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NCL diseases — clinical perspectives☆

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Abstract

The neuronal ceroid lipofuscinoses (NCLs) are lysosomal storage disorders and together are the most common degenerative brain diseases in childhood. They are a group of disorders linked by the characteristic accumulation of abnormal storage material in neurons and other cell types, and a degenerative disease course. All NCLs are characterized by a combination of dementia, epilepsy, and motor decline. For most childhood NCLs, a progressive visual failure is also a core feature. The characteristics of these symptoms can vary and the age at disease onset ranges from birth to young adulthood. Genetic heterogeneity, with fourteen identified NCL genes and wide phenotypic variability render diagnosis difficult. A new NCL classification system based on the affected gene and the age at disease onset allows a precise and practical delineation of an individual patient's NCL type. A diagnostic algorithm to identify each NCL form is presented here. Precise NCL diagnosis is essential not only for genetic counseling, but also for the optimal delivery of care and information sharing with the family and other caregivers. These aspects are challenging because there are also potential long term complications which are specific to NCL type. Therefore care supported by a specifically experienced team of clinicians is recommended. As the underlying pathophysiological mechanism is still unclear for all NCL forms, the development of curative therapies remains difficult. This article is part of a Special Issue entitled: The neuronal ceroid lipofuscinoses or Batten Disease.

Keywords

Batten; Ceroid; NCLs; Disease classification; Diagnostic algorithm

1. Introduction and definition

Diagnosis of childhood dementia represents a huge challenge. The neuronal ceroid lipofuscinoses (NCLs) are the most common cause of dementia in children. They are a

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group of diverse disorders linked by the characteristic accumulation of abnormal storage material in neurons and other cell types, and a degenerative disease course. They form a heterogeneous group of incurable lysosomal storage diseases which lead to dementia, epilepsy, blindness (usually) and motor deterioration [1,2]. The number of different NCL causing genes is high with significant variability within and across forms.

The authors of this article, clinicians with particular interest and experience of the NCLs, want to show that it is possible to diagnose NCL disease in an economical manner and give hints for the management of disease-specific problems.

2. New nomenclature of NCL diseases

Traditionally, NCL diseases were classified according to the age at disease onset (congenital, infantile, late infantile, juvenile, adult) and sometimes also according to the respective authors (Haltia-Santavuori, Jansky-Bielschowsky, Batten, Spielmeyer-Vogt, Kufs) [2].

NCL diseases are however much more genetically heterogeneous than initially thought. Mutations in the same gene may also lead to very different disease courses [3,4]. Other designations such as “Finnish” or “Turkish” NCL variant are outdated, as mutations in the respective genes in fact occur worldwide [5]. Therefore, the hitherto existing nomenclature is obsolete.

An internationally developed new NCL nomenclature clearly identifies each NCL disease both genetically and clinically (Table 1) [2,6]: it classifies both the defective gene as well as the age at disease onset (congenital, infantile, late infantile, juvenile or adult). An exact diagnosis is essential for genetic counseling, sharing information regarding prognosis and future disease course, and for optimal symptom care.

3. The genetic spectrum of NCL diseases

To date, fourteen different NCL forms have been described (Table 1) [3,7–13]. More NCL genes remain to be identified as in some patients mutations cannot be demonstrated in any of the known NCL genes although they present with the typical NCL symptoms and characteristic lysosomal storage material.

Intracellular localisation and function (where known) of the defective NCL proteins are different: four NCL types are caused by defects in lysosomal enzymes (CLN1, CLN2, CLN10, CLN13), others by defects in transmembrane proteins (CLN3, CLN6, CLN7, CLN8) [7]. Mutations in an ATPase gene (CLN12) [10] and a potassium channel gene (CLN14) [12] also cause NCL disease. The recently identified *CLN4* gene (*DNAJC5*) codes for a protein with putative function in synapses [8]. How these genetic defects lead to neurodegeneration is still not understood.

Clinically, the different NCL diseases have much in common despite their heterogeneity. This is important both for diagnosis and (palliative) treatment. To date, there is no disease-modifying or curative treatment for any of the NCLs.

