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BATTEN'S DISEASE: UNDERSTANDING THE GENETIC AND MOLECULAR MECHANISMS

Neurology

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ABSTRACT

Is a group of inherited neurodegenerative disorders also called as neuronal ceroid lipofuscinoses(NCLs) characterized by the accumulation of autofluorescent material in lysosomes,leading to progressive vision loss,cognitive decline,seizures and motor impairment. It is the most common inherited neurological disease in children that can be managed by therapies like enzyme replacement therapy although a cure is still not known. This review paper provides the current understanding of Batten's Disease and its various forms which cause genetic mutations in genes, its etiology,epidemiology, pathophysiology of the disease,clinical presentation,diagnosis and its symptomatic management to slow down the progression of the disease. New emerging experimental and future approaches like gene therapy,stem cell transplants and small molecular drugs are being approached currently.

KEYWORDS

Ceroid Lipofuscinoses, CLN, Lysosomal Storage Disorder, Cognitive Decline, Vision Loss Leading to Blindness, Enzyme Replacement Therapy, Gene Therapy.

INTRODUCTION

Batten's disease(neuronal ceroid lipofuscinoses) is a group of lethal neurodegeneration lysosomal storage disorder. It usually affects children.(1)

Batten disease is named after Frederick Eustace Batten an english pediatrician and neurologist known as the father of pediatric neurology.

The disease itself is known to have 14 forms, each of them results from mutations in a distinct gene.

Each form of disease of ceroid lipofuscinosis and given a different number based on subtype- CLN1 and CLN2, each form can vary according to the levels of severity, age of onset and progression at different rates.

Genetic disorders associated with formation of toxic endo-lysosomal storage.

This disorder affects the cellular removal of a waste product known as ceroid lipofuscin, cellular accumulation of ceroid lipofuscin indicates lysosomal dysfunction.(2)

Lysosomal problems can lead to the death of neurons over a certain period of time.

Patients with NCLs generally grow and develop normally in their initial phases of life, as they reach developmental milestones at appropriate time. But at the onset of the disease, the progress in the development stops and there is a decline in the acquired skills.

Disease can be congenital(at birth), Infantile(within 1st year of life to within 6-18months), Late Infantile(2-4years of age),Juvenile onset(4-10 years of age), Late Juvenile onset(8-10 years) and adult onset(late teenage years to mid-adulthood.(3)

Etiology

Primary by genetic mutations, also could be due to autoimmune etiology.

More than 430 genes with underlying mutations in human NCLs have been found.

Some genes encode lysosomal enzymes(CLN 1,2,10,13), a soluble lysosomal protein(CLN 5), a protein in secretory pathway(CLN 11),cytoplasmic proteins peripherally associate with the membranes(CLN 4,14) and many transmembrane proteins with different subcellular locations(CLN 3,CLN 6,CLN 7,CLN 8,CLN12).

CLN 3 is caused by bi-allelic mutations, encoding a lysosomal proteins, without CLN 3 proper functions, the ceroid lipopigments accumulate in all body cells,mainly affecting the retina of the eye and the brain.(4)

Epidemiology

Can result from genetic mutations in various genes and the global prevalence is about 1 in 100,000 live births.

The epidemiology of neuronal ceroid was studied in Scandinavia which concluded maximum prevalence in Scandinavianian countries such as in Finland,Sweden and Iceland respectively.

The most common form of NCL worldwide is CLN 3 as its incidence of mutations have been reported which ranges from 0.02 to 4.8 per 100,000 worldwide, other types and forms include adult NCL(CLN 4,kufs or Parry disease) and late infantile NCL(CLN 2, tansky-bielschowsky disease), CLN 1 (Santavuori- haltia disease).(5)

Pathophysiology

Lysosomes are the part of our cells that function as a recycling center as it helps breakdown and remove fat and sugar waste. Gene mutation linked to Batten's disease cause deficiency in enzymes within lysosomes which are required for metabolic degradation removal from lysosomes through the actions of specific transport proteins in the lysosomal membrane, that due to the deficiency leads to buildup of waste in lysosomes i.e accumulation of lipoproteins complex known as lipofuscin that can't be degraded and can cause injuries to tissues and cell especially the Central Nervous System. The effector CLN gene determines the age of symptom onset and rate of progression.(6)

Signs and Symptoms

Progressive vision loss which leads to blindness.

