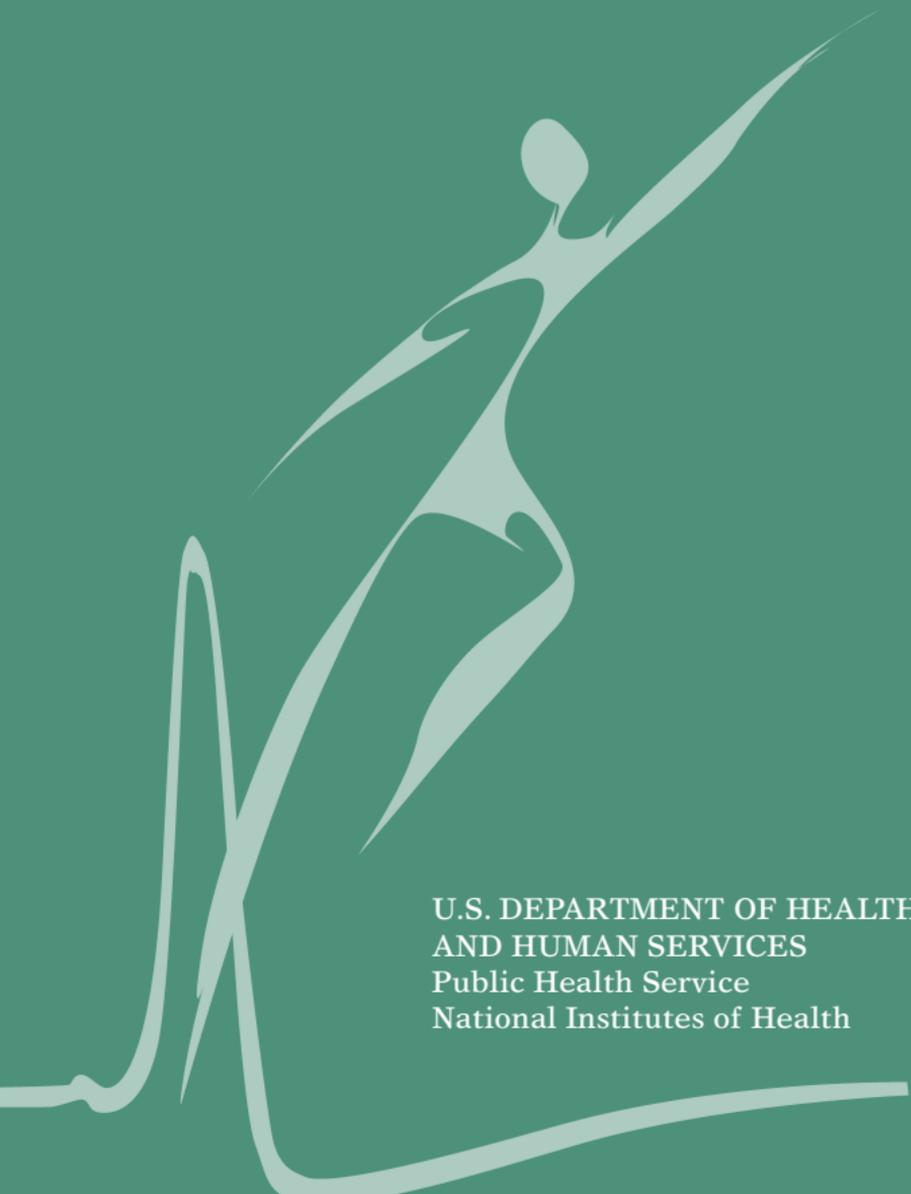


# Batten Disease

*and other Neuronal  
Ceroid Lipofuscinoses*



U.S. DEPARTMENT OF HEALTH  
AND HUMAN SERVICES  
Public Health Service  
National Institutes of Health



# Batten Disease

## *and other Neuronal Ceroid Lipofuscinoses*

### What is Batten disease?

**B**atten disease is a fatal, inherited disorder of the nervous system that typically begins in childhood. Early symptoms of this disorder usually appear between the ages of 5 and 10 years, when parents or physicians may notice a previously normal child has begun to develop vision problems or seizures. In some cases the early signs are subtle, taking the form of personality and behavior changes, slow learning, clumsiness, or stumbling. Over time, affected children suffer mental impairment, worsening seizures, and progressive loss of sight and motor skills. Eventually, children with Batten disease become blind, bedridden, and demented. Batten disease is often fatal by the late teens or twenties.

Batten disease is named after the British pediatrician who first described it in 1903. Also known as Spielmeier-Vogt-Sjögren-Batten disease, it is the most common form of a group of disorders called the neuronal ceroid lipofuscinoses, or NCLs. Although Batten disease originally referred specifically to the juvenile form of NCL (JNCL), the term Batten disease is increasingly used by pediatricians to describe all forms of NCL.