4. The clinical spectrum of NCL diseases

In almost all NCL forms the patients are initially healthy and have a normal developmental profile. The main alerting symptoms are the combination of two or more of dementia, visual loss, epilepsy, and motor deterioration. The age at disease onset can range from birth to adulthood. The order in which symptoms occur is variable and depends both on age at onset and on genetic form. In a young child, first symptoms are developmental slowing followed by standstill, then later regression of psychomotor development, or epilepsy. In a school child, first symptoms are usually visual loss and behavior change, followed by dementia [2]. The different disease courses are described as follows [2]:

4.1. Congenital onset NCL

Congenital CLN10 disease is the only NCL form where patients are already severely affected at birth. Intrauterine or immediate postnatal onset of epileptic seizures as well as congenital microcephaly should lead to the suspected diagnosis. The disease leads to death in early infancy. It is associated with the deficiency of the lysosomal enzyme cathepsin D. Confirmation of the diagnosis is based on demonstration of the enzymatic deficiency and a mutation in the *CLN10* gene [14].

4.2. Infantile onset NCL

4.2.1. CLN1 disease—In patients with this NCL form [15], early development appears normal until 6–18 months of age. At onset, there is typically decreased tone and decreased social interaction followed by rapidly progressive psychomotor regression, myoclonus, seizures, and visual failure. By 2 years of age, there is blindness with optic atrophy and macular and retinal changes but no pigment aggregation. Fulminant brain atrophy leads to progressive microcephaly. The electroencephalogram becomes flat. There is also early extinction on the electroretinogram. Seizures in infantile NCL may not be as prominent as in later-onset forms. Ultimately, spasticity develops and patients become vegetative [16]. The disease is associated with the deficiency of the lysosomal enzyme palmitoyl protein thioesterase 1 (PPT1) and is caused by mutations in *CLN1*. Diagnosis is based on the enzyme deficiency and mutation of the gene.

4.2.2. CLN14 disease—Two infant siblings have been reported who presented with myoclonus, developmental regression and visual failure. A mutation in *KCTD7*, a gene responsible for the function of a potassium channel, was found [12].

4.3. Late-infantile onset NCL

The classic late infantile onset NCL is caused by mutations in *CLN2*, but many other forms also present between ages 1 and 4 years.

4.3.1. CLN2 disease—Patients with this classic late infantile NCL [17] typically present with slowing of development and psychomotor regression, usually in the second or third year of life. Epilepsy typically develops between 2 and 4 years of age. Epilepsy takes many forms in this NCL form and is often refractory to medical treatment. Vision loss is associated with abnormal ERG and visual evoked potential (VEP). Retinal degeneration is

most visible in the macula. The general decay of psychomotor functions is rapid and uniform between the third and fifth birthday [18]. Children with later onset (after 4 years) tend to have milder course with more prominent ataxia and less prominent epilepsy. The disease is associated with the deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1) and is caused by mutations in *CLN2*, the demonstration of both of which serves for diagnosis.

4.3.2. CLN1 disease—CLN1 disease is characterized by visual and cognitive decline followed by ataxia and myoclonus [19].

4.3.3. CLN5 disease—This form of late-infantile NCL [20] has been called the "Finnish variant," but it occurs world-wide [5]. Age at onset is more variable than in classic CLN2 disease, a mean age at onset of 5.6 years (range 4–17 years). Clinical features include psychomotor regression, ataxia, myoclonic epilepsy, and visual failure. Vision loss may be the presenting sign. Diagnosis depends on analysis of *CLN5*.

4.3.4. CLN6 disease—CLN6 disease [21] has a variable age at onset ranging from 18 months to 8 years. Clinical features include motor delay, dysarthria, ataxia, vision loss, and seizures. Seizures are an early feature, starting before age 5 years in the majority of patients. Early vision loss occurs in about half of patients with this disease. Deterioration is rapid and death usually occurs between 5 and 12 years of age. Diagnosis depends on analysis of *CLN6*.

4.3.5. CLN7 disease—CLN7 disease [22] has also been called the "Turkish" variant but has been shown to occur world-wide. Age at onset is 2–7 years. The initial symptom is typically seizures followed by progressive motor decline, myoclonus, cognitive changes, and vision loss. Diagnosis is through gene analysis.