Cognitive and Behavioural

- Behaviour changes, mood swings and sleep disturbances or insomnia are most common.
- Dementia and progressive cognitive decline leads to memory loss and speech and language difficulties.
- Episodes of psychosis &/or hallucinations.

Motor and Physical

- Seizures, movement problems lead to clumsiness, loss of coordination and balance issues.
- Abnormal muscle movements leading to tremors,tics,spasms and myoclonus.
- Muscle rigidity and spasticity.(7)
- Weakness can lead to paralysis.
- Difficulty swallowing &/or walking.

Other presentations- In some infantile forms microcephaly (abnormal small head), arrhythmia caused by heart problems.

DIAGNOSIS

Clinical evaluation by physical examination and medical history of the patient to assess symptoms.

Eye Examination- a test called electroretinography(ERG) to check for damage to the retina and optic nerve.

Skin and Blood Test- to measure the levels of lipopigments which can

often identify changes that signal Batten's disease which is confirmed by genetic testing.(8)

Genetic Testing- to identify mutations in specific genes associated with Batten's disease.

Biopsy- To examine tissue under microscope for the buildup of lipofuscins, which are fatty protein deposits present in Batten's disease.

Electroencephalogram- to assess brain electrical activity and to detect abnormal patterns in seizures.

Magnetic Resonance Imaging(MRI)- to visualize brain structure and identify any abnormalities to treat the underlying cause.

TREATMENT

There is no sure cure for Batten's disease but the treatment is mainly symptomatic and slows the progression of the disease in certain forms of CLN.

Symptom Management

- Anticonvulsants- Carbamazepine, oxcarbazepine, phenytoin, valproic acid, gabapentin, lamotrigene, topiramate and levetiracetam can be used.
- Antiepileptics-Isradipine is a neuroprotective agent that can help patients with neurological disorders.
- Antispasmodics-Baclofen for generalised spasticity,a high dose is needed for the patients with CLN2 due to high intensity of spasticity.(9)

Targeted Therapy

FDA approved- Enzyme Replacement Therapy(ERT) with intraventricular recombinant pro-enzyme of TPP-1 i.e Cerliponase alfa(Brineura) can slow the loss of ambulation(walking ability) in children with the CLN 2 form of disease, they require bi-weekly infusions directly into the fluid surrounding the brain.(10)

Supportive Care

- Balanced diet with adequate calorie intake.
- Sleep management- Melatonin helps to regulate the sleep and wake cycle and magnesium helps to have a relaxed sleep pattern.
- Physical rehabilitation to maintain strength and to manage pain.
- Psychological rehabilitation to provide emotional support and cognitive behavioural therapy as well.(11)

Experimental and Future Approaches

- Gene therapy is still being explored by various researchers to correct the underlying genetic defects.
- Stem cell transplants are being studied to replace the mutated gene.
- Small molecule drugs are being approached to address secondary effects of the disease.

Differential Diagnosis

To rule out other neurodegenerative diseases which have similar symptoms,metabolic disorders, infections affecting the Central nervous system such as-

- Niemann Pick type C
- Retinitis Pigmentosa
- Stargardt Disease
- Cone Rod Dystrophies

PROGNOSIS

Prognosis highly depends on the age of onset, the earlier the onset the more severe the disease can be and has higher risk of disability and early death of the patient.Most forms of the NCL are fatal diseases which reduce the life expectancy despite the adequate treatment. Most of them have an early death at about the ages 15 and 30. Most become bilaterally blind by the age 10 to 14. The adult variant may have milder symptoms and even maybe a normal life expectancy depending on the severity of the disease.

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