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Review Article

Epilepsy in neuronal ceroid lipofuscinoses

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Abstract. The neuronal ceroid lipofuscinoses (NCL) are a group of genetic lysosomal storage diseases characterized by dementia, epilepsy, motor deterioration and mostly also visual loss through retinal degeneration. As a group, they represent one of the most frequent etiologies of dementia in young persons. The present classification of the NCL disorders is based on the different genes involved and on the age at clinical onset, which can be anytime between the infantile and young adult age. We describe typical clinical pictures that may be caused by NCL types in the different age groups and an economic strategy for their diagnosis. While experimental therapies aiming to stop disease progression are being developed, palliative therapies may be disease-specific and can bring significant relief. This applies particularly to the therapy of the frequently drug-resistant epilepsy in NCL.

Keywords: Degenerative brain disease, genetics, dementia, epilepsy, retinopathy

1. Introduction

The neuronal ceroid lipofuscinoses (NCL) are a heterogenous group of genetic lysosomal disorders characterized by the accumulation of intracellular storage material and progressive neurological deterioration, usually associated with dementia and epilepsy, frequently also with visual loss due to retinopathy. Among the degenerative brain diseases, they show typical patterns of gray matter disease. As a group, NCL represent one of the most frequent etiologies of dementia in young persons [1, 2]. Although NCL are incurable, palliative therapies, which frequently are disease-specific, can bring significant relief. This applies particularly to anticonvulsive therapy of these frequently drug-resistant disorders.

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2. Present classification of NCL diseases

Traditionally, NCL diseases were classified according to the age at clinical onset (congenital, infantile, late infantile, juvenile, adult), sometimes also according to the respective authors (Haltia-Santavuori, Jansky-Bielschowsky, Batten, Spielmeyer-Vogt, Kufs) or according to ethnic groups with presumed specific occurrence such as Finish or Turkish NCL variants. Later on it was recognized that NCL diseases are genetically much more heterogeneous than initially thought, that mutations in the same gene can lead to very different disease courses [3, 4] and that many mutated genes occur worldwide. Therefore, a new gene-based classification was developed that clearly identifies each NCL disease both genetically and according to the age at onset [5]. Presently 13 defined genetic forms are known (Table 1) while other forms are waiting to be defined. Inheritance of NCL diseases is mostly autosomal recessive; exceptions are mentioned in the Table 1.

Table 1
Present classification of neuronal ceroid lipofuscinosis diseases

Designation of disease (according to mutated gene and possible age at clinical onset)	Online Mendelian inheritance in man (OMIM) Catalogue number	Gene (Alternative name)	Deficient protein
CLN1 disease (infantile, late-infantile, juvenile, adult)	256730	*CLN1* (*PPT1*)	Palmitoyl-protein thioesterase 1*
CLN2 disease (late-infantile, juvenile)	204500	*CLN2* (*TPP1*)	Tripeptidyl peptidase 1*
CLN3 disease (juvenile)	204200	*CLN3*	Transmembrane protein
CLN4 disease (adult [autosomal dominant inheritance])	162350	*CLN4* (*DNAJC5*)	Soluble cysteine string protein alpha
CLN5 disease (late-infantile, juvenile, adult)	256731	*CLN5*	Soluble lysosomale protein
CLN6 disease (late-infantile, adult [Kufs type A])	601780	*CLN6*	Transmembrane protein
CLN7 disease (late-infantile)	610951	*CLN7* (*MFSD8*)	Transmembrane protein
CLN8 disease (late-infantile, "Northern epilepsy")	600143	*CLN8*	Transmembrane protein
CLN10 disease (congenital, late-infantile, juvenile, adult)	610127	*CLN10* (*CTSD*)	Cathepsin D*
CLN11 disease (adult)	614706	*CLN11* (*GRN*)	Progranulin**
CLN12 disease (juvenile)	610513	*CLN12* (*ATP13A2*)	ATPase type 13A2***
CLN13 disease (adult [Kufs type B])	615362	*CLN13* (*CTSF*)	Cathepsin F
CLN14 disease (infantile)	611725	*CLN14* (*KCTD7*)	Potassium channel tetramerization domain-containing protein type 7****

