

Neuronal Ceroid Lipofuscinoses

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Abstract

Keywords

Disease names and synonyms

Infantile NCL (Hagberg-Santavuori disease, CLN1)

Late infantile NCL (Jansky-Bielschowsky disease, CLN2)

Juvenile NCL (Batten disease, Spielmeyer-Vogt disease, CLN3)

Adult NCL (Kufs disease)

General diagnostic strategy in suspected cases of neuronal ceroid lipofuscinosis

Abstract

The neuronal ceroid lipofuscinoses (NCL or CLN) are a mixed group of genetic progressive storage disorders of the brain and eyes with mostly autosomal recessive inheritance. The overall incidence of NCL in Europe, North America, and some other countries is up to 1 in 12,500. They usually manifest during childhood and adolescence, but very rarely in young adults. These heterogeneous disorders, genetically classified as CLN1 to CLN8, share similar symptoms and signs such as retinopathy with loss of vision, epilepsy, dementia, and accumulation of unusual waxy material termed ceroid lipofuscin (autofluorescent lipopigments) in brain and other tissues. Their pathophysiology is poorly understood and involves the combination of an intracellular storage process and a progressive loss of nerve cells. Two NCL disorders are caused by deficient lysosomal enzymes, namely palmitoyl-protein thioesterase in CLN1 and tripeptidyl-peptidase in CLN2. In some others, it has been found that membrane proteins with unknown function are deficient. The genetic defect can be identified in most cases and forms the basis for family counseling and prenatal diagnosis. All NCL disorders are incurable, progress relentlessly, and lead to early death.

Keywords

Retinopathy, dementia, epilepsy, storage disorder, enzyme deficiency.

Disease names and synonyms

This review contains information on a number of different disorders termed neuronal ceroid lipofuscinoses (NCL or CLN) [Goebel *et al.* 1999] [Wisniewski and Zhong 2001]. [Table 1](#) shows the designations used for the different forms of NCL disorders, along with the chromosomal locations of the corresponding gene defects and gene products. In the following sections, each NCL form is described separately.

Infantile NCL (Hagberg-Santavuori disease, CLN1)

Definition

CLN1 is an autosomal recessively inherited and, in most cases, rapidly progressive brain disease with onset toward the end of the first year of life. It is associated with loss of all motor and cognitive capabilities, marked brain atrophy, death in early childhood, granular cell inclusion bodies. Infantile NCL is caused by mutations in the *CLN1* gene leading to palmitoyl-protein thioesterase 1 deficiency. The designation "infantile" NCL is correctly used when these findings are present. There are also late-onset forms of the disease caused by other *CLN1* mutations.

Differential diagnosis

During the early phase of the disease, CNL1 is clinically similar to Rett syndrome that affects only girls. Infantile neuroaxonal dystrophy occurs at about the same age, but it can be distinguished from CLN1 by the presence of peripheral neuropathy.

Etiology

A defect in the *CLN1* gene on chromosome 1p32 leads to deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1). The pathophysiology is unknown.

Clinical description

The children appear healthy until the end of the first year of life when a delay in their psychomotor development is noted. During the second year, a dramatic loss of acquired skills and reduced growth of the head circumference are evident. The children become floppy and later spastic. In addition, they lose eye contact, suffer from hyperexcitability, myoclonic jerks, and seizures. Within two or three years, they are completely stiff and motionless. They may survive several years.

Diagnostic methods

Early in the disease, MRI shows brain atrophy with increasing severity as the disease process progresses. During later stages, the EEG becomes flat. Routine laboratory studies are not helpful. Electron microscopy of isolated blood lymphocytes or tissue biopsy material reveals characteristic granular osmiophilic deposits (GRODs). The deficiency of palmitoyl-protein thioesterase 1 (PPT 1) can be detected in isolated leukocytes, cultivated fibroblasts, and dried blood samples on filter paper cards [Lukacs *et al.* 2003]. Molecular genetic identification of the defect in the *CLN1* gene on chromosome 1p32 is possible.

Epidemiology

The disease is relatively frequent in Finland (1 in 20,000 newborns). It has only rarely been reported in other European countries and North America.

