Clinical Summaries

CLN1 Disease, infantile onset and others

What is the cause?

The gene called CLN1 lies on chromosome 1. CLN1 disease is inherited as an autosomal recessive disorder, which means that both chromosomes carry mutations in the CLN1 gene, and both parents are unaffected carriers. The gene was discovered in 1995. CLN1 normally directs production of a lysosomal enzyme called Palmitoyl protein thioesterase 1 or PPT1. A deficiency of PPT1 results in abnormal storage of proteins and lipids in neurons and other cells and impaired cellular function. The cells cannot function as they should and symptoms develop.

How is it diagnosed?

The diagnosis is usually made by enzyme (PPT1) and genetic (*CLN1*) tests on blood samples. Occasionally a skin biopsy may be necessary. Granular osmiophilic deposits (GRODSs) are the characteristic storage body at the electron microscope level.

Does it have any alternative name?

CLN1 disease was first described in the 1970s in Finland and is sometimes called Haltia-Santavuori Disease, Infantile neuronal ceroid lipofuscinoses, or INCL.

How common is it?

1-2 children are diagnosed with infantile Batten disease each year in the UK. We estimate there are between 15 and 30 affected children in the UK. Children have been diagnosed in many countries although when the condition was first described most cases came from Scandinavian backgrounds

How does the disease progress? Genotype/phenotype correlations

Classical CLN1 disease, infantile

Babies are healthy and develop normally for the first few months of life. Towards the end of the first year, developmental progress starts to slow down. Infants may have difficulty sleeping through the night and may become more restless and irritable during the day. Some infants develop repetitive hand movements and fiddling. They often become floppy and developmental skills such as walking, standing and speech are lost. Children become less able and increasingly dependent during the toddler years. By the age of 2 years, most will have epileptic seizures and jerks. Vision gets worse until they are no longer able to see.

From about the age of three years, children are completely dependent, unable to play, feed themselves, sit independently or communicate. They may need a feeding tube and their arms and legs usually become stiff. Some children get frequent chest infections.

Death usually occurs in early to mid childhood.

CLN1 disease, juvenile

Some children with mutations in CLN1 have a later onset of symptoms and slower disease progression. Occasionally the symptoms resemble those of children with mutations in the CLN3 gene and juvenile onset disease, with onset around 5-6 years of age. They present with behavioural difficulties and early visual deterioration followed by seizures in mid-childhood. Death commonly occurs in the teenage years.

CLN1 disease, variant late infantile and adult types.

A wide variety of age at symptom onset and disease progression is seen with mutations in CLN1.

CLN2 disease, late-infantile

What is the cause?

The gene called CLN2 lies on chromosome 11. CLN2 disease is inherited as an autosomal recessive disorder, which means that both chromosomes carry mutations in the CLN2 gene, and both parents are unaffected carriers. The gene was discovered in 1998. CLN2 normally directs production of a lysosomal enzyme called tripeptidyl peptidase1 or TPP1. A deficiency of TPP1 results in abnormal storage of proteins and lipids in neurons and other cells and impaired cellular function. The cells cannot function as they should and symptoms develop.

How is it diagnosed?

The diagnosis is usually made by enzyme (TPP1) and genetic (*CLN2*) tests on blood samples. Occasionally a skin biopsy may be necessary. Curvilinear bodies (CVB) are the characteristic storage body at the electron microscope level.

Does it have any alternative name?

CLN2 late infantile disease is sometimes called Jansky-Bielschowsky Disease or late infantile NCL (LINCL).

How common is it?

5-6 children are diagnosed with late-infantile Batten disease each year in the UK. We estimate there are between 30 and 50 affected children in the UK. Children have been diagnosed in many countries and from a variety of ethnic backgrounds.

How does the disease progress?

Children are healthy and develop normally for the first few years of life. Towards the end of the second year, developmental progress may start to slow down. Some children are slow to talk. The first definite sign of the disease is usually epilepsy. Seizures may be drops, vacant spells or motor seizures with violent jerking of the limbs and loss of consciousness. Seizures may be controlled by medicines for several months but always recur, becoming difficult to control. Children tend to become unsteady on their feet with frequent falls and gradually skills such as walking, playing and speech are lost. Children become less able, and increasingly dependent. By 4-5 years the children usually have myoclonic jerks of their limbs and head nods. They may have difficulties sleeping and become distressed around this time, often for no obvious reason. Vision is gradually lost. By the age of 6 years, most will be completely dependent on families and carers for all of their daily needs. They may need a feeding tube and their arms and legs may become stiff. Some children get frequent chest infections. Death usually occurs between the ages of 6 and 12 years (but occasionally later).