*Lysosomal enzymes. **Mutations in the *granulin (GRN)* gene also in frontotemporal lobar degeneration with ubiquitin-positive inclusions (OMIM 607485). ***Mutations in the *ATPase type 13A2 (ATP13A2)* gene also in Kufor-Rakeb syndrome (OMIM 606693). ****Mutations in the *potassium channel tetramerization domain containing 7 (KCTD7)* gene also seen in progressive myoclonic epilepsy type 3 (OMIM 611726).

An exact diagnosis on the basis of this combined genetic and clinical classification is essential for genetic counseling, for making an educated guess at the future disease course, and for optimizing symptomatic care (Table 2).

3. Clinical presentation of NCL diseases

In almost all types of an NCL disease, the patients are initially healthy and show a normal psychomotor development. Main alerting symptoms are a standstill of psychomotor development followed by obvious dementia, in variable combination with visual loss, epilepsy, and motor deterioration. The age at disease onset can range from birth to adulthood. The order in which symptoms occur depends on the genetic form. In the following, we describe the different disease courses that are to be expected, listed according to the age at onset and the genetic forms associated with the respective age period.

3.1. Congenital onset

Congenital NCL (CLN10 disease) is a rare form associated with the deficiency of the lysosomal enzyme cathepsin D [6–8]. Clinical features include primary (congenital) microcephaly with brain atrophy, neonatal seizures, and respiratory failure. Infants with this disease rarely live more than a few days.

3.2. Infantile onset (1st yr of life)

The classic infantile onset NCL is caused by mutations in *CLN1* and is associated with the deficiency of the lysosomal enzyme palmitoyl protein thioesterase 1 [9, 10]. Early development appears normal until around six mo of age, sometimes into the second yr of life. At onset, there is typically decreased tone and decreased social interaction followed by dramatically progressive psychomotor decay, myoclonus, seizures, and visual failure. By 2 yr of age, blindness has developed

Table 2
Diagnostic algorithm for neuronal ceroid lipofuscinosis diseases

Age at onset of symptoms	Necessary diagnostic tests	Possibly affected genes
Newborn with epilepsy and microcephaly	Enzyme testing for cathepsin D in leucocytes or fibroblasts	Cathepsin D deficient: *CLN10*
Young child (>6 mo) with developmental standstill or regression or newly occurring severe epilepsy of unknown cause	Enzyme testing for PPT1 and TPP1 in dry blood sample	PPT1 deficient: *CLN1*; TPP1 deficient: *CLN2*
	If PPT1 and TPP1 are normal: electron microscopy. 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 in blood smear). If vacuoles are present: genetic testing of *CLN3* gene	*CLN3*
	If no lymphocyte vacuoles, enzyme testing for PPT1, TPP1 and cathepsin D in dry blood sample	PPT1 deficient: *CLN1*; TPP1 deficient: *CLN2*; Cathepsin D deficient: *CLN10*
	If no lymphocyte vacuoles, enzyme testing for PPT1, TPP1 and cathepsin D in dry blood sample	PPT1 deficient: *CLN1*; TPP1 deficient: *CLN2*; Cathepsin D deficient: *CLN10*
Young adult with newly occurring non-specific mental, motor or behavioural abnormalities	Enzyme testing for PPT1, TPP1 and cathepsin D in dry blood sample	PPT1 deficient: *CLN1*; TPP1 deficient: *CLN2*; Cathepsin D deficient: *CLN10*
	If PPT1, TPP1 and cathepsin D are normal: electron microscopy. If storage material is present: genetic testing. Consider mode of inheritance	Autosomal dominant: *CLN4*; Autosomal recessive: *CLN6*, *CLN11*, *CLN13*

Dry blood sample positive results to be confirmed in leucocytes or fibroblasts; electron microscopy of skin or lymphocytes negative results may not always rule out a storage disorder. PPT1 = Palmitoyl protein thioesterase 1; TPP1 = Tripeptidyl peptidase 1.

with optic atrophy and retinal abnormalities without pigment aggregation. The electroretinogram is extinguished early. Seizures in this form of NCL may not be as prominent as in later-onset forms. Ultimately, spasticity develops and patients develop a vegetative state.