CLN8 disease occurs in two primary forms [23]. The late-infantile form is characterized by vision loss, myoclonic seizures, progressive motor and cognitive decline, and early death. Age at onset is 5–10 years of age. *CLN8* mutations have also been associated with "Northern Epilepsy" which is a form of progressive myoclonus epilepsy but does not have the vision loss associated with NCL [24]. Diagnosis is through gene analysis.

4.4. Juvenile onset NCL

Classic juvenile NCL is due to mutations in the *CLN3* gene, but juvenile onset has been reported in other forms.

4.4.1. CLN3 disease—This classic juvenile NCL form [25] presents between ages 4 and 7 years with insidious onset of blindness caused by retinal degeneration (Fig. 1). Progressive cognitive decline and behavioral problems follow. The behavior problems are typically characterized as angry outbursts, physical violence, and anxiety with features of depression. Seizures develop slightly later. Generalized tonic–clonic seizures are the most common in CLN3 disease, but are typically well-controlled with medication at least initially. The movement disorder in CLN3 disease is parkinsonism, that is sometimes responsive to L-DOPA. CLN3 disease has a severe, characteristic dysarthria that is most prominent after 10

years of age. In addition to the neurologic features, CLN3 patients manifest a cardiac conduction abnormality in the second decade of life. Age at death is usually in the third decade. Diagnosis relies on the demonstration of vacuolated lymphocytes in peripheral blood and on mutations in *CLN3*, where a typical deletion is found in the wide majority of cases.

4.4.2. CLN1 disease—Juvenile-onset NCL due to *CLN1* mutations [26] differs from both CLN3 disease and classic infantile NCL [15]. Age at onset is 5–10 years with cognitive decline as the earliest symptom in most. Seizures occur in multiple forms. Motor decline occurs, but there is typically neither parkinsonism nor myoclonus. Spasticity and ataxia may develop. Vision loss is late in this form, occurring usually between ages 10 and 14 years. Diagnosis is as for the infantile form of CLN1 disease.

4.5. Adult onset NCL

Classic adult onset NCL (Kufs disease) had been categorized as CLN4 disease, but it is now apparent that there are multiple causes of adult-onset NCL.

4.5.1. CLN4 disease—This has recently been reclassified to refer to “Parry disease” associated with mutations in *DNAJC5* [11]. This is the only autosomal dominant NCL. Symptom onset occurs after age 30 years. Clinical features include ataxia, progressive dementia, seizures, and myoclonus with no visual loss. Diagnosis depends on mutations in *CLN4* (*DNAJC5*).

4.5.2. CLN6 disease—The Kufs type A variant of adult-onset NCL [27] was recently associated with mutations in *CLN6* [8]. This form of NCL has onset around 30 years of age with progressive myoclonic epilepsy followed by development of dementia and ataxia. Dysarthria is prominent. There is no vision loss in this disease. Death typically occurs within 10 years. Kufs Type B is clinically similar, but without the epilepsy and dysarthria. Mutations in the *CLN6* gene are diagnostic.

4.5.3. CLN13 disease—The Kufs type B variant [27] presents in the same age range as type A with dementia as well as cerebellar and/or extra-pyramidal signs. The disease is associated with a deficiency of the lysosomal enzyme cathepsin F. Mutations in the responsible gene [13] allow diagnosis.

4.5.4. CLN1 disease—Adult onset NCL due to *CLN1* mutations is characterized by onset after 18 years of age [28]. Cognitive decline and depression are the initial manifestations followed by development of ataxia, parkinsonism, and vision loss. Diagnosis, as in other forms of CLN1 disease, is through testing of PPT1 activity and mutation analysis.

The NCLs described above have several features in common suggesting biological similarities or functional interactions between involved genes. The clinical manifestations of the different NLCs differ in age at onset, order of progression, and specific symptoms. This variability suggests either differential gene expression within the CNS or differential vulnerability of different neuronal populations. Knowledge of clinical presentations can help guide diagnostic evaluation in patients with features of NCL. However, more quantitative

study of the natural history in NCLs is required to inform neurobiological investigations and development of outcome measures for clinical trials.

