Review Article

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Batten Disease

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Abstract

Batten disease is extremely rare juvenile inherited disorder but it is the most common of neuronal ceroid lipofuscinoses (NCLs). It is fatal disorder that affects the nervous system. After 4 to 6 years of normal development, children with this condition develop progressive vision loss, intellectual and motor disability, behavior and personality changes, speech difficulties, and seizures. Most people with Batten disease die in their teens or early twenties. it can be diagnosed with help of Fluorescent deposits, Visual Evoked Potentials and Electroretinograms, Blood tests, Urine tests, Skin or tissue sampling, Electroencephalogram (EEG), Brain scans, Measurement of enzyme activity and DNA analysis. There is cure for Juvenile Batten disease. Therefore specialist symptom management and therapy is essential to assist in maintaining a good quality of life for children and their families. Holistic support for parents, siblings and wider family members is extremely important throughout their journey.

Keywords: Juvenile Batten Disease; Inherited Disorder; Neuronal Ceroid Lipofuscinoses (NCLs).

Introduction

Juvenile Batten disease is one of a group of progressive degenerative neurometabolic disorders, known as the neuronal ceroid lipofuscinoses (NCLs). NCLs are characterized by genetic mutations which disrupt cells' ability to dispose of wastes, resulting in the abnormal accumulation of certain proteins and lipids (fats) within the nerve cells of the brain and other tissues of the body resulting in progressive neurological impairment including developmental regression, seizures, blindness, behavior changes and dementia. *Neuronal Ceroid Lipofuscinoses (NCLs)* **is** commonly referred to as Batten disease. The Neuronal Ceroid Lipofuscinoses (NCLs) denote several different genetic life-limiting neurodegenerative diseases that share similar features. Batten disease is named after the British paediatrician who first described it in 1903 by Dr Frederik Batten.. Although Batten disease is the *juvenile* form of NCL, most doctors use the same term to describe all forms of NCL.

Synonyms

Spielmeyer-Vogt-Sjögren-Batten disease, Batten-Mayou disease, Vogt-Spielmeyer disease, neuronal ceroid lipofuscinoses (NCLs).

Common Forms of Batten Disease

There are many forms of NCL. Mutations in at least eight different genes are known to cause Batten disease . There are four main types of Batten disease each was named according to its age of onset. The symptoms of each are similar, but the age of onset and rate of progression vary.

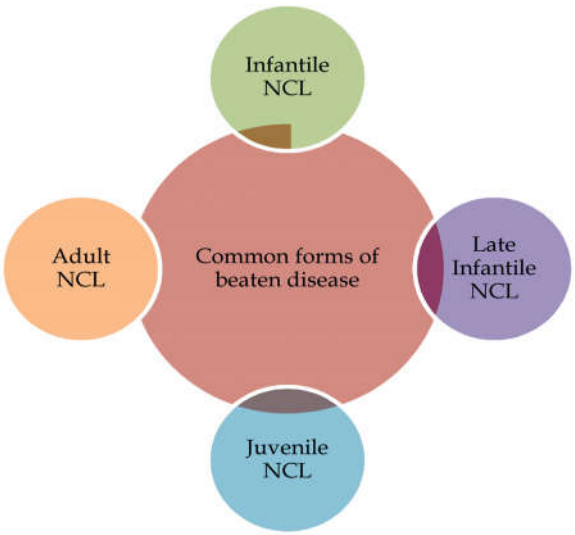

Fig. 1: Forms of beaten disease

1. Infantile NCL begins before age 2 and progresses quickly; most children live into their mid-childhood years.
2. Late infantile NCL begins between 2 to 4 years of age; the normal lifespan is 8 to 12 years.
3. Juvenile NCL begins between ages 5 and 8; the normal lifespan is teens to early 20s.
4. Adult NCL usually begins before age 40; the lifespan varies.

However, several variant late forms were discovered complicating the matter. It wasn't until the first genes associated with Batten disease were discovered that researchers learned that different mistakes in the same gene can result the same disease with various ages of onset. Like mistakes in the *CLN1* gene can cause disease beginning in the infantile, late infantile, juvenile or adult periods.

