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Classification and Natural History of the Neuronal Ceroid Lipofuscinoses

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Abstract

The neuronal ceroid lipofuscinoses represent a group of disorders characterized by neurodegeneration and intracellular accumulation of an auto-fluorescent lipopigment (ceroid lipofuscin). Together, they represent the most prevalent class of childhood neurodegenerative disease. The neuronal ceroid lipofuscinoses encompass several distinct biological entities that vary in age of onset, specific neurological phenotype, and rate of progression. In this review, we describe 9 major forms and present a classification scheme. Understanding the age of onset, clinical features, and natural history can inform rational diagnostics. Better knowledge the natural histories of these disorders is necessary to shed light on the underlying pathobiology and to develop new therapeutics.

Keywords

Batten Disease; Neurodegeneration; Blindness; Dementia; Epilepsy; Movement Disorders

The neuronal ceroid lipofuscinoses represent a group of disorders characterized by neurodegeneration and intracellular accumulation of an auto-fluorescent lipopigment. Together, they represent the most prevalent class of childhood neurodegenerative disease.¹ The neuronal ceroid lipofuscinoses encompass several distinct biological entities that vary in age of onset, specific neurological phenotype, and rate of progression. Substantial progress has been made toward identifying the genetics of the neuronal ceroid lipofuscinoses and understanding the pathobiology of some forms. However, clinical recognition and diagnosis remains challenging.

The first description of a neuronal ceroid lipofuscinosis in the medical literature was by Otto Christian Stengel.² He described a juvenile-onset disorder with blindness and progressive dementia. In 1903, Frederick Batten described a similar clinical entity and was the first to describe the neuropathology of “cerebral degeneration with macular changes.”³ In 1905, Spielmeyer⁴ and Vogt⁵ reported a similar disorder. Hence, juvenile neuronal ceroid lipofuscinosis is often referred to eponymously as Batten-Spielmeyer-Vogt disease. Within a few years, Janský⁶ and Bielschowsky⁷ described a somewhat similar disorder but with a “late-infantile” onset. This form came to be known as late-infantile neuronal ceroid lipofuscinosis or Janský-Bielschowsky disease. Subsequently, Kufs described an adult-onset disease with similar pathological characteristics but without the vision loss that was so prominent in juvenile neuronal ceroid lipofuscinosis and late-infantile neuronal ceroid

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lipofuscinosis.⁸ This came to be known as adult-onset neuronal ceroid lipofuscinosis or Kufs disease. Approximately 50 years later, a distinct infantile-onset form was described by Haltia and Santavuori.^{9,10} Classic infantile neuronal ceroid lipofuscinosis is also known as Haltia-Santavuori disease.

Prior to the discovery of the causative genes, the neuronal ceroid lipofuscinoses were classified primarily by age of onset and ultrastructural abnormalities found with electron microscopy. The distinctive ultrastructural patterns are granular osmiophilic deposits in infantile neuronal ceroid lipofuscinosis, curvilinear profiles in late-infantile neuronal ceroid lipofuscinosis, fingerprint bodies in juvenile neuronal ceroid lipofuscinosis, and rectilinear profiles in adult-onset neuronal ceroid lipofuscinosis.¹¹ These 4 primary forms have common features of a neurodegenerative course with epilepsy, dementia, a movement disorder, and retinal degeneration (except adult-onset neuronal ceroid lipofuscinosis), and storage of ceroid lipofuscin in neurons. However, in addition to ultrastructural abnormalities, other features distinguish the neuronal ceroid lipofuscinoses. These include age of onset, specific clinical features, underlying cell biology and biochemistry, and rate of progression.

Several additional forms of neuronal ceroid lipofuscinosis have been described more recently with clinical and ultrastructural features that overlap those of the 4 classic forms. With the diversity of disorders now known to share some features in common with the classic neuronal ceroid lipofuscinoses, a general definition of neuronal ceroid lipofuscinosis has been proposed: “A progressive degenerative disease of the brain and, in most cases, the retina, in association with intracellular storage of material that is morphologically characterized as ceroid lipofuscin or similar.”¹ Most experts in neuronal ceroid lipofuscinosis now recommend primary classification by gene (or protein), with secondary classification by age of onset and clinical features.¹² However, a more extensive taxonomy has been proposed, including 7 axes: (1) affected gene (*CLN* gene symbol); (2) mutation diagnosis; (3) biochemical phenotype; (4) clinical phenotype; (5) ultrastructural features; (6) level of functional impairment (descriptive or using a universally recognized scoring system); and (7) other remarks (additional genetic, environmental, or clinical features).¹³ Although comprehensive, the 7-axis system is unwieldy for use in clinical practice and the authors have suggested combining axes 1 and 4 for routine use.