5. Strategy for the diagnosis of NCL types

The clinical approach to diagnosis of an NCL disorder starts at the age at which symptoms appear. Suggestive situations can be divided in four typical groups: (1) very young infants, including newborns with congenital epilepsy and microcephaly, (2) young children with developmental standstill or regression and severe epilepsy, (3) school children with visual loss, followed by dementia and epilepsy, and (4) young adults with non-specific mental, motor or behavioral abnormalities. In each of these groups, a characteristic set of NCL types can be expected, caused by variable mutations in the known NCL genes.

Table 2 provides an algorithm of diagnostic investigations once an NCL is considered in a person with suggestive symptoms. Initial laboratory studies comprise enzymatic tests, light and electron microscopic investigations of intracellular storage that, when performed in the logical order shown, lead straight and economically to adequate molecular genetic confirmation.

6. Specialized palliative therapies in NCL

Palliative therapies in NCL diseases represent a significant challenge due to multiple symptom complexes and affected body systems. Moreover, treatment is difficult as most patients have severe visual impairment and may not be able to communicate verbally with caregivers. Collaboration with a team of clinicians with NCL experience is recommended in order to improve palliative medication: Table 3 is based on experience collected by such teams and gives an overview of medication found to be helpful in treating the most common symptoms of NCLs.

Epilepsy in NCL is therapy-resistant in most cases. Progressive brain degeneration leads to changes in the effectiveness of medication and to unexpected toxicity. Therefore, the following rules should be followed for treating seizures in NCL:

1. Neither complete absence of seizures nor normalization of electroencephalogram (EEG) is realistic goal of treatment.
2. The EEG in NCL is mainly for monitoring. Therapy should be adjusted to clinical symptoms.
3. Therapy with more than two anticonvulsants may result in increased side effects rather than reduction of seizures.
4. Some anticonvulsants are recommendable for NCL patients (valproate and lamotrigine), others may have negative effects on the disease course and should be avoided (carbamazepine, phenytoin, vigabatrin). See Table 3.
5. Use only as many drugs as necessary and as few as possible.

Myoclonus is a symptom difficult to treat. However, it is often more distressing for caregivers than to the patients. Levetiracetam and piracetam are at least partially effective

treatments (Table 3). Some antiepileptic drugs can aggravate myoclonus and should be avoided (carbamazepine, gabapentin and lamotrigine in late infantile NCL types). Reduction or rationalization of a patient's medication load may sometimes improve myoclonus.

Spasticity, when it causes discomfort, should be treated with physical therapy and medication. Baclofen and tizandine are effective. Tetrahydrocannabinol has also been used. Benzodiazepines may be effective but have frequent side effects, lose their efficacy with time, and sometimes appear to have a negative effects on the general disease course. Underlying painful events (see below) may trigger terrifying spastic exacerbations and must be recognized.

Episodes of apparent or suspected pain are frequent and are caused by a great variety of factors. Some of them are related to chronic immobility such as pathological skeletal fractures, renal calculi, or venous thrombosis. Abdominal pain may be caused by constipation due to disease-related intestinal hypomotility or malnutrition. Recognition and management of pain in NCL patients requires particular skills [29].

Diagnosis and treatment of tormenting psychopathological symptoms such as sleep disturbance, fear, aggressive behavior, depression, and hallucinations represent a particular challenge. Careful and painstaking documentation of these symptoms, recognition of context and possible triggers can be extremely helpful in managing environmental exacerbating factors. Psychopharmacologic medication should be given only after careful consideration and in consultation with child neurologists and child psychiatrists, parents, and caregivers. Drugs to consider for psychotic symptoms in juvenile NCL are risperidone for hallucinations or panic attacks and fluvoxamine for anxiety and depression.