CLN3 disease, juvenile

What is the cause?

The gene called *CLN3* lies on chromosome 16 and was discovered in 1995. CLN3 disease is inherited as an autosomal recessive disorder, which means that both chromosomes carry mutations in the CLN3 gene, and both parents are unaffected carriers. This gene codes for a transmembrane protein. The nerve cells cannot function as they should and symptoms develop.

How is it diagnosed?

The diagnosis is usually made by genetic (*CLN3*) tests on blood samples. Occasionally a skin biopsy may be necessary.

Does it have any alternative name?

At the beginning of the 20th century Dr Frederick Batten described a group of disorders that now bear his name. Over time it was discovered that there were several types of the disease with similar but distinct features and ages at onset of symptoms: infantile, late infantile, juvenile, and adult. CLN3 disease is often called Batten disease, or Spielmeyer-Sjogren-Vogt disease.

How common is it?

3-4 children are diagnosed with juvenile Batten disease each year in the UK. We estimate there are between 30 and 60 affected children and young adults in the UK. Children have been diagnosed in many countries and from a variety of ethnic backgrounds.

How does the disease progress?

Children are healthy and develop normally for the first few years of life. The first sign of the disease is usually a gradual loss of vision between 4 and 7 years of age. This may be noticed first at nursery or at school. Vision changes rapidly over 6 to 12 months initially but children retain some awareness of colour and light/dark until later. By the end of primary school, children are beginning to show some difficulties with concentration, short-term memory and learning. Many are still able to attend mainstream school but may need extra learning support in the classroom. The next stage of the disease starts with the onset of epileptic seizures (average age of onset of seizures is 10 years). Often the first seizures are motor seizures with violent jerking of the limbs and loss of consciousness. Seizures may be controlled by medicines for several months or years, but always recur, eventually becoming difficult to control completely. The pattern of seizures may change over time and other seizure types may evolve, such as vacant spells and episodes of partial awareness with fiddling and muddled speech.

During the teenage years children tend to slowly become more unsteady on their feet. At around the same time speech may become repetitive and gradually more difficult to understand. Not uncommonly children become anxious and tend to worry. Some feel things, hear voices or see things that are unreal. Teenagers become less able and increasingly dependent. The course of the disease is extremely variable even for children from the same family. The teenagers and young adults are much more able some days than others, especially in terms of mobility, communication and feeding skills. The disease progresses with periods of stability which may last months or years alternating with periods of deterioration lasting several months which may be triggered by intercurrent illness.

Death usually occurs between the ages of 15 and 35 years (but occasionally later).

Variant late infantile onset NCLs: CLN5, CLN6, CLN7 and CLN8 diseases & others

What is the cause?

Late-infantile variant Batten disease is caused by a genetic mistake in one of the Batten disease genes. We now know of at least eight different genes that can cause Batten disease. Those responsible for late infantile variant are usually *CLN1, CLN5, CLN6, CLN7, CLN8 and CLN10*. These genes code for proteins which are either soluble lysosomal proteins or proteins embedded within membranes. These diseases are inherited as autosomal recessive disorders, which means that both chromosomes carry mutations in the disease gene, and both parents are unaffected carriers. The nerve cells cannot function as they should and symptoms develop.

How is it diagnosed?

The diagnosis is usually made by histological and genetic tests on blood samples. A skin biopsy may be necessary and the abnormal storage material takes on a mixed appearance with granular osmiophilic deposits (GRODS), curvilinear bodies (CVB), rectilinear profiles (RLP), and/or fingerprint profiles (FPP). The appearance of the storage material can guide the genetic diagnostic tests in some cases.

Does it have any alternative name?

Several forms of late infantile variants have been recognised since the 1980s and different names have been used: variant late infantile NCL, early juvenile NCL, Finnish variant, Turkish variant, Indian variant, Mediterranean variant NCLs and so on.

How common is it?

1-2 children are diagnosed with late-infantile variant Batten disease each year in the UK. We estimate there are between 10 and 20 affected children in the UK. Children have been diagnosed in many countries and from a variety of ethnic backgrounds.

How does the disease progress?

Children are healthy and develop normally for the first few years of life. Children with late infantile variant NCL can be very different from each other, making the disease course difficult to predict in individual cases. The first symptoms may be apparent within the first few years of life but may ne develop until after school entry. Challenging behaviour is common especially in retrospect. Slowing of developmental progress, epilepsy and later loss of thinking and learning skills should prompt diagnostic investigations, especially where vision may also be deteriorating. Vision is gradually lost at some stage but this is variable. Some children will be completely dependent on their families and carers for all their daily needs by the age of six years whereas others will lose their walking and talking much later.

