Methylmalonic Acidemia with Homocystinuria

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Methylmalonic acidemia with homocystinuria is an inherited disorder in which the body is unable to properly process protein building blocks (amino acids), certain fats (lipids), and a waxy fat-like substance called cholesterol.

genetic conditions

1. Introduction

Individuals with this disorder have a combination of features from two separate conditions, methylmalonic acidemia and homocystinuria. The signs and symptoms of the combined condition, methylmalonic acidemia with homocystinuria, usually develop in infancy, although they can begin at any age.

When the condition begins early in life, affected individuals typically have an inability to grow and gain weight at the expected rate (failure to thrive), which is sometimes recognized before birth (intrauterine growth retardation). These infants can also have difficulty feeding and an abnormally pale appearance (pallor). Neurological problems are also common in methylmalonic acidemia with homocystinuria, including weak muscle tone (hypotonia) and seizures. Most infants and children with this condition have an unusually small head size (microcephaly), delayed development, and intellectual disability. Less common features of the condition include eye problems and a blood disorder called megaloblastic anemia. Megaloblastic anemia occurs when a person has a low number of red blood cells (anemia), and the remaining red blood cells are larger than normal (megaloblastic). The signs and symptoms of methylmalonic acidemia with homocystinuria worsen over time, and the condition can be life-threatening if not treated.

When methylmalonic acidemia with homocystinuria begins in adolescence or adulthood, the signs and symptoms usually include psychiatric changes and cognitive problems. Affected individuals can exhibit changes in their behavior and personality; they may become less social and may experience hallucinations, delirium, and psychosis. In addition, these individuals can begin to lose previously acquired mental and movement abilities, resulting in a decline in school or work performance, difficulty controlling movements, memory problems, speech difficulties, a decline in intellectual function (dementia), or an extreme lack of energy (lethargy). Some people with methylmalonic acidemia with homocystinuria whose signs and symptoms begin later in life develop a condition called subacute combined degeneration of the spinal cord, which leads to numbness and weakness in the lower limbs, difficulty walking, and frequent falls.

2. Frequency

The most common form of the condition, called methylmalonic acidemia with homocystinuria, cblC type, is estimated to affect 1 in 200,000 newborns worldwide. Studies indicate that this form of the condition may be even more common in particular populations. These studies estimate the condition occurs in 1 in 100,000 people in New York and 1 in 60,000 people in California. Other types of methylmalonic acidemia with homocystinuria are much less common. Fewer than 20 cases of each of the other types have been reported in the medical literature.

3. Causes

Methylmalonic acidemia with homocystinuria can be caused by mutations in one of several genes: *MMACHC*, *MMADHC*, *LMBRD1*, *ABCD4*, or *HCFC1*. Mutations in these genes account for the different types of the disorder, which are known as complementation groups: cblC, cblD, cblF, cblJ, and cblX, respectively.

Each of the above-mentioned genes is involved in the processing of vitamin B12, also known as cobalamin or Cbl. Processing of the vitamin converts it to one of two molecules, adenosylcobalamin (AdoCbl) or methylcobalamin (MeCbl). AdoCbl is required for the normal function of an enzyme that helps break down certain amino acids, lipids, and cholesterol. AdoCbl is called a cofactor because it helps the enzyme carry out its function. MeCbl is also a cofactor, but for another enzyme that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds.

Mutations in the *MMACHC*, *MMADHC*, *LMBRD1*, *ABCD4*, or *HCFC1* gene affect early steps of vitamin B12 processing, resulting in a shortage of both AdoCbl and MeCbl. Without AdoCbl, proteins and lipids are not broken down properly. This defect allows potentially toxic compounds to build up in the body's organs and tissues, causing methylmalonic acidemia. Without MeCbl, homocysteine is not converted to methionine. As a result, homocysteine builds up in the bloodstream and methionine is depleted. Some of the excess homocysteine is excreted in urine (homocystinuria). Researchers have not determined how altered levels of homocysteine and methionine lead to the health problems associated with homocystinuria.

Mutations in other genes involved in vitamin B12 processing can cause related conditions. Those mutations that impair only AdoCbl production lead to methylmalonic acidemia, and those that impair only MeCbl production cause homocystinuria.

3.1. The Genes Associated with Methylmalonic Acidemia with Homocystinuria

- ABCD4
- HCFC1
- LMBRD1
- MMACHC
- MMADHC

4. Inheritance

Methylmalonic acidemia with homocystinuria is usually 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.

When caused by mutations in the *HCFC1* gene, the condition is inherited in an X-linked recessive pattern. The *HCFC1* gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

5. Other Names for This Condition

- methylmalonic acidemia and homocystinemia
- methylmalonic acidemia and homocystinuria
- methylmalonic aciduria and homocystinuria
- vitamin B12 metabolic defect with combined deficiency of methylmalonyl-coA mutase and homocysteine:methyltetrahydrofolate methyltransferase
- vitamin B12 metabolic defect with combined deficiency of methylmalonyl-coA mutase and methionine synthase activities

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