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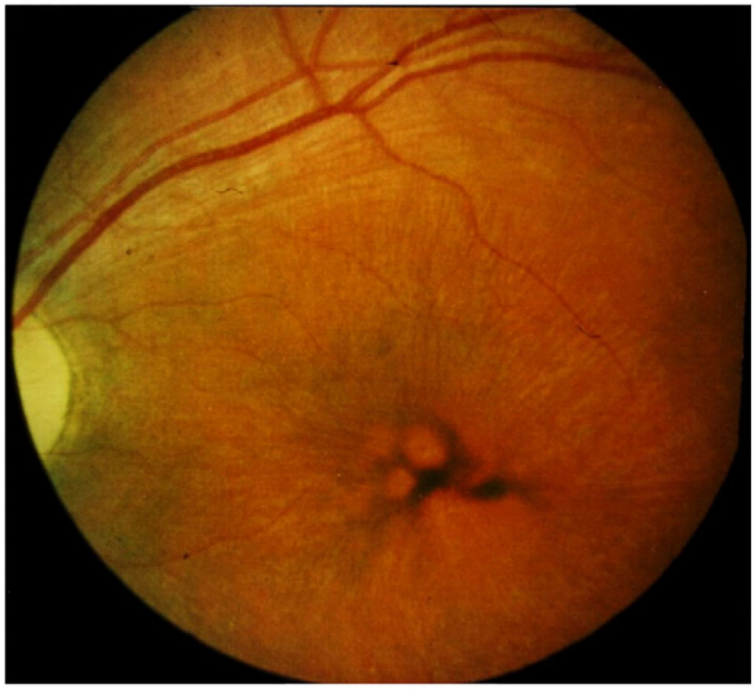

Fig. 1.
Fundoscopic appearance of the retina of a patient with juvenile CLN3 disease. Irregular pigment distribution and thin blood vessels are visible.

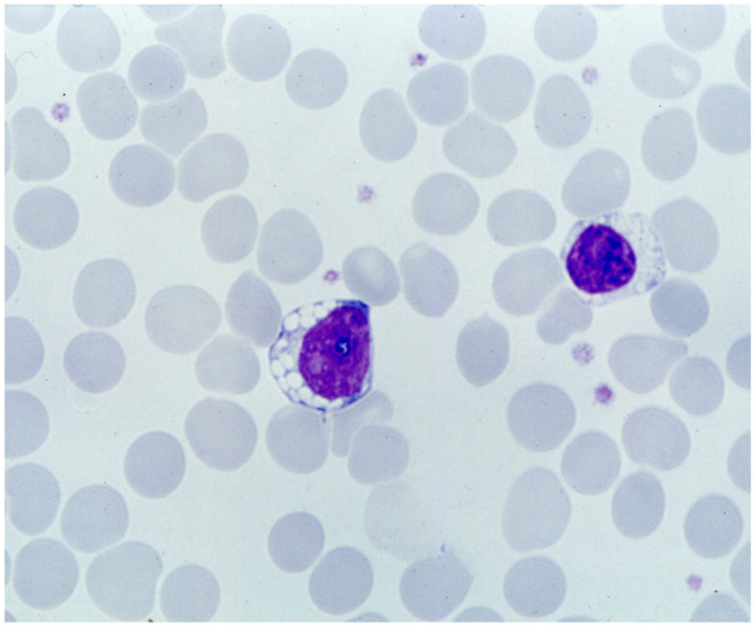

Fig. 2.

Vacuoles in the cytoplasm of a peripheral blood lymphocyte from a patient with juvenile CLN3 disease. Routine blood smear.

Table 1

Genetic spectrum and new nomenclature of NCL diseases.

Disease	MIM number/reference	Gene	Protein
CLN1 disease, infantile	#256730	*CLN1/PPT1*	PPT1[a]
CLN1 disease, late-infantile			
CLN1 disease, juvenile			
CLN1 disease, adult			
CLN2 disease, late-infantile	#204500	*CLN2/TPP1*	TPP1[a]
CLN2 disease, juvenile			
CLN3 disease, juvenile	#204200	*CLN3*	Transmembrane protein
CLN4 disease, adult (AD inheritance)	#162350	*CLN4/DNAJC5*	Soluble cysteine string protein α
CLN5 disease, late-infantile	#256731	*CLN5*	Soluble lysosomal protein
CLN5 disease, juvenile			
CLN5 disease, adult			
CLN6 disease, late-infantile	#601780	*CLN6*	Transmembrane protein
CLN6 disease, adult (Kufs type A)			
CLN7 disease, late-infantile	#610951	*CLN7/MFSD8*	Transmembrane protein
CLN8 disease, late-infantile	#600143	*CLN8*	Transmembrane protein
CLN8 disease, EPMR			
CLN10 disease, congenital	#610127	*CLN10/CTSD*	Cathepsin D[a]
CLN10 disease, late-infantile			
CLN10 disease, juvenile			
CLN10 disease, adult			
CLN11 disease, adult	[9]	*CLN11/GRN*	Progranulin[b]
CLN12 disease, juvenile	[10]	*CLN12/ATP13A2*	ATPase type 13A2[c]
CLN13 disease, adult (Kufs type B)	[13]	*CLN13/CTSF*	Cathepsin F[a]
CLN14 disease, infantile	[12]	*CLN14/KCTD7*	Potassium channel tetramerization domain containing protein type 7[d]

[a] Lysosomal enzymes.

