Department of Biochemistry

Newsletter

All India Institute of Medical Sciences,Rajkot

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This issue is dedicated to

Rare Diseases-Batten Disease

Rare diseases affect one in 17 people in their lifetime and 350 million people worldwide. Rare diseases also disproportionately impact children, and a third of those affected die before their fifth birthday.

What Is Batten Disease?

Batten disease (also known as neuronal ceroid lipofuscinosis, NCL) is a rare inherited nervous system disorder that most often begins in childhood. They interfere with a cell's ability to recycle a cellular residue called lipofuscin.

It is included in the broad category of Lysosomal storage diseases: Inborn errors of lipid metabolism (Lipid storage disorders) group of fatal genetic disorders.

There are 13 types. The disorder affects the body's ability to get rid of cellular waste (lipids and proteins), so they build up in cells all over the body. The buildup causes seizures, vision loss, problems with thinking and movement, and eventually, death. There is no cure for Batten disease.

Often, it is autosomal recessive.
Although Batten disease is usually regarded as the juvenile form of NCL (or "type 3"), some physicians use the term Batten disease to describe all forms of NCL.

Historically, the NCLs were classified by age of disease onset as infantile NCL (INCL), late infantile NCL (LINCL), juvenile NCL (JNCL), or adult NCL (ANCL).

At least 20 genes have been identified in association with Batten disease, but juvenile NCL, the most prevalent form of Batten disease, has been linked to mutations in the CLN3 gene

Signs & Symptoms

1. Early signs and symptoms usually appear around ages 2–10, with gradual onset of vision problems or seizures.
2. Early signs may be subtle personality and behavioral changes, slow learning or regression, repetitive speech or echolalia, clumsiness, or stumbling.
3. Slowing head growth in the infantile form, poor circulation in lower extremities (legs and feet), decreased body fat and muscle mass, curvature of the spine, hyperventilation and/or breath-holding spells, teeth grinding, and constipation may occur.
4. Over time, affected children experience mental impairment, worsening seizures &progressive loss of sight, speech & motor skills. Batten disease is a terminal disease; life expectancy varies depending on the type or variation.
5.
6.
7.

India-specific genes behind Batten disease

In a paper titled 'Batten disease: Biochemical and molecular characterization revealing novel PPT1 and TPP1gene mutations in Indian patients' published in December 2018 wherein Dr. Jayesh Sheth & his team from Ahmedabad discussed findings from 34 patients. Dr. Sheth's lab in Ahmedabad is the nodal centre for Batten Disease research. NCL2 subtype is more prevalent in Indian children

Diagnosis

Batten disease is rare; misdiagnosis may lead to increased medical expenses, family stress, and the chance of using incorrect forms of treatment

- Blood or urine tests - elevated levels of Dolichol in urine have been found in many individuals with NCL. The presence of vacuolated lymphocytes can also indicate Batten disease.

- **Measurement of enzyme activity specific to Batten disease may help confirm certain diagnoses caused by different mutations. Elevated levels of palmitoyl-protein thioesterase is involved in CLN1.**
  Acid protease is involved in CLN2.
  Cathepsin D is involved in CLN10

- **DNA analysis - to help confirm the diagnosis of Batten disease. When the mutation is known, DNA analysis can also be used to detect unaffected carriers of this condition for genetic counseling. Recent molecular advances have made it possible to sequence all of the known NCL genes, increasing the chances of finding the responsible mutation(s)**

Treatment

Batten disease is a terminal illness; the FDA has approved Brineura (cerliponase alfa) as a treatment for a specific form of Batten disease. Brineura is the first FDA-approved treatment to slow loss of walking ability (ambulation) in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase-1 (TPP1) deficiency.

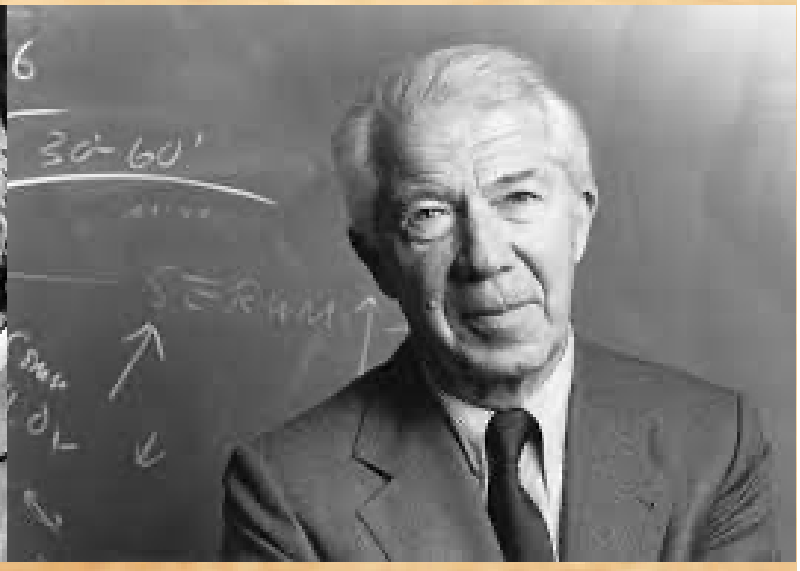
Palliative treatment is symptomatic and supportive. One drug, an antisense oligonucleotide, Milasen, described in The New England Journal of Medicine, is believed to be the first "custom" treatment for a genetic disease. It is named after Mila Makovec, the only patient who may ever take it.

