CLN2 Disease

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CLN2 disease is an inherited disorder that primarily affects the nervous system. The signs and symptoms of this condition typically begin between ages 2 and 4. The initial features usually include recurrent seizures (epilepsy) and difficulty coordinating movements (ataxia). Affected children also develop muscle twitches (myoclonus) and vision loss. CLN2 disease affects motor skills, such as sitting and walking, and speech development. This condition also causes the loss of previously acquired skills (developmental regression), intellectual disability that gradually gets worse, and behavioral problems. Individuals with this condition often require the use of a wheelchair by late childhood and typically do not survive past their teens.

Keywords: genetic conditions

1. Introduction

Some children with CLN2 disease do not develop symptoms until later in childhood, typically after age 4. These individuals tend to have milder features overall compared to those diagnosed earlier, but with more severe ataxia. They have a shortened life expectancy, although they tend to survive into adulthood.

CLN2 disease is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs), which may also be collectively referred to as Batten disease. All these disorders affect the nervous system and typically cause worsening problems with vision, movement, and thinking ability. The different NCLs are distinguished by their genetic cause. Each disease type is given the designation "CLN," meaning ceroid lipofuscinosis, neuronal, and then a number to indicate its subtype.

2. Frequency

In the Newfoundland province of Canada, the incidence of CLN2 disease is estimated to be 9 in 100,000 births. The incidence of the condition outside of this population is unknown. More than 300 cases worldwide have been described in the scientific literature.

3. Causes

Mutations in the *TPP1* gene cause CLN2 disease. The *TPP1* gene provides instructions for producing an enzyme called tripeptidyl peptidase 1. This enzyme is found in cell structures called lysosomes, which digest and recycle different types of molecules. Tripeptidyl peptidase 1 breaks down protein fragments, known as peptides, into their individual building blocks (amino acids).

Mutations in the *TPP1* gene greatly reduce or eliminate the production or activity of the tripeptidyl peptidase 1 enzyme. A reduction in functional enzyme results in the incomplete breakdown of certain peptides. CLN2 disease, like other NCLs, is characterized by the accumulation of proteins or peptides and other substances in lysosomes. These accumulations occur in cells throughout the body; however, nerve cells seem to be particularly vulnerable to their effects. The accumulations can cause cell damage leading to cell death. The progressive death of nerve cells in the brain and other tissues leads to the signs and symptoms of CLN2 disease.

Individuals who are diagnosed with CLN2 disease later in childhood likely have *TPP1* gene mutations that result in the production of an enzyme with a small amount of normal function. Protein function in these individuals is higher than in those who have the condition beginning earlier in childhood. As a result, it takes longer for peptides and other substances to accumulate in the lysosomes and damage nerve cells.

3.1. The Gene Associated with CLN2 Disease

- TPP1

4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- Jansky-Bielschowsky disease
- late-infantile Batten disease
- late-infantile neuronal ceroid lipofuscinosis
- LINCL
- neuronal ceroid lipofuscinosis, late-infantile

References

1. Elleder M, Dvoráková L, Stolnaja L, Vlásková H, Hůlková H, Druga R, Poupetová H, Kostálová E, Mikulástík J. Atypical CLN2 with later onset and prolongedcourse: a neuropathologic study showing different sensitivity of neuronalsubpopulations to TPP1 deficiency. Acta Neuropathol. 2008 Jul;116(1):119-24. doi:10.1007/s00401-008-0349-3.
2. Fietz M, AlSayed M, Burke D, Cohen-Pfeffer J, Cooper JD, Dvořáková L,Giugliani R, Izzo E, Jahnová H, Lukacs Z, Mole SE, Noher de Halac I, Pearce DA,Poupetova H, Schulz A, Specchio N, Xin W, Miller N. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. Mol Genet Metab. 2016 Sep;119(1-2):160-7. doi:10.1016/j.ymgme.2016.07.011.
3. Getty AL, Pearce DA. Interactions of the proteins of neuronal ceroidlipofuscinosis: clues to function. Cell Mol Life Sci. 2011 Feb;68(3):453-74. doi:10.1007/s00018-010-0468-6.
4. Kohan R, Carabelos MN, Xin W, Sims K, Guelbert N, Cismondi IA, Pons P, Alonso GI, Troncoso M, Witting S, Pearce DA, Dodelson de Kremer R, Oller-Ramírez AM,Noher de Halac I. Neuronal ceroid lipofuscinosis type CLN2: a new rationale forthe construction of phenotypic subgroups based on a survey of 25 cases in SouthAmerica. Gene. 2013 Mar 1;516(1):114-21. doi: 10.1016/j.gene.2012.12.058.
5. Moore SJ, Buckley DJ, MacMillan A, Marshall HD, Steele L, Ray PN, Nawaz Z,Baskin B, Frecker M, Carr SM, Ives E, Parfrey PS. The clinical and geneticepidemiology of neuronal ceroid lipofuscinosis in Newfoundland. Clin Genet. 2008 Sep;74(3):213-22. doi: 10.1111/j.1399-0004.2008.01054.x.
6. Schulz A, Kohlschütter A, Mink J, Simonati A, Williams R. NCL diseases -clinical perspectives. Biochim Biophys Acta. 2013 Nov;1832(11):1801-6. doi:10.1016/j.bbadis.2013.04.008.
7. Sleat DE, Gin RM, Sohar I, Wisniewski K, Sklower-Brooks S, Pullarkat RK,Palmer DN, Lerner TJ, Boustany RM, Uldall P, Siakotos AN, Donnelly RJ, Lobel P.Mutational analysis of the defective protease in classic late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. Am J HumGenet. 1999 Jun;64(6):1511-23. Erratum in: Am J Hum Genet. 2004 Dec;75(6):1158.