

Physician's Guide to  
**The Homocystinurias**





*This booklet is the eleventh in a series of free publications for physicians and other medical professionals. It is NORD's hope that patients and their families will benefit from this and other efforts to enhance awareness of the almost 7,000 rare diseases affecting an estimated 30 million Americans.*

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NORD's Rare Disease Database and Organizational Database may be accessed at [www.rarediseases.org](http://www.rarediseases.org).

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## What is homocystinuria?

The homocystinurias is a general term for a group of disorders that cause elevated levels of the amino acid homocystine in the urine. These disorders primarily occur because of deficiency of any of several enzymes required for the proper degradation or reformation of an essential amino acid called methionine. Elevated levels of homocysteine and abnormal levels of methionine can cause a variety of health problems.

The three primary homocystinurias are genetic metabolic disorders:

1. Classic homocystinuria (homocystinuria due to cystathionine ( $\beta$ -synthase deficiency)
2. Methylene tetrahydrofolate reductase (MTHFR) deficiency
3. Homocystinuria due to cobalamin (vitamin B<sub>12</sub>) metabolic defects

## Classic homocystinuria

Classic homocystinuria is the most well known of these disorders. It is usually referred to simply as homocystinuria or HCU. Symptoms are highly variable and can range from mild clinical manifestations to severe, life-threatening complications. Classic homocystinuria is generally broken down into two groups – pyridoxine responsive homocystinuria and pyridoxine nonresponsive homocystinuria – based upon an individual's response to treatment with large doses of pyridoxine (vitamin B<sub>6</sub>).

Infants with classic homocystinuria are usually normal at birth. Symptoms usually develop during infancy or early childhood. Common symptoms may include:

- Ectopia lentis – displacement of the lenses of the eyes.
- Myopia - nearsightedness (often severe).
- Developmental delays and cognitive impairment – but in approximately one-third of cases, intelligence may be unaffected.
- Skeletal abnormalities – include scoliosis, knock-knees, chest deformities, irregularly long, thin fingers (arachnodactyly), and abnormally thin, lengthened long bones (dolicoostenomelia). Skeletal abnormalities contribute to individuals having a tall, thin appearance.
- Thromboembolism – Increased risk of developing blood clots. Blood clots can potentially affect any vessel and develop prematurely (i.e., in individuals under 30).
- Osteoporosis.

Recurrent thromboemboli can potentially lead to serious life-threatening complications including stroke, seizures, permanent neurological damage and death.

Thromboembolism is the leading cause of morbidity and early death in classic homocystinuria.

Additional features that can potentially be associated with classic homocystinuria include hypopigmentation, malar flush, dystonia, pancreatitis and a variety of psychiatric or behavioral problems.

## **What causes classic homocystinuria?**

Classic homocystinuria is caused by mutations of the CBS gene. This gene is responsible for the production of the enzyme, cystathionine  $\beta$ -synthase (CBS). CBS is essential for the conversion of homocysteine to another amino acid known as cystathionine. Deficiency of this enzyme leads to increased levels of methionine and homocysteine in the body and, ultimately, the symptoms of classic homocystinuria.

The genetic mutation that causes classic homocystinuria is inherited as an autosomal recessive trait. Recessive genetic disorders occur when an individual inherits an abnormal gene for the same trait from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease and will not show symptoms. The risk for two carrier parents to both pass the defective gene and, therefore, have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%. The risk is the same for males and females.

## **How is classic homocystinuria diagnosed?**

Today classic homocystinuria is often diagnosed as a result of newborn screening – the screening test having detected an increase in the level of methionine. Most states screen all newborns for homocystinuria. If not detected in newborn screening classic homocystinuria is diagnosed based upon a thorough clinical examination, the identification of characteristic findings and specialized tests. Such tests can detect elevated levels of homocystine, homocysteine and methionine in the plasma or urine. Tests that can detect deficient activity of the enzyme CBS in certain tissues and cells of the body (e.g., liver and skin cells) can also aid in a diagnosis of classic homocystinuria.

## How is classic homocystinuria treated?

There is no cure for classic homocystinuria, but if the treatment is begun in the newborn period, the complications can be prevented. Treatment is aimed at preventing or reducing the symptoms commonly associated with the disorder by controlling the levels of homocyst(e)ine in the plasma. The main treatment options for classic homocystinuria are:

### Pyridoxine (vitamin B6)

High doses of pyridoxine may be administered and can lead to improvement of symptoms in some cases. The degree of improvement can vary. All patients should receive a trial of pyridoxine to determine who is responsive to this therapy.

Whether individuals who respond to pyridoxine require additional therapy is controversial. The majority of patients who respond to pyridoxine may still require a protein-restricted diet or a special medication known as betaine (see below).