Death usually occurs in childhood or during the teenage years.

CLN8 Disease, EPMR and late infantile variant

What is the cause?

The gene called CLN8 lies on chromosome 8. CLN8 disease is inherited as an autosomal recessive disorder, which means that both chromosomes carry mutations in the CLN8 gene, and both parents are unaffected carriers. The gene was discovered in 1999. CLN8 normally directs production of a protein that is embedded in internal cell membranes. The cells cannot function as they should and symptoms develop.

How is it diagnosed?

The diagnosis is usually made by histological and genetic (*CLN8*) tests on blood samples. A skin biopsy may be necessary. The characteristic storage bodies at the electron microscope level often show a mixture of fingerprint profiles (FPP) and curvilinear bodies (CVB).

How does the disease progress? Genotype/phenotype correlations

Epilepsy with Progressive Mental Retardation (EPMR) or Northern Epilepsy

This disease is caused by mutations in CLN8 but has seldom been described outside Scandinavian countries. Symptoms usually start between the ages of 5 and 10 years, with seizures. Cognitive decline occurs at around the same time. Seizure frequency increases until puberty. Cognitive deterioration is more rapid during puberty. Behavioural disturbances can occur, eg: irritability, restlessness, inactivity and these features may continue into adulthood. Epilepsy is partially responsive to treatment. The number of seizures decreases spontaneously after puberty, even with no change in treatment, and by the second-third decade they become relatively sporadic. Cognitive decline continues and in some cases loss of speech has been reported. Motor function is also impaired. In a number of cases, visual acuity is reduced (without evidence of retinal degeneration). The disease has a chronic course and survival to the sixth or seventh decade has been reported. EPMR is very unusual amongst the NCLs of childhood onset in this respect.

CLN8 disease, variant late infantile

All children have developmental delay before the onset of symptoms at 2 -7 years of age: myoclonic seizures and an unsteady gait are commonly the initial symptoms; other seizures follow soon after. Cognitive decline and visual impairment usually occur. Behavioural abnormalities are frequent. Rapid disease progression with loss of cognitive skills is observed over two years from the time of diagnosis. By the age of 8-10 years severe deterioration of neurological and cognitive skills is apparent together with medication resistant epilepsy. Spasticity, dystonic posturing, tremors, and other extrapyramidal signs are also observed commonly. In the second decade of life children are unable to walk or stand without support. The life-expectancy of children affected by this disease is not yet known. The eldest patients known are now in their second decade, and their general health remains good.

CLN10 disease, congenital, neonatal and late infantile

This is a very rare form of NCL and only a small number of cases have been written about. There may be undiagnosed cases.

What is the cause?
This disease is caused by mutations in a gene called Cathepsin D also called CLN10, which lies on chromosome 11. CLN10 disease is inherited as an autosomal recessive disorder, which means that both chromosomes carry mutations in the CLN10 gene, and both parents are unaffected carriers. The gene was discovered in 2006. CLN10 normally directs production of a lysosomal enzyme called cathepsin D. If no enzyme is produced, symptoms start very early in life, or even before birth. If some enzyme is working, symptoms develop later and disease progression is slower.

How is it diagnosed?
The diagnosis is usually made by enzyme (CTSD) and genetic (*CLN10*) tests on blood samples. Occasionally a skin biopsy may be necessary. Granular deposits are the characteristic storage body at the electron microscope level.

How does the disease progress? Genotype/phenotype correlations

CLN10 disease, congenital
Seizures occur before birth. In the newborn period the babies have refractory seizures and apnoeas. Babies may die within the first weeks of life.

CLN10 disease, late infantile
Some children with mutations in CLN10 have a later onset of symptoms and slower disease progression, like variant late infantile NCL. Children become unsteady, develop seizures and visual impairment. Later they lose skills.

Adult onset NCLs

Adult NCL is very rare although affected families have been described from several different countries. Adult NCL has often been called Kufs disease and doctors recognise two main types – called type A and type B. Unlike the childhood NCLs, vision is not affected in either type. In some families inheritance is recessive but in others a dominant inheritance pattern is seen. Until the genetic basis for the adult NCLs is fully understood, diagnosis is usually dependent on a brain biopsy. It is emerging that several genes can cause adult onset NCL diseases, some of which have been presented at this meeting.

Type A presents in early adulthood with a progressive myoclonic epilepsy, ataxia and slow cognitive deterioration over many years.

Type B usually presents with an early dementia or evolving movement disorder.

Mild mutations in childhood NCL genes may also cause NCL disease with delayed age of onset and slow disease progression but vision is generally affected and abnormal storage is seen more reliably in peripheral tissues.