At least 9 genetic forms of neuronal ceroid lipofuscinosis have been identified. A few other diseases have been identified that show evidence of accumulation of ceroid lipofuscin, but there is some debate as to whether these are proper neuronal ceroid lipofuscinoses.¹⁴ This review is limited to the forms for which there is consensus regarding inclusion as a neuronal ceroid lipofuscinosis. These are summarized in Table 1. With the availability of molecular analysis, it has become increasingly clear that causative gene and mutation do not always predict phenotype either within or across genes. Furthermore, age of onset does not necessarily predict genotype. However, there are general guidelines about phenotype, including age of onset, that can guide rational diagnostic testing. In the following section, we discuss the diverse clinical presentations associated with specific gene defects. However, we also describe the disorders most commonly seen with each gene. With the exception of *CLN4* disease, all *CLNs* are recessive disorders.

CLN1 Disease

Mutations in *CLN1* cause the classic infantile-onset form. The *CLN1* gene codes for palmitoyl-protein thioesterase 1, a soluble lysosomal protein.¹⁵ In classic infantile neuronal ceroid lipofuscinosis, early development appears normal, but between 6 and 24 months there is rapid psychomotor regression, ataxia, myoclonus, seizures, and visual failure.¹⁶

Ultimately, patients become vegetative, with prominent spasticity. Visual failure is usually present by 2 years of age with optic atrophy retinal changes but no pigment aggregation. There is early extinction on the electroretinogram. In the early stages there is generalized cerebral atrophy, and hypointensity on T2-weighted images of thalamus and basal ganglia.¹⁷

Other mutations in *CLN1* can cause later-onset and longer-duration disease courses. All forms progress to premature death, but in general, the later the onset, the more protracted the course. There is a late-infantile variant of CLN1 disease that typically begins between 2 and 4 years of age. The clinical course is characterized by initial visual and cognitive decline followed by development of ataxia and myoclonus.^{18,19} A juvenile-onset form of CLN1 disease has also been described and has been referred to “juvenile neuronal ceroid lipofuscinosis with granular osmiophilic deposits.”^{19,20} The juvenile-onset form starts between the ages of 5 years and 10 years, with cognitive decline followed by seizures (7 to 17 years), motor decline (7 to 15 years), and vision loss (10 to 14 years). The vision loss in juvenile-onset CLN1 disease occurs late compared with that seen in classic juvenile neuronal ceroid lipofuscinosis (CLN3 disease). A rarer adult-onset form of CLN1 disease has been described with onset after 18 years of age, beginning with cognitive decline and depression, followed by ataxia, parkinsonism, and vision loss.^{21,22}

In all forms of CLN1 disease, granular osmiophilic deposits are present on electron microscopy and correlate with palmitoyl-protein thioesterase 1 deficiency. There is a rough association between age of onset and genotype; mutations predicted to cause severe truncation or loss of protein are more likely to be seen in infantile-onset cases.^{19,23}

CLN2 Disease

CLN2 disease is the classic late infantile-onset form. The *CLN2* gene codes for tripeptidyl peptidase 1, a soluble lysosomal protein.²⁴ CLN2 disease is more homogeneous than CLN1 disease, both in age of onset and clinical phenotype. Classic CLN2 disease presents between ages 1 and 4 years, but can start as late as 6 years.²⁵ Usually there is developmental standstill or psychomotor regression beginning in the second year of life, followed by refractory epilepsy (onset, 2 to 4 years of age). The seizures associated with CLN2 disease take multiple forms and include myoclonic, tonic, atypical absence, and tonic-clonic. Ataxia, myoclonus, and, ultimately, spastic quadriplegia follow. The myoclonus may be severe and refractory to treatment. Visual loss occurs but may be less obvious than in other forms of neuronal ceroid lipofuscinosis because of profound cognitive impairment. Retinal degeneration is most apparent in the macula, but there is no “cherry red spot.”²⁶ Electroretinograms and visual evoked potentials are abnormal. Children with onset after 4 years of age tend to have a milder course with more prominent ataxia and less prominent epilepsy.²⁷