## What are the other forms of NCL?

**T**here are four other main types of NCL, including three forms that begin earlier in childhood and a very rare form that strikes adults. The symptoms of these childhood types are similar to those caused by Batten disease, but they become apparent at different ages and progress at different rates.

- Congenital NCL is a very rare and severe form of NCL. Babies have abnormally small heads (microcephaly) and seizures, and die soon after birth.
- Infantile NCL (INCL or Santavuori-Haltia disease) begins between about ages 6 months and 2 years and progresses rapidly. Affected children fail to thrive and have microcephaly. Also typical are short, sharp muscle contractions called myoclonic jerks. These children usually die before age 5, although some have survived in a vegetative state a few years longer.
- Late infantile NCL (LINCL, or Jansky-Bielschowsky disease) begins between ages 2 and 4. The typical early signs are loss of muscle coordination (ataxia) and seizures that do not respond to drugs. This form progresses rapidly and ends in death between ages 8 and 12.
- Adult NCL (also known as Kufs disease, Parry's disease, and ANCL) generally begins before age 40, causes milder symptoms that progress slowly, and does not cause blindness. Although age of

death varies among affected individuals, this form does shorten life expectancy.

There are also “variant” forms of late-infantile NCL (vLINCL) that do not precisely conform to classical late-infantile NCL.

### How many people have these disorders?

**B**atten disease and other forms of NCL are relatively rare, occurring in an estimated 2 to 4 of every 100,000 live births in the United States. These disorders appear to be more common in Finland, Sweden, other parts of northern Europe, and Newfoundland, Canada. Although NCLs are classified as rare diseases, they often strike more than one person in families that carry the defective genes.

### How are NCLs inherited?

**C**hildhood NCLs are autosomal recessive disorders; that is, they occur only when a child inherits two copies of the defective gene, one from each parent. When both parents carry one defective gene, each of their children faces a one in four chance of developing NCL. At the same time, each child also faces a one in two chance of inheriting just one copy of the defective gene. Individuals who have only one defective gene are known as carriers, meaning they do not develop the disease, but they can pass the gene on to their own children. Because the mutated genes that are involved in certain forms of Batten disease are known, carrier detection is possible in some instances.

Adult NCL may be inherited as an autosomal recessive or, less often, as an autosomal dominant disorder. In autosomal dominant inheritance, all people who inherit a single copy of the disease gene develop the disease. As a result, there are no unaffected carriers of the gene.

### What causes these diseases?

**S**ymptoms of Batten disease and other NCLs are linked to a buildup of substances called lipofuscins (lipopigments) in the body's tissues. These lipopigments are made up of fats and proteins. Their name comes from the technical word *lipo*, which is short for "lipid" or fat, and from the term *pigment*, used because they take on a greenish-yellow color when viewed under an ultraviolet light microscope. The lipopigments build up in cells of the brain and the eye as well as in skin, muscle, and many other tissues. The substances are found inside a part of cells called lysosomes. Lysosomes are responsible for getting rid of things that become damaged or are no longer needed and must be cleared from inside the cell. The accumulated lipopigments in Batten disease and the other NCLs form distinctive shapes that can be seen under an electron microscope. Some look like half-moons, others like fingerprints. These deposits are what doctors look for when they examine a skin sample to diagnose Batten disease. The specific appearance of the lipopigment deposits can be useful in guiding further diagnostic tests that may identify the specific gene defect.

To date, eight genes have been linked to the varying forms of NCL. Mutations of other genes in NCL are likely since some individuals do not have mutations in any of the known genes. More than one gene may be associated with a particular form of NCL. The known NCL genes are:

*CLN1*, also known as *PPT1*, encodes an enzyme called palmitoyl-protein thioesterase 1 that is insufficiently active in Infantile NCL.

*CLN 2*, or *TPP1*, produces an enzyme called tripeptidyl peptidase 1—an acid protease that degrades proteins. The enzyme is insufficiently active in Late Infantile NCL (also referred to as CLN2).

*CLN3* mutation is the major cause of Juvenile NCL. The gene codes for a protein called CLN3 or battenin, which is found in the membranes of the cell (most predominantly in lysosomes and in related structures called endosomes). The protein's function is currently unknown.

*CLN5*, which causes variant Late Infantile NCL (vLINCL, also referred to as CLN5), produces a lysosomal protein called CLN5, whose function has not been identified.

*CLN6*, which also causes Late Infantile NCL, encodes a protein called CLN6 or linclin. The protein is found in the membranes of the cell (most predominantly in a structure called the endoplasmic reticulum). Its function has not been identified.