Table 1: Forms of Batten Diseases

Classic name	Gene	Gene make	Reported forms and age of onset
Infantile BD	CLN1 or PPT1	Soluble lysosomal enzyme (palmitoyl protein thioesterase 1)	CLN1 disease, infantileCLN1 disease, late infantileCLN1 disease, juvenileCLN1 disease, adult
Late infantile BD	CLN2 or TPP1	Soluble lysosomal enzyme (tripeptidyl peptidase 1)	CLN2 disease, late infantileCLN2 disease, juvenile
Juvenile BD	CLN3	Lysosomal & multi-organelle transmembrane protein (CLN3)	CLN3 disease, juvenileCLN3 disease, adult
Adult BD (or Parry or Kufs type A)	CLN4 or DNAJC5	Soluble cysteine string protein alpha (CSPa) chaperone protein affecting synapses (CSPa)	CLN4 disease, adult autosomal dominant
Finnish Variant late infantile BD	CLN5	Soluble lysosomal protein, but not an enzyme (CLN5)	CLN5 disease, late infantileCLN5 disease, juvenileCLN5 disease, adult
Variant of the late infantile BD	CLN6	Transmembrane protein, Endoplasmic Reticulum (ER) (CLN6)	CLN6 disease, late infantile
Adult, Kufs			CLN6 disease, adult Kufs type A
Turkish Variant late infantile BD	CLN7 or MFSD8	Major facilitator superfamily domain containing protein 8, Transmembrane protein; Endolysosomal transporter (CLN7/MFSD8)	CLN7 disease, late infantile
Northern Epilepsy Variant late infantile BD	CLN8	Transmembrane protein; ER, ER-Golgi intermediate complex (CLN8)	CLN8 disease, late infantileCLN8 disease, EPMR
Late Infantile NCL - Congenital BD	CLN10 or CTSD	Soluble lysosomal enzyme (Cathepsin D)	CLN10 disease, congenitalCLN10 disease, late infantileCLN10 disease, juvenileCLN10 disease, adult
	CLN11 or GRN	Progranulin	CLN11 disease, adultHeterozygous mutations cause frontotemporal lobar dementia
	CLN12 or ATP13A2	P-type ATPase	CLN12 disease, juvenileMutations also cause Kufor-Rakeb syndrome
Adult onset BD (or Kufs Type B)	CLN13 or CTSF	Soluble lysosomal enzyme (Cathepsin F)	CLN13 disease, adult Kufs type B
	CLN14 or KCTD7	Potassium channel tetramerization domain-containing protein 7	CLN14 disease, infantileMutation also causes progressive myoclonic epilepsy-3
Infantile Osteopetrosi	*CLCN7* encodes for CLC7		

Incidence

- Juvenile Batten disease is the most common type of NCL,
- Its exact prevalence is unknown.
- Commonly seen are 5 to 10 years old children.
- One in every 50,000 births in the United States.

- Collectively, all forms of NCL affect an estimated 1 in 100,000 individuals worldwide.
- Batten disease is more common in parts of northern Europe, such as Sweden or Finland. where approximately 1 in 12,500 individuals are affected.

Genetic Pattern of Batten Disease

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. Juvenile Batten diseases are mostly caused by mutations in the *CLN3* gene. A small percentage of cases are caused by mutations in other genes. This gene provides instructions for making a protein whose function is unknown.

Inheritance of Batten Disease

Batten disease is an autosomal recessive disorder, meaning that it only occurs in a child if both parents carry the genes for the disease.