3.3. Late infantile onset (2–5 yr of age)

In this age group, several different genetic types can make their clinical appearance. This frequently observed disorder has also been called classic late infantile NCL. It is caused by *CLN2* mutations and is associated with the deficiency of the lysosomal enzyme tripeptidyl peptidase 1 [11]. Affected children appear initially healthy and normally developed. Acquisition of speech may be retarded. First symptoms occur generally between the ages of 2 to 4 yr and consist in motor decline with clumsiness and ataxia, deterioration of speech and/or epilepsy. Seizures are the first symptom in 75% of patients. They may be partial, generalized tonic-clonic, secondarily generalized, or sometimes absences. Non-epileptic myoclonus frequently coexists and has to be distinguished from epileptic seizures as it is treated differently. Persistent myoclonus may interrupt sleep and can be difficult to treat. After the 3rd yr of life, loss of motor function and language progress rapidly and uniformly [12]. Visual ability declines gradually from four yr of age and leads to blindness. Limb spasticity, truncal hypotonia, and loss of head control lead to complete loss of independent mobility. Children lose the ability to swallow and frequently receive tube feeding. Death usually occurs around middle teenage year.

The electroencephalogram (EEG) shows typical occipital spikes in response to slow photic stimulation (Fig. 1) and visually evoked potentials are enhanced early in the course of the disease. These phenomena can be seen as a reflection of neuronal hyperexcitability during a phase of the degenerative process. The electroretinogram can be diminished even before any visual impairment is evident and becomes extinguished later. Magnetic resonance imaging shows progressive brain atrophy, initially most pronounced in the cerebellum.

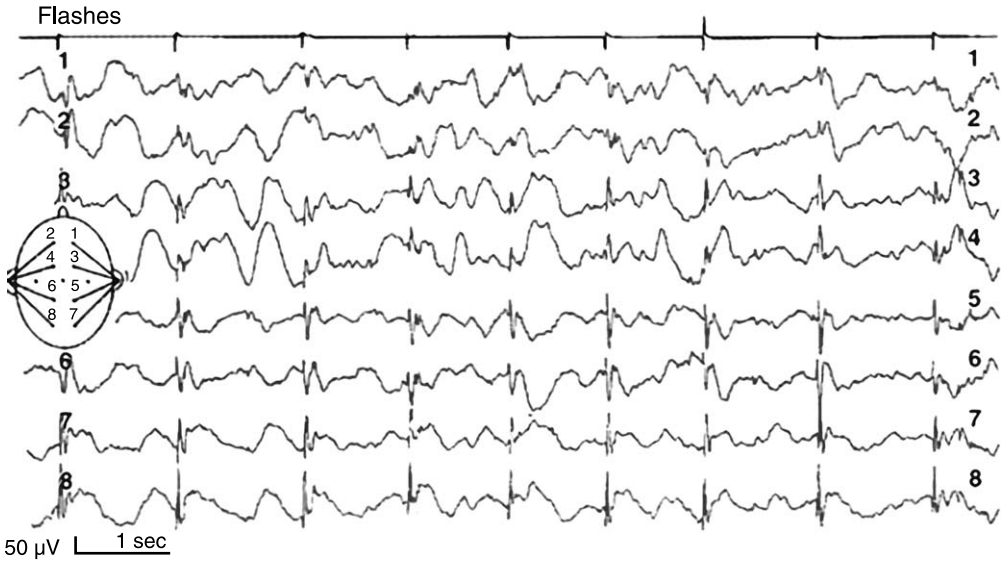

Fig. 1. Electroencephalogram of a patient with late-infantile CLN2 disease, about 4-year-old. Occipital spikes in response to slow photic stimulation.

