Citrullinemia

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Citrullinemia is an inherited disorder that causes ammonia and other toxic substances to accumulate in the blood. Two types of citrullinemia have been described; they have different signs and symptoms and are caused by mutations in different genes.

genetic conditions

1. Introduction

Type I citrullinemia (also known as classic citrullinemia) usually becomes evident in the first few days of life. Affected infants typically appear normal at birth, but as ammonia builds up, they experience a progressive lack of energy (lethargy), poor feeding, vomiting, seizures, and loss of consciousness. Some affected individuals develop serious liver problems. The health problems associated with type I citrullinemia are life-threatening in many cases. Less commonly, a milder form of type I citrullinemia can develop later in childhood or adulthood. This later-onset form is associated with intense headaches, blind spots (scotomas), problems with balance and muscle coordination (ataxia), and lethargy. Some people with gene mutations that cause type I citrullinemia never experience signs and symptoms of the disorder.

Type II citrullinemia chiefly affects the nervous system, causing confusion, restlessness, memory loss, abnormal behaviors (such as aggression, irritability, and hyperactivity), seizures, and coma. Affected individuals often have specific food preferences, preferring protein-rich and fatty foods and avoiding carbohydrate-rich foods. The signs and symptoms of this disorder typically appear during adulthood (adult-onset) and can be triggered by certain medications, infections, surgery, and alcohol intake. These signs and symptoms can be life-threatening in people with adult-onset type II citrullinemia.

Adult-onset type II citrullinemia may also develop in people who as infants had a liver disorder called neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). This liver condition is also known as neonatal-onset type II citrullinemia. NICCD blocks the flow of bile (a digestive fluid produced by the liver) and prevents the body from processing certain nutrients properly. In many cases, the signs and symptoms of NICCD go away within a year. In rare cases, affected individuals develop other signs and symptoms in early childhood after seeming to recover from NICCD, including delayed growth, extreme tiredness (fatigue), specific food preferences (mentioned above), and abnormal amounts of fats (lipids) in the blood (dyslipidemia). This condition is known as failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD). Years or even decades later, some people with NICCD or FTTDCD develop the features of adult-onset type II citrullinemia.

2. Frequency

Type I citrullinemia is the most common form of the disorder, affecting about 1 in 57,000 people worldwide. Type II citrullinemia is found primarily in the Japanese population, where it occurs in an estimated 1 in 100,000 to 230,000 individuals. Type II also has been reported in other populations, including other people from East Asia, the Middle East, the United States, and the United Kingdom.

3. Causes

Mutations in the *ASS1* and *SLC25A13* genes cause citrullinemia. The proteins produced from these genes play roles in the urea cycle. The urea cycle is a sequence of chemical reactions that takes place in liver cells. These reactions process excess nitrogen that is generated when protein is used by the body. The excess nitrogen is used to make a compound called urea, which is excreted in urine.

Mutations in the *ASS1* gene cause type I citrullinemia. This gene provides instructions for making an enzyme, argininosuccinate synthase 1, that is responsible for one step of the urea cycle. Mutations in the *ASS1* gene reduce the activity of the enzyme, which disrupts the urea cycle and prevents the body from processing nitrogen effectively. Excess nitrogen (in the form of ammonia) and other byproducts of the urea cycle accumulate in the bloodstream. Ammonia is particularly toxic to the nervous system, which helps explain the neurologic symptoms (such as lethargy, seizures, and ataxia) that are often seen in type I citrullinemia.

Mutations in the *SLC25A13* gene are responsible for adult-onset type II citrullinemia, NICCD, and FTTDCD. This gene provides instructions for making a protein called citrin. Within cells, citrin helps transport molecules used in the production and breakdown of simple sugars, the production of proteins, and the urea cycle. Molecules transported by citrin are also involved in making nucleotides, which are the building blocks of DNA and its chemical cousin, RNA. Mutations in the *SLC25A13* gene typically prevent cells from making any functional citrin, which inhibits the urea cycle and disrupts the production of proteins and nucleotides. The resulting buildup of ammonia and other toxic substances leads to the signs and symptoms of adult-onset type II citrullinemia. A lack of citrin also leads to the features of NICCD and FTTDCD, although ammonia does not build up in the bloodstream of individuals with these conditions.

Because citrullinemia is caused by problems with the urea cycle, it belongs to a class of genetic diseases called urea cycle disorders.

3.1. The Genes Associated with Citrullinemia

- ASS1
- SLC25A13

4. Inheritance

Both types of citrullinemia are inherited in an autosomal recessive pattern, which means both copies of the respective 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

- CIT
- citrullinuria

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