[b] *GRN* mutations also in Frontotemporal lobar degeneration with TDP43 inclusions MIM #607485.

[c] *ATP13A2* mutations also in Kufor–Rakeb syndrome (KRS, Parkinson disease 9) MIM #606693.

[d] *KCTD7* mutations also seen in progressive myoclonic epilepsy type 3 (EPM3) MIM #611726.

Table 2

Diagnostic algorithm for NCL diseases.

Clinical presentation	Necessary diagnostic	Possibly affected genes
Newborn with epilepsy and microcephaly	Enzyme testing for cathepsin D (CtsD) (leucocytes of fibroblasts).	
	CTSD deficient:	*CLN10*
Young child (>6 months) with developmental standstill or regression and/or newly occurring severe epilepsy of unknown cause	Enzyme testing for PPT1 and TPP1 (dry blood spots or leucocytes or fibroblasts)	
	PPT1 deficient:	*CLN1*
	TPP1 deficient:	*CLN2*
	If PPT1 and TPP1 enzyme activities are normal: Electron microscopic examination (skin biopsy or lymphocytes).	
	If storage material is present: genetic testing.	*CLN5*, *CLN6*, *CLN7*, *CLN8*, *CLN14*
School child with visual loss and/or dementia and epilepsy	Search for lymphocyte vacuoles (light microscopy of blood smear, Fig. 2).	
	If lymphocyte vacuoles are present:	*CLN3*
	If no lymphocyte vacuoles, enzyme testing for PPT1, TPP1 and CtsD (see above)	
	PPT1 deficient:	*CLN1*
	TPP1 deficient:	*CLN2*
	CTSD deficient:	*CLN10*
	If PPT1 and TPP1 enzyme activities are normal: Electron microscopic examination (skin biopsy or lymphocytes).	
	If storage material is present:	*CLN5*, *CLN6*, *CLN7*, *CLN8*, *CLN12*
Young adult with non-specific mental, motor or behavioral abnormalities.	Enzyme testing for PPT1, TPP1 and CtsD (see above)	
	PPT1 deficient:	*CLN1*
	TPP1 deficient:	*CLN2*
	CTSD deficient:	*CLN10*
	CTSF deficient:	*CLN13*
	If enzyme activities are normal: Electron microscopic examination (skin biopsy or lymphocytes).	
	If storage material is present: genetic testing (eventually in special cases even without detection of storage material), consider possible mode of inheritance.	If autosomal dominant: *CLN4* If autosomal recessive: *CLN6*, *CLN11*, *CLN13*

Table 3

Overview on medication for palliative therapies in NCL.

Symptom	Substance	Comment
Epilepsy[a]	Valproate	Advantage: mood stabilizing effect, useful in juvenile NCL patients with psychotic symptoms
	Lamotrigine	
	Topiramate	Increase dosage *slowly* to minimize side effects such as speech disturbance (starting dose 0.5 mg/kg/d). Agitation may be a side effect. In this case discontinue the drug.
	Levetiracetame	Severe agitation is a possible side effect in juvenile NLC.
	Diazepam, lorazepam	Acute therapy of prolonged grand mal seizures
Myoclonus	Levetiracetame	Also effective as anti-epileptic medication (especially in late infantile NCL)
	Zonisamide	
	Piracetame	High dosage required (300–350 mg/kg/d)
Spasticity	Baclofen (1st choice)	Frequently high dosage required
	Tizanidine (2nd choice)	Good effect also against dyskinesia
	Tetrahydrocannabinol	“Add-on” medication, increase dosage slowly up to 0.07 mg/kg/d,
	Botulinum toxin	Local application by injection to muscles; always accompanied by physical therapy

[a] Avoid overtreatment, as most seizures in NCL are treatment-resistant.