*MFSD8*, seen in variant Late Infantile NCL (also referred to as CLN7), encodes the MFSD8 protein that is a member of a protein family called the *major facilitator superfamily*. This superfamily is involved with transporting substances across the cell membranes. The precise function of MFSD8 has not been identified.

*CLN8* causes progressive epilepsy with mental retardation. The gene encodes a protein also called CLN8, which is found in the membranes of the cell—most predominantly in the endoplasmic reticulum. The protein's function has not been identified.

*CTSD*, involved with Congenital NCL (also referred to as CLN10), encodes cathepsin D, a lysosomal enzyme that breaks apart other proteins. A deficiency of cathepsin D causes the disorder.

### How are these disorders diagnosed?

**B**ecause vision loss is often an early sign, Batten disease may be first suspected during an eye exam. An eye doctor can detect a loss of cells within the eye that occurs in the childhood forms of NCL. However, because such cell loss occurs in other eye diseases, the disorder cannot be diagnosed by this sign alone. Often an eye specialist or other physician who suspects NCL may refer the child to a neurologist for additional testing.

In order to diagnose NCL, the neurologist needs the individual's medical and family history and information from various laboratory tests. Diagnostic tests used for NCLs include:

- *blood or urine tests.* These tests can detect abnormalities that may indicate Batten disease. For example, elevated levels of a chemical called dolichol are found in the urine of many individuals with NCL. The presence of vacuolated lymphocytes—white blood cells that contain holes or cavities (observed by microscopic analysis of blood smears)—when combined with other findings that indicate NCL, is suggestive for the juvenile form caused by CLN3 mutations.
- *skin or tissue sampling.* The doctor can examine a small piece of tissue under an electron microscope. The powerful magnification of the microscope helps the doctor spot typical NCL deposits. These deposits are common in skin cells, especially those from sweat glands.
- *electroencephalogram or EEG.* An EEG uses special patches placed on the scalp to record electrical currents inside the brain. This helps doctors see telltale patterns in the brain's electrical activity that suggest an individual has seizures.
- *electrical studies of the eyes.* These tests, which include visual-evoked responses and electroretinograms, can detect various eye problems common in childhood NCLs.

- *diagnostic imaging using computed tomography (CT) or magnetic resonance imaging (MRI).* Diagnostic imaging can help doctors look for changes in the brain's appearance. CT uses x-rays and a computer to create a sophisticated picture of the brain's tissues and structures, and may reveal brain areas that are decaying, or "atrophic," in persons with NCL. MRI uses a combination of magnetic fields and radio waves, instead of radiation, to create a picture of the brain.
- *measurement of enzyme activity.* Measurement of the activity of palmitoyl-protein thioesterase involved in CLN1, the acid protease involved in CLN2, and, though more rare, cathepsin D activity involved in CLN10, in white blood cells or cultured skin fibroblasts (cells that strengthen skin and give it elasticity) can be used to confirm or rule out these diagnoses.
- *DNA analysis.* If families where the mutation in the gene for CLN3 is known, DNA analysis can be used to confirm the diagnosis or for the prenatal diagnosis of this form of Batten disease. When the mutation is known, DNA analysis can also be used to detect unaffected carriers of this condition for genetic counseling. If a family mutation has not previously been identified or if the common mutations are not present, recent molecular advances have made it possible to sequence all of the known NCL genes, increasing the chances of finding the responsible mutation(s).

## Is there any treatment?

**A**s yet, no specific treatment is known that can halt or reverse the symptoms of Batten disease or other NCLs. However, seizures can sometimes be reduced or controlled with anticonvulsant drugs, and other medical problems can be treated appropriately as they arise. At the same time, physical and occupational therapy may help patients retain function as long as possible.

Some reports have described a slowing of the disease in children with Batten disease who were treated with vitamins C and E and with diets low in vitamin A. However, these treatments did not prevent the fatal outcome of the disease.

Support and encouragement can help patients and families cope with the profound disability and dementia caused by NCLs. Often, support groups enable affected children, adults, and families to share common concerns and experiences.

Meanwhile, scientists pursue medical research that could someday yield an effective treatment.

## What research is being done?

**T**he National Institute of Neurological Disorders and Stroke, a part of the National Institutes of Health, is the Federal government's leading supporter of biomedical research on the brain and central nervous system. As part of its mission, the NINDS conducts research and supports studies through grants to major medical institutions across the country. Through the work of several scientific teams, the search for the molecular basis of the NCLs is gathering speed.

