

# A Short Commentary of Neuronal Ceroid Lipofuscinoses; Phenotypes in Congenital to Preschooler

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## Abstract

The classification of neuronal ceroid lipofuscinoses (NCLs) had been clinically divided according to the age at the onset of symptoms: infantile, late infantile, juvenile and adult NCLs. However, this classification cannot always predict the causative gene; i.e., *CLN1*, for example, causes not only infantile NCL but also late onset infantile and adult NCLs. In 2012, a new classification for the NCLs that takes into account recent genetic and biochemical advances.

This short review commentary focuses on the NCLs which might cause symptoms in children from neonate to preschooler age: CLN10 (neonatal), CLN1 (6-48 months), CLN14 (8-24 months), CLN2 (1-6 years), CLN3 (4-7 years), CLN5 (4-6 years), CLN6 (18 months-8 years), CLN7 (2-7 years) and CLN8 (5-10 years). There is no fundamental therapy, but there is the trial of some cures.

**Keywords:** Neuronal ceroid lipofuscinoses; Gene; Classification; Infant; Late-infant; Preschooler

## Introduction

The neuronal ceroid lipofuscinoses (NCLs) are a group of autosomal recessive neurodegenerative disorders (other than CLN4B; autosomal dominant at adult onset [1-3] that affect from newborn to adults. NCLs have similar clinical features and the accumulation of auto fluorescent storage material. They are supposed to be the most prevalent neurodegenerative disorders of childhood. The incidence of annually affect 12,500 live-births in the European population [4] and CLN8 in Finland is 1:20,000 [5], indicating that there might be differences in incidence among countries and between urban and rural areas.

Clinical symptoms of NCLs are characterized by a progressive decline of cognitive and motor capacities, retinopathy evolving into blindness, variable cerebellar atrophy and myoclonic epilepsy, but there are some atypical forms, which visual impairment is not apparent, extra pyramidal sing stand out, and symptoms are not progressive.

NCLs had been classified by disease onset as infantile, late-infantile, juvenile and adult types. But the same gene causes different disease in different age groups, which named variant types. Genetic studies revealed that NCLs represent different diseases caused by mutations at least 14 different genes. Therefore, new nomenclature is needed. By Williams and More [6], NCLs are re-classified by "clinical, molecular genetics, biological, and morphologic interests", form disease caused by *CLN1* to *CLN14*. The function problems are divided into two groups; 1) the genes encoding lysosomal enzymes and 2) the genes encoding membrane proteins of unknown function.

Each type of CLN has ultrastructural pathological hallmarks, Neuron of, i.e., *CLN1* has granular osmiophilic deposits, *CLN2* has curvilinear profiles and *CLN7* has rectilinear profiles. However, appearance frequency by the biopsy is different by genotype [7]. Therefore, diagnose by genes are crucial for treating, educating clinical courses and mechanisms of abnormalities for CLN patients and families [7-9]. Here we review NCLs whose symptoms appear from congenital to preschooler age.

## Commentary

### CLN10

Patients with CLN10, the earliest onset form of NCL, is congenital

[10,11]. Its specific clinical symptoms are microcephaly due to brain atrophy, absence of neonatal reflexes and respiratory insufficiency. Infants with CLN10 disease rarely live more than a few days. The causal gene is located at 11p15.5 (*CLN10/CTSD*) [10,11]. Mutations in *CLN10* cause a deficiency in the activity of the lysosomal enzyme of the aspartic protease cathepsin D. Late infantile-onset and juvenile-onset forms have also been reported [11].