Tid-Bits From History

Discovery of Lysosomes

Christian René Marie Joseph, Viscount de Duve (2 October 1917 – 4 May 2013) was a Nobel Prize-winning Belgian cytologist and biochemist

He made serendipitous discoveries of two cell organelles, peroxisome, and lysosome, for which he received the Nobel Prize in Physiology or Medicine in 1974. In addition to peroxisome and lysosome, he invented scientific names such as autophagy, endocytosis, and exocytosis in a single occasion at the Ciba Foundation Symposium on Lysosomes held in London during 12–14 February 1963, while he, "was in a word-coining mood."[



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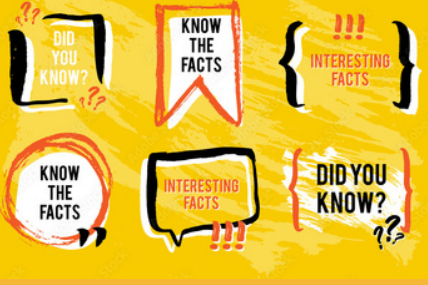
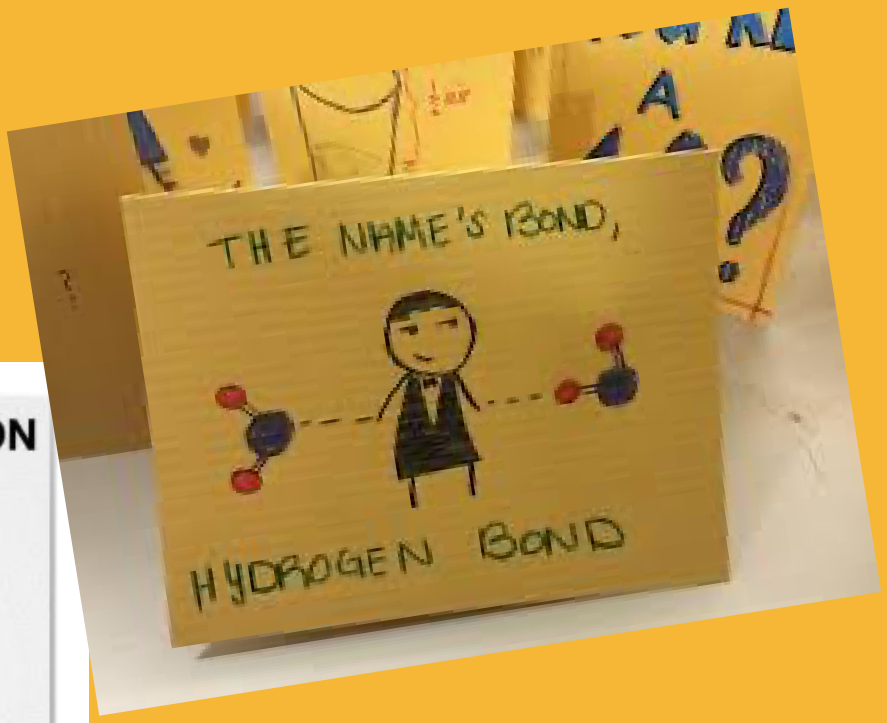
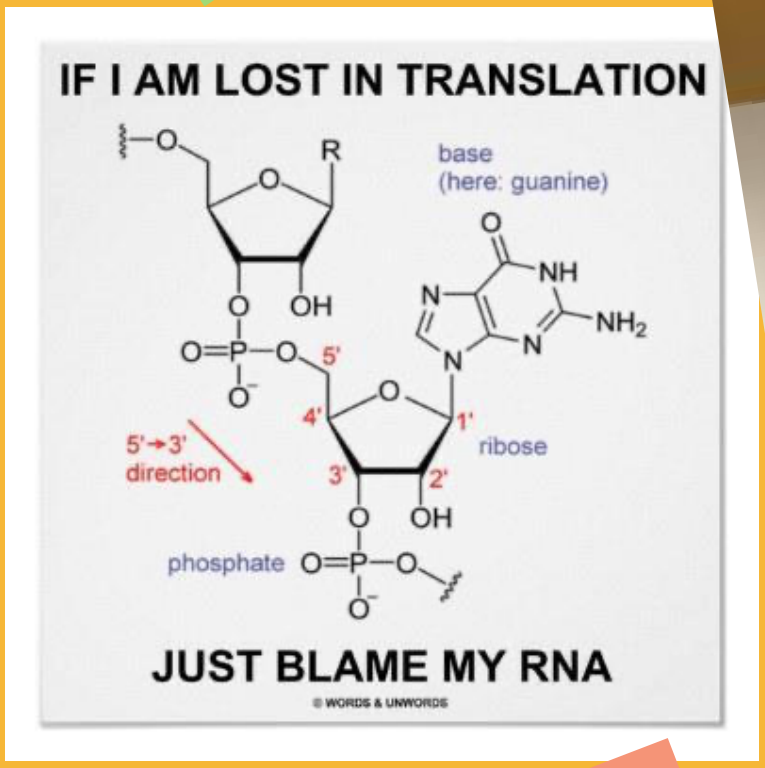
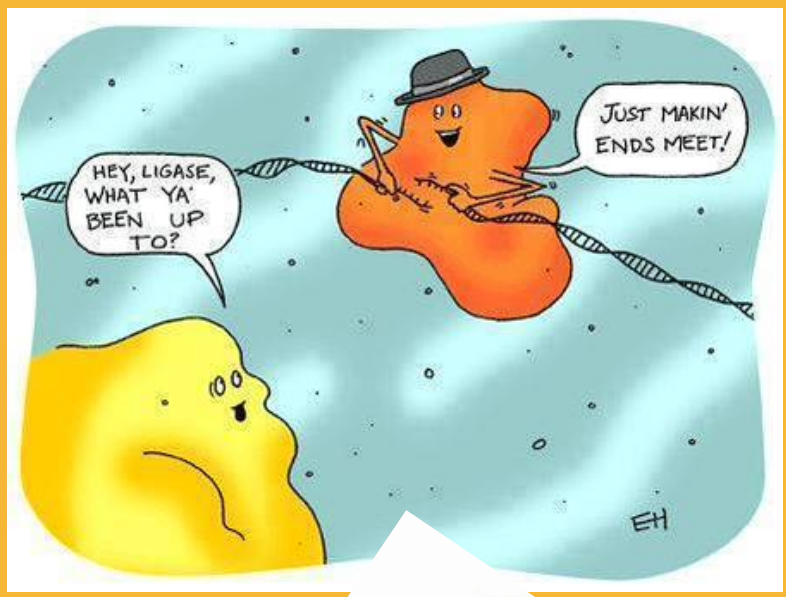


