CLN1 Disease, Juvenile
CLN1 Disease, Adult

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What are Neuronal Ceroid Lipofuscinoses (NCLs)?

These refer to several different genetic life-limiting neurodegenerative diseases that share similar features. Although the different forms of NCL are sometimes described according to the age of the child, young person or adult at the onset of the disease, they are actually classified according to the gene identified as the cause e.g. CLN1 (gene) disease, infantile (age of onset) and CLN3 (gene) disease, juvenile (age of onset).

What causes NCL?

Since the first genes causing NCL were identified in 1995, over 400 mutations in 14 different genes have been described that cause the various forms of NCL disease. Our cells contain thousands of genes that are lined up along chromosomes. Human cells contain 23 pairs of chromosomes (46 in total). Most genes control the manufacture of at least one protein. These proteins have different functions and include enzymes which act to speed up molecular chemical reactions. The NCLs are caused by abnormal genes, which are unable to produce the required proteins. As a result, the cells do not work properly and this leads to the development of symptoms associated with these diseases.

What specifically causes CLN1 disease?

The gene called CLN1 was discovered in 1995 and lies on chromosome 1. CLN1 normally directs production of a lysosomal enzyme called Palmitoyl Protein Thioesterase 1 (PPT1). A deficiency in PPT1 results in abnormal storage of proteins and lipids (fats) in neurons (nerve cells) and other cells. The cells cannot function properly and this leads to the development of the symptoms associated with CLN1 disease.

Although rarer in occurrence, CLN1 disease may also present with later ages of onset (late-infantile, juvenile and adult).

The onset of the disease for the Juvenile and Adult forms is much later in life than the infantile form and the diseases progresses more slowly. For most, life expectancy will reach adulthood.

The exact role and the impact of PPT1 within the cell and how this loss of function leads to the devastating neurodegenerative effects for all forms of CLN1 disease is not precisely understood.

However, mutations or “mistakes” in the CLN1 gene which leave higher residual enzyme activity, that is enzyme which is “working” although not as efficiently as in healthy individuals, give rise to the later onset and/or the slower progressing forms of the disease.

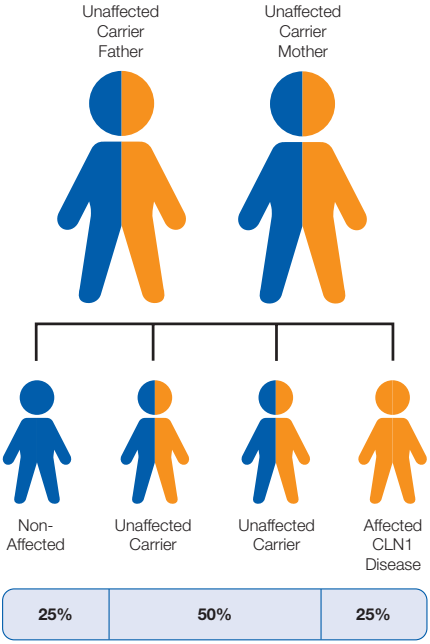
How are NCLs inherited?

Most forms of NCL are inherited as “autosomal recessive” disorders. This is one of several ways that a trait, disorder, or disease can be passed down through families. An autosomal recessive disorder means that both copies of the gene are abnormal (one inherited from

each parent) with neither working properly. The disease does not depend on the sex of an individual.

What are the chances of inheriting CLN1 disease?

CLN1 disease is inherited as an autosomal recessive disorder, which means that both chromosomes carry mutations in the CLN1 gene. Therefore both biological parents of a child with this diagnosis will be carriers of the disease but physically unaffected by it.



A child born to parents who both carry the autosomal recessive mutation in the CLN1 gene, has a 25% (1 in 4) chance of inheriting the abnormal malfunctioning genes from both parents and developing CLN1 disease.

They will have a 50% (1 in 2) chance of inheriting one abnormal gene, which would make them a carrier who is unaffected by the disease. There is a 25% (1 in 4) chance of the child being born with two normal genes and therefore being non-affected (not a carrier).

When it is known that both parents are carriers of the abnormal gene, we refer to there being a 2 in 3 chance of a child being a carrier, once it is established that they are unaffected by the disease. With any pregnancy, the probability of a child inheriting one or both genes from their parents is the same each time, irrespective of any sibling's status.

How is it diagnosed?

Symptoms such as cognitive decline, psychiatric problems, ataxia, visual problems may occur and be the first indications of an underlying health problem. Further investigations will probably have been undertaken to look for the cause of these symptoms.

Diagnosis can be confirmed by the specific enzyme test for PPT1 if requested. Some patients will be diagnosed initially by genetic testing, using a gene panel. Approximately 15% of those affected by CLN1 disease have onset as juveniles and only 2% in late teenage years or as adults.

What are the symptoms and how does the disease progress?

CLN1 disease, Juvenile onset, resembles classic CLN3 disease. Loss of vision and learning difficulties may become evident between 5-7 years. Epilepsy usually develops later and loss of motor function may become evident earlier than in CLN3 disease.

CLN1 disease, Adult onset is very rare, and the age of onset has been reported to cover a wide period. This can be from late teenage years or as late as the 3rd decade of life. The first indications can be psychiatric symptoms followed by slowly progressive cognitive decline, cerebellar ataxia and parkinsonism.

The degree, severity and age of onset of vision problems can be very variable and difficult to predict.

Are there any treatments?

Currently there is no cure for CLN1 disease and therefore specialist symptom management and therapy is essential to assist in maintaining a good quality of life for children, young people and adults affected by all forms of CLN1 disease and their families.

Epilepsy can be difficult to treat and therefore attaining complete control of seizures is not always possible.

What research is being done?

Research into possible methods for treating the disease is ongoing with current consideration of several possible therapeutic strategies being investigated. These focus mainly on methods that may replenish the activity of the PPT1 enzyme or compensate for its loss of function. These include the use of neural stem cells and gene therapy directed to the Central Nervous System (CNS).

Stem cell therapy relies upon the fact that stem cells can develop into other cells and these new cells could then produce the missing enzyme, PPT1.

Gene therapy is an experimental treatment where the aim is to introduce a healthy copy of a defective (abnormal) gene into the patient cells. As PPT1 is an enzyme, research is also being undertaken into Enzyme Replacement Therapy (ERT) administered to the CNS.

Small molecule therapies are also being investigated using compounds, or drugs, which may mimic the function of the enzyme.

For updates and information regarding developments in research please visit the BDFA website:

www.bdfa-uk.org.uk or contact the **BDFA Scientific Officer** via **0800 046 9832** email: **research@bdfa-uk.org.uk**

Where can I get additional information and support?

The BDFA offers support to any family member, friend, professional or organisation involved in caring for a child, young person or adult with CLN1 disease or any other form of NCL throughout the UK. We provide informed guidance and assistance as well as seeking to increase awareness of the disease and facilitate future research to identify potential therapies and ultimately a cure.

We organise conferences, workshops and are able to arrange connections with other affected families. The BDFA also coordinates a Small Grants Scheme that can provide assistance for a range of needs.

The BDFA has a Support & Advocacy Partner who is able to assist with many of the issues highlighted in this document and can discuss each of them in greater detail and on a more personal basis.

They can be contacted via our Freephone Helpline: **0800 046 9832** or email: **support@bdfa-uk.org.uk**

The BDFA can provide information on a number of local and national organisations who are also able to offer various forms of support and information that will be relevant to families.

It may also be appropriate for a referral to be made to a local children's or adult hospice service, as this can offer an additional experienced and skilled source of holistic support.

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