Batten Disease

Batten disease (Neuronal Ceroid Lipofuscinoses) is an inherited disorder of the nervous system that usually manifests itself in childhood.

Batten disease is named after the British paediatrician who first described it in 1903. It is one of a group of disorders called neuronal ceroid lipofuscinoses (or NCLs). Although Batten disease is the *juvenile* form of NCL, most doctors use the same term to describe all forms of NCL.

Early symptoms of Batten disease (or NCL) usually appear in childhood when parents or doctors may notice a child begin to develop vision problems or seizures. In some cases the early signs are subtle, taking the form of personality and behaviour changes, slow learning, clumsiness or stumbling.

Over time, affected children suffer mental impairment, worsening seizures, and progressive loss of sight and motor skills. Children become totally disabled and eventually die.

Batten disease is not contagious nor, at this time, preventable. To date it has always been fatal.

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What are the forms of NCL?

There are four main types of NCL, including a very rare form that affects adults. The symptoms of all types are similar but they become apparent at different ages and progress at different rates.

- **Infantile NCL:** (Santavuori-Haltia type) begins between about 6 months and 2 years of age and progresses rapidly. Affected children fail to thrive and have abnormally small heads (microcephaly). Also typical are short, sharp muscle contractions called myoclonic jerks. Patients usually die before age 5, although some have survived a few years longer.
- **Late infantile NCL:** (Jansky-Bielschowsky type) begins between ages 2 and 4. The typical early signs are loss of muscle co-ordination (ataxia) and seizures that do not respond to anticonvulsant drugs. This form progresses fairly rapidly and children live to between the ages 6 and 12.
- **Juvenile NCL:** (Spielmeyer-Vogt-Sjogren Batten type) begins between the ages of 5 to 10. The most frequent beginning symptom is visual failure, less common are seizures. Motor disturbances occur late in the disease. After a slowly progressive course patients usually live to late teens, early 20's or more rarely, into their 30's.
- **Adult NCL:** (Kufs or Parry's type) generally begins before the age of 40, causes milder symptoms that progress slowly, and does not cause blindness. Although age of death is variable among affected individuals, this form does shorten life expectancy.
- **Other Types:** Some children who definitely have Batten disease don't fall into any of the patterns described above. About 1 in 10 cases are not typical

of any of these groups of children. In some the disease progresses more quickly and in some slower.

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How many people have these disorders?

Batten disease and other forms of NCL are relatively rare, occurring in an estimated 4 of every 100,000 births in the United States. These disorders appear to be more common in Finland, Sweden, other parts of northern Europe, and Newfoundland, Canada. The incidence in Australia is not known precisely. Although NCLs are relatively rare, they can often strike more than one person in families that carry the defective gene. **A family can be affected by one type of NCL only.**

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How are NCLs inherited?

The cause of Batten disease lies in the chromosomes, which carry the hereditary characteristics and are found in the nuclei of somatic cells. The nucleaus of every cell in the body contains twenty-three pairs of chromosomes. Each gene represents the 'code' for a particular characteristic. In the case of Batten disease, there is an aberration in one of the genes in one pair of chromosomes.

RECESSIVE MODE OF INHERITANCE

Parents

B b B b

Siblings

B B B b B b b b

Normal Carriers Affected

Childhood NCLs are autosomal recessive disorders; that is, they occur when a child inherits two copies of the defective gene, one from each parent. When this occurs, each of their children has a one in four chance of developing NCL or 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 onto their own children.

Although there is no conclusive test yet available to identify carriers of the affected gene, recent breakthroughs in identification of the infantile and juvenile types have brought this one step closer.

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

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What causes these diseases?

The defective gene causes malfunction at a cellular level. This is manifested in a number of different ways which affect the cell chemistry and leads to a variety of clinical observations and symptoms. The exact procedure in the different types of NCLs is still not understood. One theory holds that the disease reflects a disorder of the normal degradation of membranes within neurons, leading to an abnormal disposal and accumulation of insoluble lipid-protein complexes. Another theory claims that the disease may be characterised by a disorder in lipid metabolism in the cells; i.e. lipids or fats, and their associated proteins are not processed correctly.

Research suggests that there is an abnormal production of lipid peroxides and an enzyme deficiency, probably among specific enzymes that digest membrane proteins.

This combination of problems leads to the accumulation of a yellow fluorescent pigment, *ceroid lipofuscin*, in the brain cells. At this time, the pigment is considered to be the end result of a combination of metabolic derangements and marks the progressive deterioration in brain function.