Biochemistry PUNS!!!!!







Laboratory Touch-up

Laboratory tests for Batten disease

A blood test is a minimally invasive, low cost, and rapid way to screen for Batten disease. False positive results in the absence of Batten disease are rare. To reduce the likelihood of a false negative result, it should be compared with a patient who actually has Batten disease.
Although a blood test is a reliable tool to detect certain types of Batten disease, the results of blood tests should be confirmed with a genetic test.

Genetic testing

A confirmatory way to diagnose Batten disease is through genetic testing through Next-generation sequencing (NGS)
Results usually become available within 2-8 weeks.

Enzyme tests

Sample: Venous blood or tissue sample (usually skin).

Marker enzymes: Lysosomal exopeptidase (TPP1) and lipid hydrolase (PPT1).

TPP1 enzymes are affected in patients with late infantile Batten, while PPT1 enzymes are involved in infantile Batten disease.

Significance: Severity and prognosis of the disease

Urine tests

The presence of Dolichol and ATP Synthase (to a certain extent) in urine is useful in aiding the diagnosis of Batten.

Dolichol normally exists between cell membranes. It also has been found in high concentrations in the brains of Batten patients.

Blood tests

The accumulation of lipofuscins leads to the formation of **abnormal and distinctive vacuoles**, or holes or cavities inside cells. The presence of these vacuoles can be detected with a simple blood test by analyzing a type of white blood cell, called lymphocytes, under a microscope.

Tissue biopsy, eye and brain tests (computed tomography or CT and Magnetic resonance imaging) can help, together with other diagnostic assessments, to diagnose Batten disease.

Quote of the day

When you get to the end of your rope, tie a knot and hang on.

THEODORE ROOSEVELT

UPCOMING EVENT!