### Diet

Individuals, especially those who are unresponsive to pyridoxine therapy, require a low-protein, methionine-restricted diet. A supplemental methionine-free formula – which contains other essential amino acids – is critical in this diet. Vitamin B<sub>12</sub> and folate supplementation may also be recommended because they may aid in reducing the level of homocysteine in the body.

A low-protein diet that restricts methionine may prevent complications associated with classic homocystinuria when given shortly after birth (usually to infants identified through newborn screening).

### Medication

The U.S. Food and Drug Administration (FDA) has approved the orphan drug betaine anhydrous for oral solution (Cystadane<sup>®</sup>) to treat homocystinuria. Betaine works by reducing the amount of homocysteine in the body. The drug may be used in conjunction with a low-protein, methionine-restricted diet.

For more information about this medication, contact:

#### Rare Disease Therapeutics

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Suite 150  
Franklin, TN 37067

Phone: 615-399-0700  
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[www.raretx.com](http://www.raretx.com)

## **Additional therapies**

Some individuals with classic homocystinuria may require surgical intervention for dislocated lenses or certain skeletal abnormalities. However, surgery should be avoided if possible because of the increased risk of a thromboembolic event. If surgery is necessary, the patient with classic homocystinuria should be admitted to the hospital the day before surgery and given 1-1/2 maintenance intravenous fluids containing 5-10% glucose beginning before fasting and continuing until after surgery and fluids are readily taken by mouth.

Genetic counseling will be of benefit for affected individuals and their families.

## **MTHFR deficiency**

MTHFR deficiency is an extremely rare disorder. Fewer than 50 cases have been reported in the medical literature. Common symptoms include developmental delays, microcephaly, lack of coordination, and psychiatric or behavioral issues. The disorder can also cause blood vessel disease, stroke, seizures, coma and death early during infancy.

MTHFR deficiency is caused by mutations of the MTHFR gene and is inherited as an autosomal recessive trait.

Treatment options for MTHFR deficiency have included a combination of folic acid and vitamins B<sub>6</sub> and B<sub>12</sub>. Since these patients have low methionine levels (in contrast to classic homocystinuria in which the methionine level is high), methionine supplementation has also been used. Betaine (Cystadane®) has been approved by the FDA for the treatment of MTHFR deficiency to enhance the methionine level and reduce the level of homocysteine.

## **Homocystinuria due to cobalamin defects**

Homocystinuria can also occur as a result of defects in the metabolism of cobalamin (vitamin B<sub>12</sub>). Affected infants have insufficient production of the form of cobalamin required for normal metabolism of homocysteine to methionine. In the most frequent subtype of this group of disorders, cobalamin C (cblC), there is also insufficient production of the form of cobalamin required for conversion of the organic acid methylmalonic acid to succinic acid. Thus, in cblC disorder there are increases in homocysteine and methylmalonic acid and a decrease in methionine.

The various defects of cobalamin are broken down into complementation classes. Symptoms can vary greatly from one person to another even within the same complementation class.

Symptoms associated with disorders of cobalamin metabolism include poor feeding, failure to thrive, developmental delays, cognitive decline, hypotonia, seizures, microcephaly and megaloblastic anemia.

Several different genetic mutations are associated with the various complementation classes of defects of cobalamin metabolism.

The most important treatment is to inject large doses of vitamin B<sub>12</sub> (hydroxocobalamin) daily or otherwise frequently. This treatment as well as betaine (Cystadane®), which has been approved for the treatment of defects of cobalamin metabolism, is required to increase methionine to at least a normal level and to reduce the increased level of homocysteine. Treatment may also include a high-calorie, low-protein diet. Supplementation with pyridoxine, carnitine, folate, or methionine may also be recommended.

## Patient Support and Resources

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- #11 The Physician's Guide to The Homocystinurias

These booklets are available free of charge. To obtain copies, call or write to NORD or download the text from [www.rarediseases.org](http://www.rarediseases.org)

*This booklet was made possible by a charitable contribution from Rare Disease Therapeutics. The series is intended to increase awareness of rare diseases and available resources. For additional copies, contact NORD.*

For information on rare disorders and the voluntary health organizations that help people affected by them, visit NORD's Web site at [www.rarediseases.org](http://www.rarediseases.org) or call (800) 999-NORD or (203) 744-0100.

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NORD helps patients and families affected by rare disorders by providing:

- Physician-reviewed information in understandable language
- Referrals to support groups and other sources of help
- Networking with other patients and families
- Medication assistance programs
- Grants and fellowships to encourage research on rare diseases
- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals

Contact NORD at:  
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