CLN3 Disease

CLN3 disease is the classic juvenile-onset form of neuronal ceroid lipofuscinosis. The CLN3 protein is a lysosomal transmembrane protein of unknown function. There appears to be less phenotypic heterogeneity for than for other forms of neuronal ceroid lipofuscinosis.^{28,29} The typical age of onset in CLN3 disease is between 4 years and 7 years, with insidious, but rapidly progressive, vision loss. Children with juvenile neuronal ceroid lipofuscinosis likely go from having normal vision to functional blindness in a matter of months, but may retain light-dark perception for several years. Cognitive decline follows (7 to 10 years of age), then behavioral problems (8 to 10 years of age), and then seizures (10 to 12 years of age). In most patients, parkinsonism develops (11 to 13 years of age). Females have slightly later onset of vision loss but also more rapid progression than males.^{30,31}

CLN3 disease is accompanied by a characteristic severe dysarthria that usually develops after age 10 years. Cardiac conduction abnormalities have been reported in older individuals.³²

CLN4 Disease

Initially, the CLN4 designation had been reserved for classic adult-onset neuronal ceroid lipofuscinosis (NCL), or Kufs disease. However, with advances in genetic knowledge and methodology, most classic patients with adult-onset neuronal ceroid lipofuscinosis have been shown to have *CLN6* mutations. There is an autosomal dominant form of neuronal ceroid lipofuscinosis, now classified as CLN4 disease, that is due to mutation in the *DNAJC5* gene that codes for a cysteine string protein. This has also been referred to as “Parry disease,” named after the family in which it was first described.³³ This is the only autosomal dominant form of neuronal ceroid lipofuscinosis. Onset of symptoms is after age 30 years. Clinical features include ataxia, progressive dementia, seizures, and myoclonus. There is no visual loss in CLN4 disease.

CLN5 Disease

CLN5 disease is one of the “variant” late infantile-onset forms of neuronal ceroid lipofuscinosis. It has been referred to as the “Finnish variant” due to its initial description in Finland,³⁴ but it is not limited to families with Finnish heritage.³⁵ The CLN5 protein is a soluble lysosomal glycoprotein of unknown function. The age of onset in CLN5 disease varies from 4 to 17 years, with a mean of 5.6 years.³⁵ Clinical features include psychomotor regression, ataxia, myoclonic epilepsy, and visual failure, which may be a presenting sign.

CLN6 Disease

CLN6 disease is another “variant” late infantile-onset neuronal ceroid lipofuscinosis, but has recently been shown to be responsible for Type A Kufs disease. The CLN6 protein is a transmembrane protein of unknown function. Like CLN5 disease, the age of onset of CLN6 disease is highly variable, ranging from 18 months to 8 years. The clinical features include vision loss, motor developmental delay, dysarthria, ataxia, and seizures.^{36,37} Seizures are an early feature in CLN6 disease, occurring before 5 years in >60% of patients. Early vision loss is reported in 50% of patients with CLN6-related variant late infantile-onset neuronal ceroid lipofuscinosis. There is rapid deterioration and death usually occurs between 5 years and 12 years of age.

Recently, *CLN6* mutations have been shown to cause autosomal recessive Kufs disease (formerly CLN4).³⁸ Kufs disease has been sub-classified as Type A and Type B.³⁹ Type A begins with a progressive myoclonic epilepsy, with later development of dementia and ataxia. Type B is characterized by dementia with cerebellar and/or extrapyramidal motor symptoms. Age of onset for both forms is around 30 years. Neither form has visual loss. Type A is caused by *CLN6* mutations,³⁸ but the cause for Type B remains unknown.

CLN7 Disease

CLN7 disease is another “variant” late infantile-onset neuronal ceroid lipofuscinosis that has been referred to as the Turkish variant due to initial description in Turkish families.⁴⁰ However, it is not limited to individuals with Turkish ancestry. The CLN7 protein is a lysosomal membrane protein that belongs to the “major facilitator” superfamily of transporter proteins.⁴¹ The gene for this protein has also been called *MFSD8*. Age of onset for CLN7 disease is typically between 2 years and 7 years. Initial symptoms are typically

seizures, followed by motor decline, myoclonus, and dementia. Vision loss is usually present.

