CLCN2-Related Leukoencephalopathy

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CLCN2-related leukoencephalopathy is a disorder that affects the brain. People with this condition have neurological problems that become apparent anytime from childhood to adulthood; the problems generally do not worsen much over time. Most affected individuals have difficulty with coordination and balance (ataxia) but can walk without support, and many have frequent headaches. Individuals diagnosed in childhood usually also have learning disabilities, while those whose symptoms begin in adulthood typically also have vision problems. These vision problems are due to breakdown of the light-sensing tissue at the back of the eyes (retinopathy) or degeneration (atrophy) of the optic nerves, which carry information from the eyes to the brain. Some affected individuals have mild muscle stiffness (spasticity). Affected males are unable to father children (infertile).

Keywords: genetic conditions

1. Introduction

Rarely, affected individuals have dizziness (vertigo), ringing in the ears (tinnitus), hearing loss, episodes of abnormal movements (paroxysmal kinesigenic dyskinesia), or psychiatric disorders. However, it is unclear whether these are features of *CLCN2*-related leukoencephalopathy or coincidental findings.

The neurological problems in *CLCN2*-related leukoencephalopathy are caused by abnormalities in the brain. People with this condition have leukoencephalopathy, an abnormality of the brain's white matter that can be detected with medical imaging. White matter consists of nerve fibers covered by a fatty substance called myelin. Myelin insulates nerve fibers and promotes the rapid transmission of nerve impulses. In affected individuals, the myelin becomes fluid-filled (edematous), impairing nerve impulse transmission.

2. Frequency

The prevalence of *CLCN2*-related leukoencephalopathy is unknown. At least 16 cases have been reported in the scientific literature.

3. Causes

As its name suggests, *CLCN2*-related leukoencephalopathy is caused by mutations in the *CLCN2* gene. The *CLCN2* gene provides instructions for making a chloride channel called ClC-2. This channel transports negatively charged chlorine atoms (chloride ions) across cell membranes and plays a key role in a cell's ability to generate and transmit electrical signals. ClC-2 channels are embedded within the outer membrane of most cells, and their function is thought to be particularly important in nerve cells (neurons) in the brain. The ClC-2 channel regulates the size (volume) of neurons by playing a role in their intake and release of water as well as maintaining a normal balance of ions in cells.

Some *CLCN2* gene mutations impair the stability of the protein, which reduces channel function. Other *CLCN2* gene mutations lead to the production of a channel protein that is trapped inside the cell and cannot get to the cell membrane, or that is nonfunctional and quickly broken down. These types of mutations cause a complete loss of ClC-2 channel function.

As a result of this reduction in ClC-2 channel activity, certain brain cells and the myelin that surrounds neurons become filled with too much water and cannot function properly. Fluid-filled myelin cannot transmit nerve impulses effectively, resulting in neurological problems such as ataxia and the other signs and symptoms of *CLCN2*-related leukoencephalopathy.

3.1. The Gene Associated with CLCN2-Related Leukoencephalopathy

- CLCN2

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

- CC2L
- leukoencephalopathy with ataxia
- leukoencephalopathy with mild cerebellar ataxia and white matter edema
- leukoencephalopathy with white matter edema
- LKPAT

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