Genetic counseling and antenatal diagnosis

Counseling and diagnosis are based on the autosomal recessive mode of inheritance and the molecular genetic defect identified in the family.

Medical management

All measures can only be aimed at alleviating symptoms. For spasticity, baclofen can be given orally in daily doses of 15-100 mg/kg body weight (b.w.) or tizanidine in initial doses

of 2-16 mg/kg b.w. When spasticity becomes painful, the dosage can be increased significantly. Fentanyl applied as skin plaster and oral morphine derivatives are then indicated. Either lamotrigine or valproate is the preferred drug for the treatment of seizures. Artificial feeding by a percutaneous endoscopic gastrostomy (PEG) tube is frequently used. Therapy with stem cell transplantation has been tried, but it is presently not recommended [Lonnqvist *et al.* 2001].

Unresolved questions

It is still unknown how the basic defect - the deficiency of palmitoyl-protein thioesterase 1 - leads to brain atrophy and to the disease symptoms. Since the enzyme cleaves thioester compounds (fatty acids bound to sulfur-containing amino acids in membranes), the use of chemical compounds with similar properties as therapeutic agents, such as Cystagon, has been suggested; Cystagon, in laboratory experiments, has helped remove ceroid from cells of patients with CLN1 [NIH 2001].

Late infantile NCL (Jansky-Bielschowsky disease, CLN2)**Definition**

CLN2 is an autosomal recessively inherited progressive brain disease that develops in the third year of life and leads to early death. It is associated with epilepsy, progressive loss of motor and cognitive capabilities, loss of vision, curvilinear cell inclusion bodies, and mutations in the *CLN2* gene leading to tripeptidyl-peptidase 1 deficiency.

Differential diagnosis

There are several variants of classical late infantile NCL. Although these variants are clinically similar, they tend to occur somewhat later and show a more protracted course. Electron microscopy shows similar inclusions, but the underlying enzyme deficiency is not yet known. For some of these variants, gene defects have been identified.

Finnish variant late infantile NCL

This variant occurs almost exclusively in Finland. It is caused by mutations in the *CLN5* gene on chromosome 13q22 [Isosomppi *et al.* 2002].

Indian variant late infantile NCL

This variant is also referred to as "early juvenile NCL" and is caused by mutations in the *CLN6* gene on chromosome 15q21. It is mainly found in the Czech Republic, Croatia, Portugal, Central and South America, and,

more rarely, in Central and Northern Europe [Sharp *et al.* 2003] [Teixeira *et al.* 2003].

Turkish variants of late infantile NCL

One variant occurring in Turkish patients is termed CLN7. Its underlying gene defect is still unknown. Another Turkish variant is caused by a defect in the *CLN8* gene, which is allelic to a mutation causing Northern epilepsy [Mitchell *et al.* 2001] and (A.-E. Lehesjoki, Helsinki, personal communication). A third variant is a specific "Turkish" mutation in the *CLN2* gene [Steinfeld *et al.* 2002].

Etiology

A defect in the *CLN2* gene on chromosome 11p15 leads to deficiency of the lysosomal enzyme tripeptidyl-peptidase 1 (PPT1, pepinase). The pathophysiology is largely unknown.

Clinical description

The disease onset is characterized by delayed psychomotor development in childhood or by epileptic seizures that may become treatment resistant. Blindness develops due to retinal atrophy, but frequently rather at a later stage of the disease. The patients gradually lose all psychomotor abilities and survive to the age of ten to fifteen years [Steinfeld *et al.* 2002].

Diagnostic methods

In the early course of the disease, the EEG can be helpful by showing posterior spikes on slow photic stimulation. In addition, there may be an increase in evoked potentials. Brain MRI findings are mainly non-specific, showing pronounced cerebral atrophy in the infratentorial region and some white matter changes. MRI changes may help to differentiate between classical and variant forms of late infantile NCL [Santavuori *et al.* 2001]. Electron microscopy reveals curvilinear cell inclusion bodies.

