, neuropsychological and behavioural manifestations, dementia disorders in childhood are commonly associated with seizures, sensory (vision and hearing) impairment, movement disorders including ataxia, spasticity, and dyskinesia, dystonia, gait disturbances, muscle weakness, abnormal muscle tone, and progressive neuromotor impairment [3], [4].

Several childhood dementia disorders also involve other organs and physiological systems besides the central nervous system, including peripheral nerve disease, visceromegaly (enlargement of the abdominal organs), liver disease, growth retardation, gastrointestinal disease, bone and joint disorders, and cardiac involvement. Timelines of disease onset and development vary among childhood dementia disorders, with some appearing in infancy, progressing rapidly and causing death in the first year of life. For other disorders, initial symptoms may not appear until childhood and develop slowly, with survival usually into adolescence or early adulthood. Causes of death in childhood dementia disorders are usually due to respiratory complications in late-stage disease (such as pneumonia), neurological complications (e.g., incurable epilepsy), or cardiac events [3], [4], [7].

### **The Burden of Dementia in Childhood**

As a result of their unique and highly complex health needs, individuals with childhood dementia usually rely heavily on health care and support services, in addition to the extensive care provided by family members and other caregivers [8].

### New nomenclature for NCL Disorder

Traditionally, NCL disease is classified according to age at onset into congenital, infantile, late infantile, juvenile, and adult forms. It has recently become clear that NCL is much more heterogeneous than previously thought and that mutations in the same gene can lead to different clinical courses. Traditional nomenclature designations have become obsolete and have recently been replaced by internationally developed ones with a combined genetic and clinical classification of NCL [9].

Table 1. Genetic and Clinical Classification of NCL [9]

Disease	MIM Number	Gene Designation
CLN1 disease, infantile CLN1 disease, late-infantile CLN1 disease, juvenile CLN1 disease, adult	256730	CLN1 (PPT1)
CLN2 disease, late-infantile CLN2 disease, juvenile	204500	CLN2 (TPP1)
CLN3 disease, juvenile	204200	CLN3
CLN4 disease, adult (autosomal dominant)	162350	CLN4 (DNAJC5)
CLN5 disease, late-infantile CLN5 disease, juvenile CLN5 disease, adult	256731	CLN5
CLN6 disease, late-infantile CLN6 disease, adult (Kufs type A)	601780	CLN6
CLN7 disease, infantile	610951	CLN7 (MFSD8)
CLN8 disease, late-infantile CLN8 disease, EPMR	600143	CLN8
CLN10 disease, congenital CLN10 disease, late-infantile CLN10 disease, juvenile CLN10 disease, adult	610127	CLN10 (CTSD)
CLN11 disease, adult	138945	CLN11 (GRN)
CLN12 disease, juvenile	(9)	CLN12 (ATP13A2)
CLN13 disease, adult (Kufs type B)	(8)	CLN13 (CTSF)
CLN14 disease, infantile	(11)	CLN14 (KCTD7)

### Clinical spectrum of NCL disease

In almost all forms of NCL, patients initially present in good health and have normal development. Cardinal clinical manifestations include developmental regression, motor disturbances, myoclonic epilepsy, progressive visual loss, behavioural disturbances,

and progressive cognitive decline resulting in dementia. The age at onset of the disease can range from birth to young adulthood. The order in which the symptoms occur varies. In young children, the first symptom is the arrest and retardation of psychomotor development, or incurable epilepsy. In school children, the first symptom is mostly loss of vision, followed by dementia. The different course of the disease is described below [3], [4], [8], [10].

### **Congenital disease onset**

This is the only form of NCL in which the patient is so severely affected at birth. Intrauterine or immediate postnatal epileptic seizures, as well as congenital congenital microcephaly, should lead to the suspected diagnosis. Confirmation is based on demonstrating cathepsin D and mutations in the CLN 10 gene. Disease The disease causes death in early infancy [3], [4], [8], [10].

### **Infantile disease onset**

The first symptom is developmental arrest and subsequent regression of psychomotor development at 10-18 months of age. This is followed by muscle hypotonia, which may turn into seizures later in life, and myoclonus and epilepsy. Fulminant brain atrophy causes progressive microcephaly. The electroencephalogram (EEG) becomes flat. Visual contact is lost due to retinopathy. Diagnosis depends on demonstrating lysosomal enzyme (PPT1) defects and CLN1 mutations. Death occurred in early childhood [3], [4], [8], [10].

