Biochimica et Biophysica Acta 1832 (2013) 1801–1806

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

NCL diseases — clinical perspectives ☆

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ARTICLE INFO

Article history:
Received 14 November 2012
Received in revised form 8 April 2013
Accepted 8 April 2013
Available online 17 April 2013

Keywords:
Batten
Ceroid
NCLs
Disease classification
Diagnostic algorithm

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.

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 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

☆ This article is part of a Special Issue entitled: The Neuronal Ceroid Lipofuscinoses or Batten Disease.

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0925-4439/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.bbadis.2013.04.008

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.

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