Several other genetic types can also manifest themselves in this age period. These types usually start somewhat later and progress more slowly than the classical CLN2 type. They used to be called ''late-infantile NCL variants" in older texts.

Late-infantile CLN1 disease is a mutational variant manifesting itself later than the infantile type described above. The disease is characterized by visual and cognitive decline followed by ataxia and myoclonus. This form is caused by the deficiency of a soluble lysosomal protein [13] and was called the ''Finnish variant" of late-infantile NCL, but it occurs world-wide [14]. Age at onset is more variable than in the classical CLN2 disease, a mean age at onset of 5-6 yr (range 4–17 yr). Clinical features include psychomotor regression, ataxia, myoclonus, and visual failure. Loss of vision may be the presenting symptom. *CLN6* mutations cause a deficiency of a transmembrane protein [15]. The disease has a variable age at onset ranging from 18 mo to 8 yr. Clinical features include motor delay, dysarthria, ataxia, visual loss, and seizures. Seizures are an early feature, starting before age 5 yr in most patients. Early visual loss occurs in about half of patients. Deterioration is rapid and death usually occurs between 5 and 12 yr of age. Late-infantile CLN7 disease is also due to the deficiency of a transmembrane protein. It was called the ''Turkish" variant but has been shown to occur world-wide [3, 16]. Age at onset is 2–7 yr. The initial symptom is typically epilepsy followed by progressive motor decline, myoclonus, cognitive changes, and loss of vision. Late-infantile CLN8 disease occurs in two main forms [17]. The late-infantile form is characterized by loss of vision, myoclonus, progressive motor and cognitive decline, and early death. Age at onset is 2–7 yr of age. *CLN8* mutations are also causative of ''Northern epilepsy", a form of progressive myoclonus epilepsy without loss of vision, with age of onset at 5–10 yr.

3.4. Juvenile onset (5 to 15 yr of life)

Juvenile CLN3 disease, also called classic juvenile NCL, is one of the most frequently seen NCL forms starting in the juvenile period [14]. It is caused by mutations in the *CLN3* gene which codes for a transmembrane protein of unknown function [18]. The disease starts between ages 4 and 7 yr with insidious onset of visual failure due to a pigmentary retinopathy. For a considerable period of time, patients are regarded as stricken by blindness only.

Progressive cognitive decline and behavioral problems (angry outbursts, physical violence, and anxiety with features of depression) follow. Seizures develop at around 10 yr of age, mostly as generalized tonic-clonic seizures, which are usually well-controlled by medication, at least initially. Any other type of seizure may occur, from subtle partial to myoclonic status. A parkinsonian movement disorder develops,

with variable response to levodopa therapy. Speech becomes affected by a severe characteristic dysarthria. Swallowing difficulties frequently lead to tube feeding. A cardiac conduction abnormality is detectable in the second decade of life. Age at death is usually in the third decade. The clinical course, however, is not uniform, even in the presence of identical mutations [4]. A striking laboratory finding are vacuolated lymphocytes, detectable in regular blood smears and not seen in other NCL types. However, vacuolated lymphocytes may not be easily detected in every case of CLN3 disease [2].

Juvenile CLN1 disease is a further mutational variant manifesting itself later than the infantile and late-infantile type described above. Age at onset is 5–10 yr 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. Visual loss is late, occurring usually between ages 10 and 14 yr.

In juvenile CLN10 disease, cathepsin D deficiency caused by mutations different from those in congenital CLN10 disease caused a neurodegenerative disorder starting at early school age with ataxia, retinopathy and dementia [19].