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

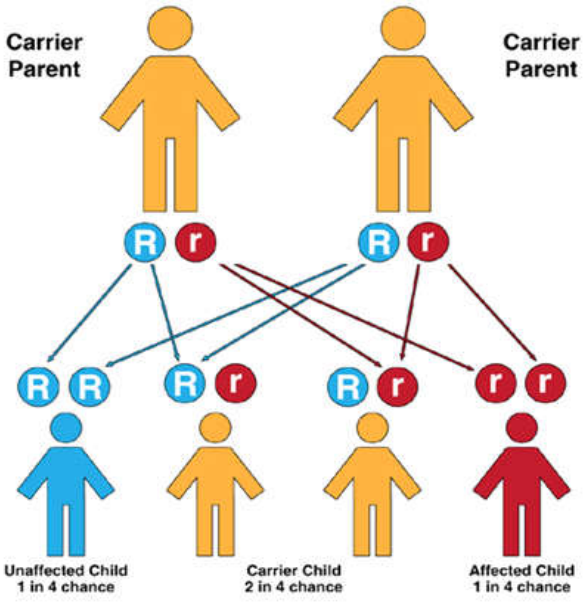

Fig. 2: Inheritance of batten disease:

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.

If a child has only one parent with the gene, that child is considered a carrier and may pass the gene on to his own child, causing Batten disease if his partner carries the gene as well.

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.

Expected Symptoms

These disorders all affect the nervous system and typically cause progressive problems with vision, movement, and thinking ability. The different types of NCLs are distinguished by the age at which signs and symptoms first appear. Some people refer to the entire group of NCLs as Batten disease, while others limit that designation to the juvenile form of the disorder.

Most people with juvenile Batten disease live into their twenties or thirties.

Children with juvenile Batten disease experience most or all of these symptoms in the following and sometimes overlapping order. However, each child is different so the exact onset and severity of symptoms cannot be predicted.

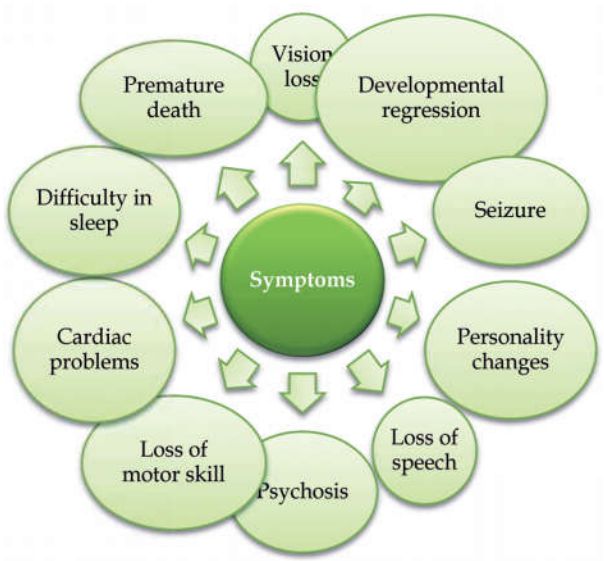

Fig. 3: Symptoms of Batten disease

1. Blindness or vision problems in previously healthy children between 5 and 10 years old. Vision impairment is often the first noticeable sign of juvenile Batten disease, beginning between the ages of 4 and 8 years. Vision loss

tends to progress rapidly, eventually resulting in blindness within 10 years.

2. After vision impairment has begun, children with juvenile Batten disease begin to fall behind in school and lose previously acquired skills (developmental regression), Intellectual decline and disability. Inability to keep up with classmates, usually beginning with the ability to speak in complete sentences. Affected children have difficulty learning new information.
3. Seizures usually begin about 9 years old but can develop at any time during the disease.
4. Subtle to more pronounced personality changes and behavioral problems beginning age 6.
5. Echolalia (repetitive speech) followed by a loss of speech.
6. Dementia, Psychosis and sometimes hallucinations.
7. Beginning usually in their teens, affected children lose motor skills starting with movement abnormalities that include rigidity or stiffness, slow or diminished movements (hypokinesia), ataxia, Parkinsonism and stooped posture. Over time, they lose the ability to walk or sit and require wheelchair assistance.
8. Potential cardiac involvement in the late teens to early 20s.
9. Affected children may have difficulty sleeping that begin in mid- to late childhood.
10. Premature death in the late teens to early 20s

