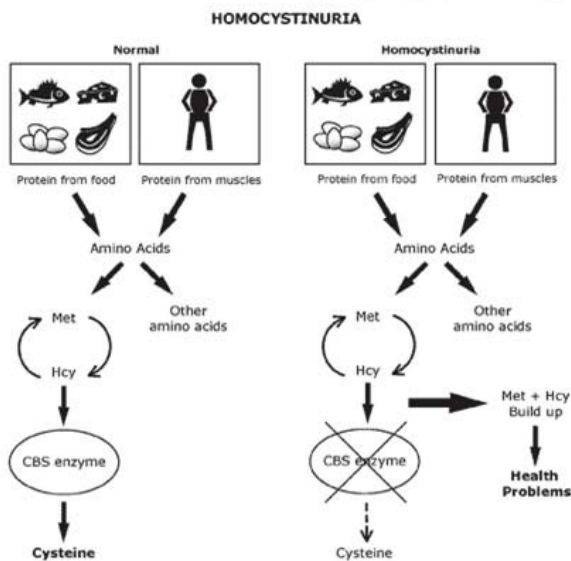


## HOMOCYSTINURIA (HYPERMETHIONINEMIA) INFORMATION FOR PARENTS/CARERS

### What is Homocystinuria (Hypermethioninemia)?



This fact sheet contains general information about Homocystinuria (Hyper-methioninemia). The finding of elevated Methionine in a dried blood spot upon newborn screening suggests one of two metabolic defects: 1) Homocystinuria due to Cystathionine  $\beta$ -Synthase (CBS) deficiency or 2) hepatic methionine adenosyltransferase deficiency. It is one type of amino acid disorder. People with this condition have problems breaking down an amino acid called methionine from the food they eat. Methionine (a precursor to homocystine, that is, an amino acid from which homocystine is made). A person with homocystinuria cannot breakdown the methionine in food.

Methionine and homocystine are amino acids needed for proper growth and development, but too much can cause serious health problems. In the case of classical homocystinuria, too much methionine builds up in the blood, which in turn causes a buildup of homocystine. High levels of methionine and homocystine penetrate and damage the brain. These high levels ultimately cause mental retardation and other serious health

### What causes Homocystinuria (Hypermethioninemia)?

In order for the body to use protein from the food we eat, it is broken down into smaller parts called amino acids. Special enzymes then make changes to the amino acids so the body can use them. This condition occurs when an enzyme called "cystathionine beta-synthase" (CBS) is either missing or not working properly. This enzyme's job is to break down methionine. When the CBS enzyme is not working correctly, methionine and another amino acid, homocystine, build up in the blood and cause problems.

### How Does Homocystinuria (Hypermethioninemia) Affect a Child?

Without treatment, children with homocystinuria develop permanent mental retardation and behavioral problems. Seizures, delayed development, dislocated lenses in the eye, and weakening of the bones is also common. In addition, life-threatening blood clots may develop and become lodged within blood vessels.



## Is There a Test for Homocystinuria (Hypermethioninemia)?

Yes. Babies are tested through newborn screening for Homocystinuria (Hyper-methioninemia) before they leave the hospital. The baby's heel is pricked and a few drops of blood are taken. The blood is sent to the newborn screening laboratory to find out if it has more than a normal amount of methionine. The finding of elevated Methionine in a dried blood spot upon newborn screening suggests one of two metabolic defects: 1) Homocystinuria due to Cystathionine  $\beta$ -Synthase (CBS) deficiency or 2) hepatic methionine adenosyltransferase deficiency.

## If homocystinuria (hypermethioninemia) is not treated, what problems occur?

Babies look healthy and normal at birth. Over time, if the condition is not treated, it can cause growth and learning delays. It can also affect the eyes, bones, heart, and blood vessels. There are two types of homocystinuria. The milder form can be treated with vitamin B6 supplements. The other type does not respond to vitamin B6. Symptoms of both types vary widely from person to person.

### Growth, learning and behavior

Delays in growth and learning are often noticed between the ages of one and three. Common effects in untreated children include:

- poor growth
- problems gaining weight
- delays in crawling, walking, and talking
- behavior and emotional problems
- serious learning disabilities or mental retardation

### Eyes

Children usually start to develop severe nearsightedness after one year of age. If this is not treated, the lens of the eye can become loose and move out of place. This is called "lens dislocation". This often happens between two and eight years of age. Glaucoma, a condition caused by increased eye pressure, can happen over time if the lens dislocation is not treated. Untreated glaucoma can cause blindness.

### Bones and skeleton

Teens and adults are often very tall and slender. They may have very long arms, legs, and fingers. By the teen-age years, about half have thinning of the bones, called osteoporosis. Muscle weakness, especially in the legs, is a problem for some children.

### Heart and blood vessels

If not treated, homocystinuria can cause blood clots resulting in heart disease or stroke. In fact, stroke and heart disease are the main causes of early death in people with untreated homocystinuria.



**Other**

Children who are not treated often have pale hair and skin. Some will have episodes of pancreatitis that causes severe pain.

What are the signs and symptoms of homocystinuria (hypermethioninemia)?

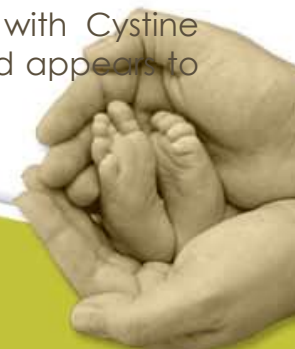
This defect leads to a multisystemic disorder of the connective tissue, muscles, CNS, and cardiovascular system. Homocystinuria represents a group of hereditary metabolic disorders characterized by an accumulation of homocysteine in the serum and an increased excretion of homocysteine in the urine. Infants appear to be normal and early symptoms, if any are present, are vague.