### CLN1

Patients with CLN1 are born and develop normally before clinical symptoms appear, typically at around 12 months. The causal gene is located at 1p34.2. They have retinal degeneration, abnormal involuntary movements (myoclonic and dystonic), rapid speech and motor deterioration, and less prominent seizures. Visual loss occurs but is not obvious because of profound cognitive impairment. A fundoscopic examination at a glance is normal in the early stages of the disease, but an electroretinogram (ERG) shows a decrease in amplitude in a and b waves, a decrease in the voltage in electroencephalography recordings (EEG) by age one [12], and premature death at two to six years of age. Brain magnetic resonance image (MRI) abnormalities -thalamic hypointensity to the white matter, the basal ganglia and thin periventricular high signal rims - are detectable in the very early stage of the disease and generalized cerebral atrophy progress rapidly. There is a decrease in the activity of palmitoyl protein thioesterase 1 (PPT-1) enzyme, which acts as a lysosomal serine lipase with a classical  $\alpha/\beta$  hydrolase, and examination by electron microscope reveals granular osmiophilic deposits (GRODs) on the rectal neurons [13]. Therefore, CLN1 can be diagnosed by measuring the PPT-1 enzyme activity in the lysosome and homozygote mutation or compound heterozygote

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in *CLN1*. Late infantile, juvenile, and adult-onset forms have also been reported [7,8].

#### CLN14

Patients with *CLN14* have early-onset progressive myoclonic epilepsy that was initially described in Mexican families but has also been reported in other ethnic groups. The age of onset is usually 8 to 24 months; patients initially present with intractable seizures, followed by myoclonic movement, progressive motor deterioration, and with or without intracellular inclusions. Visual loss also occurs [14]. Causal gene is located at 7q11 (*CLN14/KCTD7*). The *CLN14* causes changes in function of the potassium channel tetramerization domain-containing protein 7 (*KCTD7*), which is present in the cytoplasm and peripherally associated with cellular membranes. Electron microscopy studies of lymphocytes show lysosomal storage material of fingerprint-like proteins (FP) and GRODs. Only an infantile form has been reported [14].

#### CLN2

*CLN2* is the classic late infantile-onset form. Patients with *CLN2* are more homogeneous than *CLN1*, both in age of onset and clinical phenotype [15]. Classic *CLN2* disease presents between ages 1 to 4 years. Development is normal until psychomotor regression beginning in the second year of life, followed by refractory epilepsy. The seizures associated with *CLN2* take multiple forms and include myoclonic, tonic, atypical absence and tonic-clonic. Involuntary movements (ataxia, myoclonus or spastic quadriparesis) occur. Myoclonus may be severe and refractory to medications. Visual loss occurs but is less obvious for the same reason as in *CLN1*. ERG is effective to evaluate visual acuity. Patients with onset after four years of age have a milder course with more prominent ataxia and less prominent seizures. The causal gene is located at 11p15 (*CLN2*), which encodes for tripeptidyl peptidase 1 (TPP1) [15,16], a soluble lysosomal enzyme protein. Examination by electron microscope reveals curvilinear profiles (CL) in neurons. *CLN2* can be diagnosed by measurement of the TPP1 enzyme activity in the lysosomes, homozygote mutation or compound heterozygote in *CLN2*. Juvenile form has also been reported [17].

#### CLN3

Patients with *CLN3* include late infantile-onset forms of NCLs. Clinical symptom of the late infantile-onset forms appears between four to seven years, with insidious, but rapidly progressive, visual loss. Children with juvenile NCL likely have normal visual function but macular degeneration is consistent in accordance with disease progression. The clinical symptoms are insidious, but sometimes take a rapidly progressive course. Cognitive decline, then behavioral problems and seizures follow. *CLN3* is accompanied by a characteristic severe dysarthria that usually develops after age 10. At the age of late teens, Parkinsonism without tremor sometimes appeared [18,19]. Cardiac conduction abnormalities have been reported in older individuals [20]. The causal gene is located at 16p11 (*CLN3*). Examination by electron microscope reveals curvilinear profiles (CL) and rectilinear profiles (RL) in neurons of central nervous system (CNS). *CLN3* encodes proteins that localize either to the lysosomes or to the endoplasmic reticulum (ER) of unknown function. The classic juvenile-onset form is typical for *CLN3* [21].