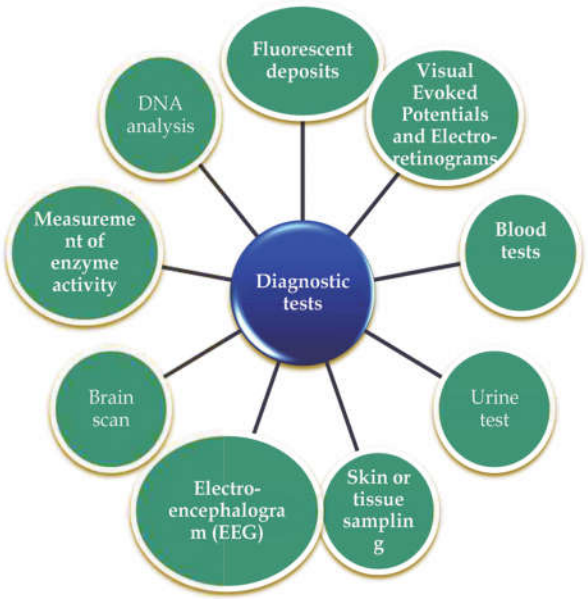

Fig. 4: Diagnostic measures

Diagnostic Methods

Juvenile and other forms of Batten disease can be diagnosed with help of combination of The following tests.

1. *Fluorescent Deposits:* The accumulation of autoflourescent ceroid lipofuscin deposits throughout the body is a hallmark sign of juvenile Batten disease. These deposits can sometimes be detected by visually examining the back of the eye. Over time, these deposits appear more pronounced, the thickness of their retina is reduced, and opthamologists see circular bands of different shades of pink and orange at the optic nerve and retina in the back of the eye. Doctors call this a "bull's eye."
2. *Visual Evoked Potentials and Electroretinograms:* These are recordings of electrical signals in the visual processing center of the brain. Several forms of NCL show some type of abnormality in these signals.
3. *Blood tests:* These tests can detect abnormalities that may indicate juvenile Batten disease, such as abnormal white blood cells (vacuolated lymphocytes), which are common in several metabolic disorders.
4. *Urine tests:* These tests can detect the presence of elevated levels of a substance called dolichol that is found in the urine of many patients with NCL.
5. *Skin or tissue sampling:* The accumulation of ceroid lipofuscin deposits throughout the body is a hallmark sign of Lysosomal Storage Diseases. These deposits can be detected by viewing skin cells under a microscope or in some cases, by visually examining the back of the eye.
6. *Electroencephalogram (EEG):* An EEG uses special patches placed on the scalp to record electrical activity inside the brain. This helps doctors see telltale patterns in the brain's electrical activity that suggest a patient has seizures and whether those seizures are typical of juvenile Batten disease or one of the other NCLs.
7. *Brain scans:* Imaging can help doctors look for changes in the brain's appearance. Two commonly used imaging techniques are computed tomography, or CT, and magnetic resonance imaging, or MRI. Both are sophisticated technologies that may be able to detect that certain brain areas are shrinking in NCL patients.
8. *Measurement of enzyme activity:* In several NCLs such as the Infantile and Late Infantile (not Juvenile) forms, certain enzymes are greatly

reduced or totally absent. Measuring the level of these enzymes in white blood or skin cells can separate JNCL from enzyme-deficient NCLs.

9. *DNA analysis:* Screening DNA blueprints obtained from blood or skin samples for mistakes in one or more of the 14 genes associated with NCL is a definitive method of diagnosing NCLs.

Inference

There can often be difficulty seeing the signs described above. For example, the interior surface of the eye can appear normal early in the disease when auto flourescent deposits are very small. Vacuolated lymphocytes and dolichols may be present at levels too low to detect in blood or urine. The only definitive diagnosis for genetic diseases like Batten is a DNA test.

Treatment

Recently there is no cure for juvenile batten disease and but treatments do exist to manage the symptoms and make the child more comfortable and supportive therapy is much essential to assist in maintaining a good quality of life for children and their families. Seizures can be controlled with antiseizure medications, and other medical problems can be treated as needed. Physical and occupational therapy can help the patient hold on to physical functioning as long as possible before the muscles atrophy.