- A family history of homocystinuria
- Nearsightedness
- Flush across the cheeks
- Tall, thin build
- Long limbs
- High-arched feet (pes cavus)
- Knock-knees (genu valgum)
- Pectus excavatum
- Pectus carinatum
- Mental retardation
- Psychiatric disease
- Eye anomalies:
  - 90% have ectopia lentis
  - Myopia
  - Glaucoma
  - Optic atrophy
- Seizure
- extensive atheroma formation at young age which affects many arteries but not the coronary arteries

Homocystinuria has several features in common with Marfan syndrome. Unlike Marfan syndrome, in which the joints tend to be “loose,” in homocystinuria the joints tend to be “tight.”

**What is the treatment for homocystinuria (hypermethioninemia)?**

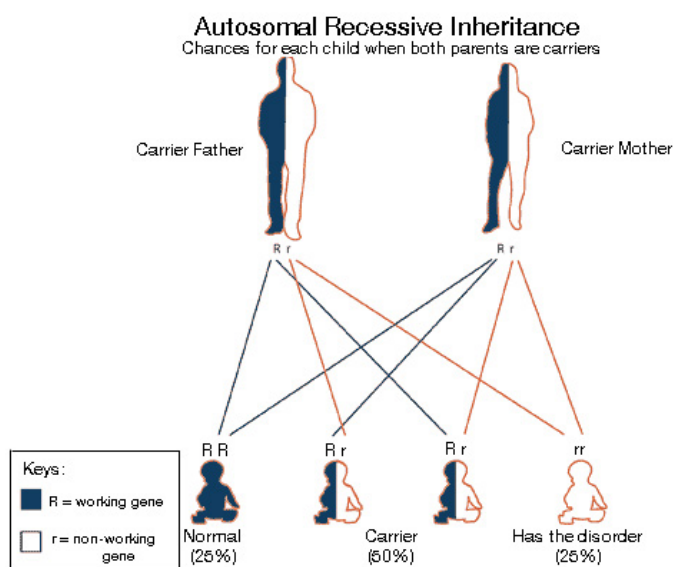
Treatment of CBS deficiency usually begins with a trial of oral vitamin B6 (pyridoxine) supplementation, with daily measurement of plasma amino acids. CBS requires pyridoxine as a coenzyme for enzymatic activity. Overall, about 25% of patients respond to large doses of pyridoxine, although the percentage may be lower for patients identified through newborn screening. This pyridoxine response usually coincides with the presence of some residual enzyme activity. Dietary restriction of Methionine in conjunction with Cystine supplementation reverses the biochemical abnormalities to some extent and appears to





reduce the clinical symptoms. Special formulas are available commercially, but the diet is difficult to maintain long term. In an attempt to decrease Homocysteine levels, folic acid, and betaine can be supplemented to induce recycling of this amino acid to Methionine for alternate metabolism. Vitamin B12 (cobalamin) may also be helpful. Because the diagnosis and therapy of Homocystinuria is complex, the pediatrician is advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist. It is recommended that parents travel with a letter of treatment guidelines from the patient's physician.

### How is homocystinuria (hypermethioninemia) inherited?



This condition is inherited in an autosomal recessive manner. It affects both boys and girls equally. Everyone has a pair of genes that make the CBS enzyme. In children with homocystinuria, neither of these genes works correctly. These children inherit one non-working gene for the condition from each parent.

Parents of children with homocystinuria rarely have the condition themselves. Instead, each parent has a single non-working gene for homocystinuria. They are called carriers. Carriers do not have the condition because the other gene of this pair is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have homocystinuria. There is a 50% chance for the child to be a carrier, just like the parents. And, there is a 25% chance for the child to have two working genes.

Genetic counseling is available to families who have children with this condition. Genetic counselors can answer your questions about how it is inherited, options during future pregnancies, and how to test other family members. Ask your doctor about a referral to a genetic counselor.

### What other testing is available?

Homocystinuria is confirmed by special blood and urine tests. People with this condition usually have high levels of homocystine and methionine in their blood. Their urine usually has high levels of homocystine. The condition can also be confirmed by testing the CBS enzyme in a skin sample.



**How common is homocystinuria (hypermethioninemia)?**

Homocystinuria caused by cystathionine beta-synthase deficiency affects at least 1 in 200,000 to 335,000 people worldwide.

What happens when homocystinuria (hypermethioninemia) is treated?

With lifelong treatment, many children have normal growth and intelligence. Treatment may lower the chance for blood clots, heart disease, and stroke. Treatment also lessens the chance of eye problems. However, even when treated, some people still develop lens dislocation. This can often be corrected by surgery or other methods. Children who begin treatment later in life may have mental retardation and behavior problems.

**What causes the CBS enzyme to be absent or not working correctly?**

Genes tell the body to make various enzymes. People with homocystinuria have a pair of genes that do not work correctly. Because of the changes in this pair of genes, the CBS enzyme either does not work properly or is not made at all.

**Where can I find more information?****National Coalition for PKU and Allied Disorders**

<http://www.pku-allieddisorders.org/>

**Children Living with Inherited Metabolic Diseases (CLIMB)**

<http://www.climb.org.uk>

**Genetic Alliance**

<http://www.geneticalliance.org>