3.5. Adult onset

In the past, the term Kufs disease was used to designate an NCL disorder manifesting itself at an adult age. It is now apparent that there are multiple causes of adult-onset NCL. Adult CLN1 disease is characterized by onset after 18 yr of age. Cognitive decline and depression are the initial manifestations followed by development of ataxia, parkinsonism, and visual loss [20]. Adult CLN4 disease is the only autosomal dominant NCL. It is caused by mutations in *CLN4* (alternative designation *DNAJC5*), which encodes the cysteine string protein alpha, a presynaptic protein of neural tissue. Onset of symptoms occurs after age 30 yr. Clinical features include ataxia, dementia, progressive myoclonus epilepsy but no visual loss [21]. Adult CLN6 disease, also referred to as Kufs type A variant of adult-onset NCL, has its onset also at around 30 yr of age with progressive myoclonic epilepsy followed by development of dementia and ataxia. Dysarthria is prominent. There is no visual loss in this disease [22]. Death typically occurs within 10 yr. Adult CLN11 disease is caused by a profound deficiency of progranulin, a growth factor that, when only partially decreased in persons with heterozygous mutations of the *CLN11* (alternatively *GRN*) gene, is associated with dementia in frontotemporal lobar degeneration. Two siblings with homozygous mutations had an NCL disorder with rapidly progressive visual failure in their twenties, followed by major convulsions and myoclonic seizures [23]. Adult CLN13 disease, (Kufs type B) is caused by cathepsin F deficiency due to mutations in the *CLN13* (or *CTSF*) gene [24]. In this type dementia and motor disturbances, rather than epilepsy, dominate the clinical picture.

4. Diagnosis of an NCL disease

An NCL disorder should be considered in patients who initially appear healthy and normally developed and then show a progressive neurological disorder most frequently characterized by dementia, visual loss, epilepsy, and motor deterioration. The diagnostic strategy depends on the age at disease onset and is systematically presented in Table 2, which lists the adequate diagnostic tests and possibly affected genes for the different age groups. Important first line tests include examination of a blood smear for lymphocyte vacuoles in a juvenile disorder (typical of CLN3 disease) and enzymatic tests in dry blood samples for suspected CLN1 and CLN2 disease [25]. In certain situations, electron microscopy is helpful to demonstrate storage material in blood cells or tissue specimens [26].

5. Treatment

NCL disorders are presently incurable. Experimental approaches to curative treatment [27, 28] are beyond the scope of this review. For patients with CLN2 disease, a phase I/II study of intra- ventricular enzyme replacement (http://clinicaltrials.gov/show/NCT01907087) and a phase I study of a gene transfer vector (http://clinicaltrials.gov/show/NCT01161576) are under way, as well as a study of the effects of an immunosuppressant on disease progression in CLN3 disease (http://clinicaltrials.gov/show/NCT01399047).

Palliative therapies, on the other hand, are of great importance in these chronic diseases and represent a significant challenge due a multiplicity of symptoms and affected body systems. Moreover, treatment is difficult as most patients have very poor vision and may not be able to communicate verbally. Some aspects of palliative treatment are specifically related to the exact molecular genetic diagnosis. Table 3 lists some

Table 3
Palliative medical treatment of patients with neuronal ceroid lipofuscinosis diseases