Some studies have shown early data that doses of Vitamin C and Vitamin E can help slow the disease, though no treatment has been able to stop it from being fatal.

Comprehensive and holistic support for child, parents, siblings and wider family members is extremely important throughout their period of survival.

Recent developments in gene therapy, enzyme replacement, and drug discovery are making clinical trials for treatments in various forms of Batten disease possible.

Genetic Consideration

After knowing that a child or young person has a form of NCL some families will have younger siblings who may be affected but have not displayed any symptoms. It may also be possible that older unaffected siblings are carriers of the disease and may want to understand how this may affect their family choices when they become older.

When only one parent is a carrier of the abnormal gene, and the other is non-affected, there is a 50% chance that any child will be an unaffected carrier. In this case if parents are considering having additional children, they can access specialist advice and support from their local clinical genetics service following a referral from their Gene product. Prenatal testing may be possible in the early stages of any future pregnancy.

Practical Implications for Families

As the illness progresses, special equipments and assistive devices will become necessary.

Items are likely to include specialist seating, buggies/wheelchairs, supportive aids and equipment for visual impairment, bathing and toileting aids, hoisting equipment and a specialist bed/mattress.

Made changes in the home environment. So that it can enable the family to appropriately care for an child with the disease. These may include installing ramps, widening doorways and providing suitable floor surfaces. A purpose-built wet room with a specialist bath or shower is commonly needed and there are various other aspects that will require consideration.

Family needs continuous educational support from various professionals

Specialist support and possibly schools or colleges will often play a role at some point in each individual's journey.

Juvenile Batten disease will cause significant financial challenges as well as having emotional challenges. Many parents find they have to take on a full-time caring role, which understandably can add to the economic as well as emotional strain.

Support groups such as the Batten Disease Support and Research Association provide support and information on treatments and research. Meeting other families who have gone through the same thing or are going through the same stages can be a great support while coping with Batten disease.

Reference

1. GeneReview: Neuronal Ceroid-Lipofuscinoses
2. Pérez-Poyato MS, Milà Recansens M, Ferrer Abizanda I, Montero Sánchez R, Rodríguez-Revenga L, Cusí Sánchez V, García González MM, Domingo Jiménez R, Camino León R, Velázquez Fragua R, Martínez-Bermejo A, Pineda Marfà M. Juvenile

neuronal ceroid lipofuscinosis: clinical course and genetic studies in Spanish patients. J Inherit Metab Dis. 2011 Oct; 34(5):1083-93. doi: 10.1007/s10545-011-9323-7. Epub 2011 Apr 16.

3. Rakheja D, Narayan SB, Bennett MJ. Juvenile neuronal ceroid-lipofuscinosis (Batten disease): a brief review and update. Curr Mol Med. 2007 Sep; 7(6):603-8.
4. Batten Disease. NORD (National Organization for Rare Disorders). http://rarediseases.org/rare-diseases/batten-disease/.
5. "Batten Disease Fact Sheet." National Institute of Neurological Disorders and Stroke. http://www.ninds.nih.gov/disorders/batten/detail_batten.htm.
6. "Understanding Batten – Prognosis." Beyond Batten Disease Foundation. http://beyondbatten.org/understanding-batten/prognosis/
7. "Understanding Batten – Diagnosis/Symptoms." Beyond Batten Disease Foundation. http://beyondbatten.org/understanding-batten/diagnosis-symptoms/.
8. Neuronal ceroid lipofuscinosis: impact of recent genetic advances and expansion of the clinicopathologic spectrum. Curr Neurol. Neurosci Rep. 2013 Aug; 13(8):366.
9. Clinical trial number NCT01399047 for "Cellcept for Treatment of Juvenile Neuronal Ceroid Lipofuscinosis (JUMP)" at ClinicalTrials.gov.
10. Clinical trial number NCT00151216 for "Safety Study of a Gene Transfer Vector for Children With Late Infantile Neuronal Ceroid Lipofuscinosis" at ClinicalTrials.gov.