### **Late infantile disease onset**

Several gene defects and enzyme deficiencies may be the cause in this age group. The first symptoms, such as muscle hypotonia, ataxia and developmental regression, occur at 2-3 years old. At the same age, therapy-resistant epileptic seizures are common. EEG may show posterior spikes under slow photic stimulation in some forms of NCL (CLN2, CLN5, CLN6), while cerebral and cerebellum atrophy is seen by magnetic resonance imaging of the brain. Vision loss is often diagnosed late due to severe neurological deficits in the patient and has become an additional problem that increases seizures and non-epileptic myoclonus. Most of the patients live to be 10-15 years old. [3], [4], [8], [10]

### **Juvenile disease onset**

Juvenile disease usually begins with visual failure due to retinal degeneration at an early school age (5-7 years). Initial eye examination findings were a blackout electroretinogram and pigmented retinopathy with thinning of blood vessels. Most of the patients in this group had the underlying CLN3 mutation and vacuolized lymphocytes in their peripheral blood. Spasticity and myoclonus are rare but may develop late during the disease. During puberty, psychogenic syndromes may occur with panic attacks, fear, and hallucinations or with depression or aggressive mood swings. These disorders are a particular challenge for psychiatric management. Older patients may suffer from cold and pale extremities due to sinus bradycardia or other circulatory disorders. Improved palliative management (e.g., IV feeding for difficulty swallowing) has increased life expectancy to 30 years or more [3], [4], [8], [10].

### **Adult disease onset**

Disease onset in adults The age at onset of the disease in the adult form of NCL is broad, with a median of about 39 years. The first symptoms vary. Clinically, type A (early progressive myoclonus epilepsy, dementia, and ataxia) and type B (early behavioural abnormalities and motor problems) have been differentiated, both without visual problems. Identification of affected genes, as well as the number of cases diagnosed, are currently increasing [3], [4], [8], [10].

Table 2. NLC of Childhood Onset and Major Symptoms<sup>11</sup>

Clinical Form	Age of Onset	Diseases	Major Symptoms at onset
Congenital	Birth	CLN10	Microcephaly, dysmorphic features, seizures, hyperkinetic movements
Infantile	6-18 months	CLN1	Decreased head growth, neuro-developmental regression, seizures
		CLN10	Decreased head growth, neuro-developmental regression
		CLN14	Decreased head growth, seizures (myoclonus)
Late Infantile			
Classical	2-4 years	CLN2	Seizures, ataxia, visual loss, delayed language development;
Variant	2-5 years	CLN1	Seizures, neuro-developmental regression, behavioural disturbances;
		CLN 5	Impaired learning and cognition; <sup>[11]</sup>
		CLN6	Seizures, ataxia, delayed language development;
		CLN7	Seizures, visual loss, motor and cognitive regression;
		CLN8	Seizures, visual loss, motor and cognitive regression;
Juvenile			
Classical	3-5 years	CLN3	Visual loss, behavioural problems, cognitive decline
	5-7 years	CLN1	Motor and cognitive regression, behavioural problems, Visual loss, cognitive decline;
Late	8-12 years	CLN6	Myoclonic seizures, cognitive decline; ataxia, cognitive decline, visual loss;
		CLN10	Myoclonic seizures, cognitive decline; ataxia, cognitive decline, visual loss;
	13-16 years	CLN12	Rigidity, hypokinesia

### Specific aspects of palliative therapy in NCL

Palliative management of patients with NCL disease is a significant challenge due to several clinical problems, some disease-specific. In addition, recognizing some complications is difficult because most patients can no longer communicate verbally in

the late stages of their disease. Overt episodes of pain warrant a thorough clinical examination. Abdominal pain may be caused by constipation due to intestinal hypomotility related to disease or inadequate nutrition. However, many other causes must be considered, such as unrecognized fractures or kidney stones, which are frequent consequences of immobility. Collaboration with other clinicians with experience in clinical NCL issues can help improve palliative care based on the author's experience, providing an overview of palliative treatment to treat the most common symptoms of NCL.<sup>12</sup>

## Epilepsy

Seizures in NCL are primarily resistant to treatment. Some commonly used antiepileptic drugs may have unusual effects on patients whose brains are undergoing a degenerative process<sup>3,4</sup>

- 1) Absence of seizures or normalization of the electroencephalogram is not a realistic goal in NCL patients.
- 2) EEG on NCL functions mainly for monitoring. Therapy must be adjusted according to clinical symptoms.
- 3) Treatment with more than two antiepileptic drugs may cause side effects rather than reduce seizures.
- 4) Some antiepileptic drugs are recommended in NCL patients (valproate and lamotrigine); others may harm the course of the disease and should be avoided (carbamazepine, phenytoin, vigabatrin).
- 5) Use as much medicine as necessary and as little as possible.

## Myoclonus

Myoclonus is a problematic symptom to treat. However, patients are often less bothered by jerking myoclonus. Levetiracetam, zonisamide and piracetam are effective treatments. Benzodiazepines should be avoided. Some antiepileptic drugs can exacerbate myoclonus. Therefore, reducing the number of different drugs can improve myoclonus [3], [4].

## Spasticity

Painful spasticity is another symptom to treat. Substances such as baclofen are effective. Tetrahydrocannabinol can be used as an adjunctive drug. Benzodiazepines and tetrazepam appear less effective (less potency, adverse effect on disease course, increased mucus secretion). Physical therapy and finding the trigger underlying the seizure crisis should always be considered [3], [4].

## Other problems

Diagnosis and treatment of torture with psychopathological symptoms such as sleep disturbances, fears, aggressive behaviour, depression and hallucinations is challenging. Psychopharmacological treatment should be administered in collaboration with pediatric neurologists and child psychiatrists, parents and caregivers. Only in this way can drug side effects and undetected causes for fear and anxiety be identified in time [3], [4].