Problem	Treatment	Comment
Epilepsy	Valproate	Usually well tolerated. Hyperammonemia [29] has not been a significant experience in our patients. In juvenile patients with psychotic symptoms, an additionally mood stabilizing effect of the drug is useful. Probably first choice medication
	Lamotrigine	Generally well tolerated. May improve myoclonus. (Worsening of myoclonus seen with excessive blood drug levels.) Single report of reversible hastening of symptoms in CLN2 disease. Good experience for most neuronal ceroid lipofuscinoses patients. Synergistic with valproate [30]
	Topiramate	Many side effects such as deterioration of speech and panic attacks in juvenile patients
	Levetiracetame	Generally well tolerated in patients with late-infantile disease onset. Severe agitation is a possible side effect especially in juvenile patients [31]
	Diazepam, lorazepam	Acute therapy of prolonged grand mal seizures
	Clonazepam, clobazam	Good effect for myoclonus, decreases spasticity. Tolerance and increased oral secretions may be a problem
	Zonisamide	Benefit in some cases
	Phenobarbitone	Treatment of prolonged and frequent seizures and myoclonic status
	Ketogenic diet	Was found useful in patients with late infantile CLN2 disease as mentioned in [32]. This experience was confirmed by additional cases (Ruth Williams, London, personal communication 31 March 2014)
	Carbamazepine	Probably not to be used. Benefit in some patients, seizure activation in others
	Phenytoin	Not be used as a continuous treatment
	Other antiepileptic drugs	No relevant data on treatment of neuronal ceroid lipofuscinoses using other antiepileptic drugs. Single report on ethosuximide (myoclonic seizures)
Myoclonus	Zonisamide	Effective
	Levetiracetame	Is also effective as anticonvulsant (especially in late infantile neuronal ceroid lipofuscinoses)
	Piracetame	High dosage required (300–350 mg/kg/d)
Spasticity	Baclofen (First choice)	Frequently high dosage required
	Tizanidine (Second 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

problems occurring in NCL patients that lend themselves to medical treatment.

5.1. Treatment of epilepsy in NCL patients

Epilepsy in NCL is therapy resistant in most cases and, during certain phases of the degenerative process in the brain, the severity of seizures may acerbate or diminish. It is also an effect of the brain degeneration that effectiveness of a familiar drug and tolerance for it may vary from what we are used to see in other epileptic disorders. Therefore, when treating seizures in NCL, the following rules should be followed: (a) Neither complete absence of seizures nor normalization of the EEG are realistic goals of treatment. (b) The purpose of EEG in NCL is mainly for monitoring and to distinguish non-epileptic myoclonus from myoclonic seizures. Therapy should be adjusted to clinical symptoms. (c) Therapy with more than two anticonvulsants may result in increased side effects rather than reduction of seizures. (d) Some anticonvulsants are recommended in NCL patients (valproate and lamotrigine), others seem to have negative effects on the disease course and should be avoided (carbamazepine, phenytoin, vigabatrin). (e) Overtreatment should be avoided. Use only as many drugs as necessary and as few as possible.

5.2. Other palliative therapies

Myoclonus is a symptom which is difficult to treat. It can be very disturbing and frequently interferes with sleep, but sometimes it is more distressing to caregivers than to the patient. Zonisamide is effective while levetiracetam and piracetam are at least partially effective (Table 3). Some anticonvulsants can aggravate

myoclonus (carbamazepine, gabapentin; sometimes lamotrigine when blood levels are too high). Therefore, reduction and rationalization of medication load may sometimes improve myoclonus.

Painful spasticity must be treated with physical therapy and spasmolytic agents. Baclofen and tizanidine are effective. Tetrahydrocannabinol can also be used cautiously. Benzodiazepines may be effective but their use is frequently complicated by side effects (a seemingly negative effect on the disease course, increased production of mucous secretions) and development of drug tolerance. A spastic crisis can be triggered by unrecognized discomfort or pain. Abdominal pain may be caused by constipation due to disease-related intestinal hypomotility or inadequate nutrition. Other causes of pain in immobile non-communicative patients include pathological skeletal fractures, joint luxation and renal calculi.

Psychopathological symptoms such as sleep disturbance, fear, aggressive behavior, depression, and hallucinations can be tormenting. Careful documentation of these symptoms, their context and possible triggers helps to differentiate environmental exacerbating factors from organic brain disease. Psychopharmacologic medication should be given only after careful consideration and in consultation with child neurologists and child psychiatrists, parents, and caregivers.

6. Conclusion

Although the NCL disorders are incurable, the precise diagnosis of the particular form occurring in a family is important. As in many rare diseases, consultation with a specially experienced medical team is helpful in the recognition of one of these distressing diseases, for family counseling and for improving palliative management.

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