#### CLN5

Patients with *CLN5* is a variant of late infantile-onset forms of NCL, with age of onset varying from four to 17 years. Many patients have

been described in Finnish families, but it has also been reported in other ethnic groups [22]. Clinical features include psychomotor regression, involuntary movements (ataxia and myoclonus), progressive myoclonic epilepsy, and visual decline. The causal gene is located at 13q22 (*CLN5*). The *CLN5* encodes a soluble lysosomal glycoprotein of unknown function. Examination by electron microscope reveals rectilinear profiles (RF), CL and FP in neurons of CNS. *CLN5* can be diagnosed by homozygote mutation or compound heterozygote in *CLN5* [19]. Juvenile and adult forms have also been reported [23,24].

#### CLN6

Patients with *CLN6* is a variant of late infantile-onset NCL. Like *CLN5*, the age of onset is highly variable, clinically and genetically heterogeneous groups [25]. The clinical features include visual decline, motor developmental delay, dysarthria, ataxia, and seizures. Seizures are an early feature in *CLN6*, occurring before 5 years in more than 60% of patients. Early visual loss is reported in 50% of patients. There is rapid deterioration, and death usually occurs between 5 years and 12 years of age. The causal gene is located at 15q21-23 (*CLN6*). The *CLN6* encodes a transmembrane protein of an endoplasmic reticulum of unknown function [7]. Examination by electron microscope reveals FP and GRODs in lysosomes. *CLN6* mutations of adult-onset (Kufs) disease (formerly *CLN4*) have been reported. Kufs disease has been sub-classified into two types [25]. Type A begins with a progressive myoclonic epilepsy, with later development of dementia and ataxia. Visual loss is not apparent. Type B is characterized by dementia with cerebellar and/or extrapyramidal motor symptoms [7]. Precise of the disease is not understood.

#### CLN7

Patients with *CLN7* is a variant of late infantile-onset NCL, known as Turkish NCL due to its initial description in Turkish families [26]. Although clinically is rather uniform, variant late-infantile onset forms are genetically heterogeneous [24]. The age of onset is typically between 2 and 7 years. Initial symptoms are typically seizures, followed by motor decline, myoclonus, and dementia. Visual impairment is usually present. The causal gene is located at 4q28.1-28.2, which may effects as a major facilitator superfamily domain containing eight (*CLN7/MFSD8*). Precise mechanism of *MFSD8* is unknown [26,27]. Examination by electron microscope reveals RL and FP in CNS lysosomes. A juvenile-onset form has also been reported [27].

#### CLN8

Patients with *CLN8* are another variant of late infantile-onset NCL that was initially described in Turkish families, but has also been reported in other ethnic groups [28,29]. The age of onset is usually 5 to 10 years. Patients initially present with seizures, followed by progressive motor and cognitive decline. Visual loss also occurs. The causal gene is located at 8p32 (*CLN8*). The *CLN8* mutation caused a change in transmembrane protein of the endoplasmic reticulum which may work as an endoplasmic reticulum-Golgi intermediate complex, but its real function is unknown [18,30]. A second form, referred to as Northern epilepsy, is also characterized by seizures with cognitive and motor decline and unapparent visual impairment. Examination by electron microscope reveals CL-like architecture and FP in CNS lysosomes.

#### Conclusion

It is supposedly easy to diagnose NCL if patients have the typical clinical signs and their causes are known enzymes, such as cathepsin D, PPT1 or TPP1 for *CLN10*, *CLN1* and *CLN 2*, respectively, although it

might be difficult to diagnose the variant types of CLN by conservative clinical and histopathologic examinations. Therefore, if patients have deterioration with some feature of the NCLs in preschooler age, we recommend an examination of whole-exome sequencing on DNA for the nine genes described above. There is no fundamental therapy, but ongoing studies have provided some evidence of improved in NCLs [16].

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