Epidemiology

The disease seems to occur worldwide. The minimal incidence in Germany was estimated to be about 1 in 200,000 newborns [Claussen *et al.* 1992].

Genetic counseling and antenatal diagnosis

Counseling and diagnosis are based on the autosomal recessive mode of inheritance and the molecular genetic defect identified in the family.

Medical management

Therapy is only supportive. Lamotrigine and valproate are preferred anticonvulsants.

Carbamazepine, phenytoin, and vigabatrin seem to be inefficient and sometimes even detrimental.

Unresolved questions

The pathophysiology is largely unknown, in particular the question of how the deficiency of palmitoyl-protein thioesterase 1 leads to the neurodegenerative process. Since apoptotic mechanisms are involved in the loss of nerve cells, substances that inhibit apoptosis, such as flupirtine, have been considered as possible therapeutic agents [Dhar *et al.* 2002].

Juvenile NCL (Batten disease, Spielmeier-Vogt disease, CLN3)

Definition

Juvenile NCL is an autosomal recessively inherited degenerative disease affecting the retina and brain with onset in the early school-age years. It is associated with loss of vision, progressive dementia, epilepsy, motor dysfunction, helplessness, microscopical detection of lymphocyte vacuoles and fingerprint cell inclusion bodies, and mutations in the *CLN3* gene.

Differential diagnosis

As long as loss of vision is the only symptom, progressive retinopathies must be taken into account, among them extraocular metabolic disorders such as hyperornithinemia (gyrate atrophy). When neurological symptoms appear, mitochondrial, peroxisomal (Refsum disease), and lysosomal disorders need to be ruled out.

Atypical CLN1 and CLN2 Mutations

When a patient presents with the characteristic clinical findings of juvenile NCL but without lymphocyte vacuoles, the possibility of atypical ("mild") mutations in the *CLN1* and *CLN2* genes must be considered [Stephenson *et al.* 1999] [Wisniewski *et al.* 2001] [Steinfeld *et al.* 2002]. For the relevant diagnostic procedures, please see the above sections on infantile NCL (*CLN1*) and late infantile NCL (*CLN2*).

Northern epilepsy

It is an autosomal recessive childhood-onset epilepsy syndrome, which is clinically characterized by seizures with onset at five to ten years of age and subsequent slowly progressive mental deterioration. The patients have no loss of vision. Autopsy studies showed intracellular inclusions that were very similar to those of the known NCL disorders. A mutation responsible for the disease was identified in a gene on chromosome 8p23, encoding a

putative membrane protein with unknown function [Herva *et al.* 2000]. Other mutations of this gene cause the Turkish variants of late infantile NCL (see above).

Etiology

A defect in the *CLN3* gene on chromosome 16p12 leads to deficiency of a membrane protein consisting of 438 amino acids. The function of this protein is not yet known.

Clinical description

The onset of the disease is usually marked by loss of vision due to retinal degeneration. The first signs appear at the age of five to six years. Abnormal ocular fundus findings include thin arteries, pigmentary anomalies, and an extinguished electroretinogram at a later stage. The children are blind by the age of nine years. At this time, the first signs of dementia become evident, and grand mal epilepsy develops between ten and twelve years. Parkinson-like motor problems occur during late adolescence. Reactive depression and psychotic states with hallucinations can be severe. Progressive mental and motor deterioration leads to death in the third or fourth decade of life.

Diagnostic methods

The most useful diagnostic method is the careful light microscopical examination of a regular blood smear for the presence of a large number of vacuoles in the cytoplasm of lymphocytes. If these are present, a search for a mutation in the *CLN3* gene can be initiated. The most commonly observed mutation is a 1.02-kb deletion, but some point mutations are found as well. Electron microscopy of isolated lymphocytes, skin biopsy specimens, or other tissues reveals mainly "fingerprint-like" intracellular inclusions. Other methods are not helpful.

Epidemiology

Juvenile NCL seems to occur worldwide and the incidence is comparable to that of late infantile NCL, namely about 1 in 200,000 newborns in Germany [Claussen *et al.* 1992]. However, the prevalence is probably higher due to the longer life span.