CLN8 Disease

CLN8 disease is due to mutations in a transmembrane protein of the endoplasmic reticulum of unknown function. Two forms of disease are associated with mutations of CLN8. The first is a “variant” late-infantile neuronal ceroid lipofuscinosis that was initially described in Turkish families,⁴² but has also been reported in other ethnic groups. Age of onset is usually 5 years to 10 years; patients initially present with seizures, followed by progressive motor and cognitive decline. Vision loss also occurs. The second form has been referred to as “Northern epilepsy,” a variant of progressive myoclonus epilepsy.⁴³ It is also characterized by seizures with cognitive and motor decline, but there is no vision loss in this form.

CLN10 Disease

CLN10 disease is a severe congenital form of neuronal ceroid lipofuscinosis, caused by mutations in the lysosomal aspartic protease cathepsin D gene (*CTSD*).⁴⁴ This is the earliest-onset form of neuronal ceroid lipofuscinosis. It presents in the neonatal period with microcephaly due to brain atrophy, absence of neonatal reflexes, and respiratory insufficiency. Infants with CLN10 disease rarely live more than a few days.

Summary

The neuronal ceroid lipofuscinoses represent a class of neurodegenerative disorders with most forms affecting children. They have several features in common that suggest biological similarities or perhaps functional interactions between involved genes. However, this has not been demonstrated. The clinical manifestations of the different neuronal ceroid lipofuscinoses differ in age of onset, order of progression, and specific symptoms. This variability suggests either differential expression of the causative genes within the central nervous system or differential vulnerability of different neuronal populations. Recognition of the typical age of onset is a useful starting point for understanding the different neuronal ceroid lipofuscinoses (Table 2). However, neuronal ceroid lipofuscinoses with similar ages of onset may have quite different presenting symptoms and natural histories. Quantitative study of the natural history in neuronal ceroid lipofuscinoses can be helpful to better understand the disorders and to inform the clinician’s diagnostic approach.⁴⁵ Ultimately, this information is required to inform neurobiological investigations and development of outcome measures for clinical trials. With rapid advances in genetics and the improving knowledge of the clinical features of these rare diseases, meaningful therapeutics may be on the horizon.

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Table 1

Classification of NCLs

Gene	Age of Onset	Chromosome	Protein	Ultrastructure
<i>CLN1</i>	Infantile, but also late-infantile, juvenile, and adult	1p32	PPT1	Granular osmiophilic deposits (GRODS)
<i>CLN2</i>	Late-infantile, but also juvenile	11p15	TPP1	Curvilinear profiles
<i>CLN3</i>	Juvenile	16p12	lysosomal transmembrane protein	Fingerprint profiles
<i>CLN4 (DNAJC5)</i>	Adult (Parry)	20q13.33	Cysteine string protein	Rectilinear profiles
<i>CLN5</i>	Late-infantile (Finnish variant)	13q22	soluble lysosomal protein	Rectilinear profiles, Curvilinear profiles, Fingerprint profiles
<i>CLN6</i>	Late-infantile Adult (Kufs Type A)	15q21	transmembrane protein of ER	Rectilinear profiles, Curvilinear profiles, Fingerprint profiles
<i>CLN7</i>	Late-infantile, Turkish variant	4q28	<i>MFSD8</i> , lysosomal membrane protein	Fingerprint profiles
<i>CLN8</i>	Late-infantile, Northern epilepsy	8q23	transmembrane protein of ER	Curvilinear profiles
<i>CLN10</i>	Congenital Later onset ?	11p15	Cathepsin D	GRODS?

ER, endoplasmic reticulum; GRODS, granular osmiophilic deposits; NCLs, neuronal ceroid lipofuscinoses.

Table 2

Characteristic Ages of Disease Onset in the NCLs

Age of Onset	NCL Gene
Congenital	<i>CLN10</i> (neonatal)
Infantile	<i>CLN1</i> (6 – 24 mos)
Late-infantile	<i>CLN1</i> (2 – 4 y)
	<i>CLN2</i> (1 – 6 y)
	<i>CLN5</i> (4 – 6 y)
	<i>CLN6</i> (18 mos – 8 y)
	<i>CLN7</i> (2 – 7 y)
	<i>CLN8</i> (5 – 10 y)
	<i>CLN1</i> (5 – 10 y)
Juvenile	<i>CLN3</i> (4 – 7 y)
	<i>CLN5</i> (7 – 17 y)
	<i>CLN1</i> (> 18 y)
Adult	<i>CLN4</i> (> 30 y)
	<i>CLN6</i> (> 25 y)

The classic forms are represented in **BOLD**.

mos, months; NCL, neuronal ceroid lipofuscinosis; y, years.