The ceroid pigment is similar biochemically to materials accumulated more slowly during the normal ageing process. In Batten disease however, the accumulation is quite rapid and destructive. The specific reasons for the loss in brain function are not known. Thus, while there are some promising leads, and some very recent breakthroughs in gene research, we still have little understanding of the specific cause or biochemical mechanism involved in Batten disease.

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Clinical course of Batten disease

Symptoms vary with each child. Early symptoms of Batten disease are confusing and not easily recognised even by medical personnel. The following is an outline of the most typical symptomatology:

- Visual impairment often progressing to complete blindness;
- Seizures, which may be frequent and difficult to control;
- Decline in cognitive function;
- Personality and behavioural changes;
- Loss of communication skills;
- Loss of fine and gross motor skills;
- Abnormal body movements;
- A general progressive deterioration.

Other symptoms that may develop include:- slowing of head growth with age in the infantile form, poor circulation in lower extremities with legs and feet cold as well as bluish-red in colour, decreased body fat and muscle mass, curvature of the spine, hyperventilation and/or breath-holding spells, difficulty in swallowing and feeding, teeth grinding and constipation.

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How are these disorders diagnosed?

Batten disease is rarely diagnosed immediately because of the variability in symptoms and age of onset. Children are often mistakenly thought to have epilepsy or a form of mental retardation. Adults are sometimes labelled schizophrenics. This can be a difficult and frustrating time for all concerned.

Vision loss is often an early sign, and therefore Batten disease may be first suspected during an eye examination. A doctor can detect a loss of cells within the eye that occurs in the three childhood forms of NCL. However, because such cell loss occurs in other eye diseases, the disorder cannot be diagnosed by this sign alone. A doctor who suspects NCL may refer the child to a neurologist, a doctor who specialises in diseases of the brain and nervous system.

In order to diagnose NCL, the neurologist needs the patient's medical 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 NCL patients.
- **skin or tissue sampling**. The doctor can examine a small piece of tissue under a electron microscope. The powerful magnification will show typical NCL deposits. These deposits are common in skin cells, especially those from sweat glands and samples may be taken from the skin or a rectal biopsy.
- **electroecephalogram 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.
- **electrical studies of the eyes**. These tests, which include visual-evoked responses and electroretinograms, can detect various eye problems common in childhood NCLs.
- **brain scans**. Imaging can help detect changes in the brain's appearance. The most commonly used imaging technique is computed tomography, or CT, which uses x-rays and a computer to create a sophisticated picture of the brain's tissues and structures. A second image technique that is increasingly common is magnetic resonance imaging, or MRI. MRI uses a combination of magnetic fields and radio waves, instead of radiation, to create a picture of the brain.

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Tests Available

An accurate diagnosis of Batten's disease and the particular type is essential before prenatal or presymptomatic tests can be done.

Carrier, prenatal and pre-genetic embryo (IVF) testing is available for the more common forms. Please liaise with your Medical Practitioner and a Geneticist for information.

Presymptomatic testing of younger children is possible using a skin or rectal biopsy, when the diagnosis in an older child has been confirmed with similar tests.

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Is there any treatment?

As yet, no specific treatment is known that can halt or reverse the symptoms of Batten disease. However, seizures can be reduced or controlled with anti-convulsant drugs, and other medical problems can be treated appropriately as they arise. At the same time, physical and occupational therapy can 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 vitamin supplements. Attention is being focussed on controlling some of the cell chemistry through dietary trials including fish oils and anti-oxidants. There are other studies also being carried out in the USA, UK, Australia and the Netherlands. However, so far these treatments have not prevented the final outcome of the disease.

Support and understanding can help patients and families cope with the profound disability and loss of cognitive function 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 (hopefully in the near future), yield an effective treatment. More government and public support are needed to provide the resources to help them.

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Recent and Current Research

Through the work of several scientific teams in different countries, the search for the genetic cause of NCLs is gathering speed.

We have moved into the next decade of research since the first breakthrough of isolating the infantile gene.

Some scientists are investigating the theory that children with Batten disease have a shortage of a key body enzyme. Investigators are searching for enzymes that might be scarce, defective, or completely missing.

Trials of treatments are a reality …. Stem Cell transplants and Gene Therapy. For more information regarding these trials, please visit the BDSRA, USA via our Contacts page. Both these trials are dependent upon public funding and support.

Many animal models are available to researchers now, such as dogs (used in Australia), cow (used in Australia), sheep (used in New Zealand), fly, worm, fish and of course, mice.

Overall, while many scientists are still trying to discover the whys of Batten Disease, several others are forging ahead developing treatments.