Studying the lipopigment deposits that contain fats and proteins, one NINDS-supported scientist, using animal models of NCL, found that a large portion of this built-up material is a protein called *subunit c*. This protein is normally found inside the cell's mitochondria, small structures that produce the energy cells need to do their jobs. Scientists are now working to understand what role this protein may play in NCL, including how this protein accumulates inside diseased cell and whether its accumulation—or the accumulation of other components in the storage material—is harmful to the cell. An important aspect of these studies is looking at how the different gene mutations lead to the lipoprotein deposits, which may involve the same processes.

In addition, research scientists are working with NCL animal models to improve understanding and treatment of these disorders. These include naturally occurring sheep and dog models, and genetically engineered mouse models. Simpler models in lower organisms (such as yeast, zebrafish, and the fruit fly) are useful tools that are being implemented by scientists to study the function of the NCL proteins, most of which remain unknown. Research suggests that many of the NCL genes have conserved functions in the lower organisms; in other words, they work the same way in yeast, fly, or zebrafish cells as they do in humans. Because mice and lower organisms breed or propagate quickly and can be genetically manipulated, their use can speed NCL research.

More recently, advances in human cell research will assist the translation of findings in the model organisms to individuals with NCL disorders. Skin or other cell types taken from those with an NCL disorder can now be manipulated in the laboratory to become “pluripotent,” meaning they can be made into cells that have the potential to become any cell type—including brain cells. This process—known as cellular reprogramming—is used to establish patient-derived induced pluripotent stem cells (iPS cells).

Although no therapies are currently available for NCL disorders, a number of NINDS-funded science teams are working toward developing therapies and identifying therapy targets for NCL. The approaches undertaken by scientists include:

- gene therapy (for example, in CLN1 and CLN2)
- enzyme replacement therapy (CLN1 and CLN2)
- stem cell therapy
- identification of the normal protein functions that are lost as a result of the gene mutations
- testing candidate drugs that modify known disease abnormalities (for example, immune suppression to eliminate the observed autoimmunity in JNCL/CLN3); and
- screening to identify drugs or other factors that normalize cellular abnormalities in the NCL disease models.

## How can I help research?

**T**he NINDS supports two national human brain specimen banks. These banks supply investigators around the world with tissue from patients with neurological and psychiatric diseases. Both banks need brain tissue from Batten disease patients to enable scientists to study this disorder more intensely. Prospective donors or their families should contact:

### **Human Brain and Spinal Fluid Resource Center**

Neurological Research (127A)  
W. Los Angeles Healthcare Center  
11301 Wilshire Boulevard  
Building 212, Room 16  
Los Angeles, CA 90073  
310-268-3536  
24-hour pager: 310-636-5199  
*[www.loni.ucla.edu/uclabrainbank](http://www.loni.ucla.edu/uclabrainbank)*

### **Harvard Brain Tissue Resource Center**

McLean Hospital  
115 Mill Street  
Belmont, MA 02478  
617-855-2400  
800-BRAIN-BANK (800-272-4622)  
*[www.brainbank.mclean.org](http://www.brainbank.mclean.org)*

Two organizations not funded by the NINDS also provide research scientists with nervous system tissue from individuals with neurological disorders. Interested donors should write or call:

**National Disease Research Interchange**

8 Penn Center, 15th floor

1628 JFK Boulevard

Philadelphia, PA 19103

215-557-7361

800-222-NDRI (6374)

*www.ndriresource.org*

**University of Miami**

**Miller School of Medicine**

Brain Endowment Bank

1501 NW 9th Avenue, Room 4013 (D4-5)

Miami, FL 33136

305-243-6219

800-UM-BRAIN (862-7246)

*http://brainbank.med.miami.edu*

**Where can I get more information?**

**F**or more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

**BRAIN**

P.O. Box 5801

Bethesda, MD 20824

800-352-9424

*www.ninds.nih.gov*

Information on Batten disease is also available from the following organizations:

**Batten Disease Support and  
Research Association**

120 Humphries Drive, Suite 2  
Reynoldsburg, OH 43068  
740-927-4298  
800-448-4570  
*www.bdsra.org*

**Children's Brain Disease Foundation  
[A Batten Disease Resource]**

Parnassus Heights Medical Building  
Suite 900  
350 Parnassus Avenue  
San Francisco, CA 94117  
415-665-3003

**Nathan's Battle Foundation  
[For Batten Disease Research]**

459 South State Road 135  
Greenwood, IN 46142  
317-888-7396  
*www.nathansbattle.com*

**Hide and Seek Foundation for  
Lysosomal Storage Disease Research**

6475 East Pacific Coastal Highway  
Suite 466  
Long Beach CA 90803  
877-621-1122  
*www.hideandseek.org*







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