Genetic counseling and antenatal diagnosis

Counseling and diagnosis are based on the autosomal recessive mode of inheritance and the molecular genetic defect identified in the family. If an affected patient has younger siblings who appear healthy, they can be tested to see whether they are also affected by the same condition. The disease-specific

lymphocyte vacuoles are present long before onset of symptoms.

Management

Although there is no curative treatment, the clinical management of a child or adolescent with juvenile NCL comprises a wide array of medical, psychological, and educational measures that cannot be dealt with here. Appropriate schooling is important. Families and teachers must acquaint themselves with an exceptionally difficult situation that confronts the prepubertal child or adolescent not only with the loss of his/her vision, but also with a progressive decline in mental and emotional capabilities. The patient is in dire need of help to cope with the frustrations associated with the disease [Schlegel 1999; Aberg 2001]. Either valproate or lamotrigine in usual dosages is the preferred anticonvulsant for the treatment of generalized seizures. Carbamazepine and phenytoin should be avoided. For motor restlessness at night, chloral hydrate can be given either as capsules or as pharmacy-made syrup (concentration 10 g/100 mL). Psychotic symptoms may necessitate the expertise of a psychiatrist. Minor hallucinations can be treated with levomepromazine, while more severe conditions may require drugs such as clozapine or risperidone. Both medications are associated with serious side effects. Sportive activities should be encouraged, tandem bicycle riding being a good example. In later stages of the disease when patients refuse fluid intake because of fear of aspiration, feeding by a PEG gastrostomy tube can improve the quality of life significantly.

Unresolved questions

The pathophysiology of the disease is not yet understood, because the physiological role of the protein deficient in *CLN3* is unknown.

Adult NCL (Kufs disease)

Kufs disease is a very rare disease, the definition of which is not clear. Progressive myoclonic epilepsy, dementia, and dyskinesias are part of the clinical picture, while visual loss, typical of most childhood cases of NCL, has not been reported so far. The genetic locus is designated *CLN4*, although it is still unknown and may be heterogeneous. In two adult sisters with this NCL type, a mutation was found in the *CLN1* gene [van Diggelen *et al.* 2001]. It is a matter of debate whether the diagnosis of adult NCL can be reliably made during life. The condition is not further described here.

General diagnostic strategy in suspected cases of neuronal ceroid lipofuscinosis

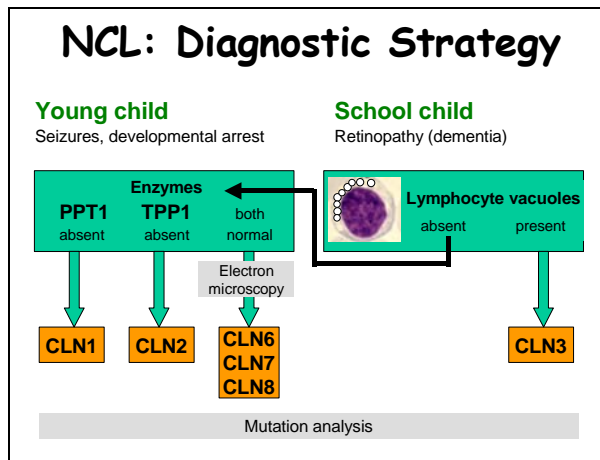


Figure 1. Diagnostic strategy in a suspected case of NCL in childhood

The diagnostic strategy strongly depends on the age of manifestation.

When onset of infantile or late infantile NCL is suspected, the enzymatic tests for CLN1 and CLN2 are always done first. A molecular genetic analysis is performed when an enzyme is deficient. Electron microscopic examination of lymphocytes or other cells is indicated when the enzymes are normal. If NCL-typical deposits are found, a search for mutations in the CLN6 or CLN8 gene should be conducted. The first step to be taken in the case of a school student with retinopathy is the search for lymphocyte vacuoles. When present, the diagnosis of CLN3 can be made, and the corresponding mutation can be searched for. If no vacuoles are found, atypical CLN1 or CLN2 mutations may be present, in which case the corresponding enzymatic tests need to be performed.

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