## Case Report

A 7-year-old girl was brought by her parents to the hospital with complaints of seizures. When he arrived at the Emergency Room Installation, the seizures had stopped, and the patient was treated to treat the seizures. According to the patient's mother, at home, the patient had two seizures, with both feet and hands stomping; the seizure duration was approximately 5 minutes. Previously, the patient also had a history of seizures at the age of 4 years. So far, no one has received medication for seizures. The patient's mother said that before the seizure, there was no fever or headache. The seizure occurred suddenly when the os just woke up. Previously, the patient played as usual; it is just that in recent years, according to the patient's mother, the patient has experienced a decline in development. At first, the patient forgot more often; for example, the patient

forgot where the room was, forgot where the bathroom was, and the os often looked confused. The patient also experienced emotional changes; he became angry more often, cried more quickly, and became cowardly. When she was four years old, the patient often fell while walking, making it difficult for her to walk. After showing symptoms of decreased function, she had a seizure for the first time, lasting more than 5 minutes. Since birth, there have been no problems with the process of growth and development. In the past six months, os has only been able to say "mother" until now; previously, os was able to speak fluently. According to the os mother, aged 1 -2 years, sensorimotor development was good; at seven months old, the patient could sit and walk at 12 months, and at the age of 2 years, os is already fluent in speaking.

The patient's weight also decreased because of her lack of appetite. So far, he has never been taken for treatment by his parents because his parents think that what is happening to her is caused by spirits. Apart from her parents, her neighbours also thought the same thing. Because in the patient's area, children born preterm will be more often disturbed by spirits. According to the patient's mother, the patient was born with a gestational age of less than eight months. So, the patient is often taken to a shaman and given medicine in the form of water to drink and take a bath.

In the past month, the patient complained that both of his eyes were blurry; when the mother examined the patient's eyes, the patient's eyes were not red or watery, no eye discharge was found, and the os denied eye pain. Starting from birth, he has no history of trauma. Breastfeeding until one year old, the patient was born with a body weight of 2.5 kg and an incomplete immunisation history. The patient's mother said that on the advice of the nurse in primary healthcare, she was taken to the hospital because she had a seizure.

## Discussion

Neuronal ceroid lipofuscinoses (NCL) are typically autosomal recessive, neurodegenerative paediatric disorders and represent the most common cause of childhood dementia. Common symptoms occur over different time courses according to subtype and onset of dementia, before death during childhood or adolescence. In most cases, cognitive decline, ataxia, amaurosis, and early seizures are the clinical manifestations at onset. They become evident sequentially over a short time frame (6–24 months) in infantile and late-infantile NCLs; spasticity follows, leading to loss of motor function and dependence on carers for all activities of daily living within 5–8 years of symptom onset [11].

In this case, the patient, seven years old, came with a complaint of seizure. Previously, the patient had experienced a seizure at the age of 4 years. Based on the theory previously described, this case can be categorized as a late infantile clinical case because the patient experienced his first complaint at the age of 4 years. In this patient, none of the patient's relatives had similar complaints, so it could not be proven that the patient's condition was an autosomal recessive genetic disorder.

In recent years, the patient has experienced a decline in development. The patient quickly forgot things; she always looked confused and also experienced emotional changes. The patient also often fell while walking, making it difficult for her to walk. These changes occurred when the patient was four years old, before the first seizure. The first seizure occurred a few months later. Seizure is the most common symptom of NCL. Generalized motor seizures, absences, and myoclonus (including negative myoclonus), starting 2 to 6 months after the earliest clinical manifestations, are the main seizure types observed in classical CLN2 disease. Another symptom in this patient is loss of the ability to speak. Previously, the patient was said to have been able to speak fluently since the age of 2 years, but for the last six months, the patient could only say the word "mama". The patient also complained that her eyes were blurry in the past month. Based on the patient's condition, who experiences symptoms such as seizures, mood changes, body movement disorders or ataxia, communication disorders, and visual disturbances, the patient was diagnosed with NCL. The patient's condition in this case is in line with the theory that explains the symptoms of NCL, especially CLN2 [11], [13].

Early diagnosis is crucial; however, due to rarity and non-specific presenting



symptoms, diagnostic delays are frequent and may be linked to a rapid disease progression. Early assessment features include cerebellar atrophy on magnetic resonance imaging (MRI) and electroencephalography (EEG) abnormalities. No specific treatment is available to cure or slow the progression of the disease. Treatment is done to manage symptoms and make children feel more at ease. Seizures in this patient can be controlled with anti-seizure drugs, and other medical problems can be treated as needed [14], [15].

## Conclusion

Childhood dementia has symptoms that involve cognitive impairment, motor disturbances, visual disturbances, and seizures. Dementia in children can cause a lot of worry, anxiety, and difficulties during therapy due to its complicated symptoms. It is essential to take a collective approach to childhood dementia that can influence the prognosis and efficacy of therapy. Based on the condition of the patient who experiences several symptoms such as seizures, mood changes, body movement disorders or ataxia, communication disorders, and visual disturbances. The patient's condition aligns with the theory that explains the symptoms of NCL, especially CLN2.

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