Newborn Screening ACT Sheet

Increased Methionine
Homocystinuria (CBS Deficiency)

Differential Diagnosis: Classical homocystinuria (cystathionine β-synthase (CBS) deficiency); hypermethioninemia due to MAT I/III deficiency; GAMT deficiency; adenosylhomocysteine hydrolase deficiency; liver disease; hyperalimentation.

Condition Description: Methionine from ingested protein is normally converted to homocysteine. In classical homocystinuria due to CBS deficiency, homocysteine cannot be converted to cystathionine. As a result, the concentration of homocysteine and its precursor, methionine, will become elevated. In MAT I/III deficiency and the other hypermethioninemas, methionine is increased in the absence of, or only with, a slightly increased level of homocysteine.

You Should Take the Following Immediate Actions

- Contact family to inform them of the newborn screening result and ascertain clinical status.
- Consult with pediatric metabolic specialist. (See attached list.)
- Evaluate the newborn with attention to liver disease and refer as appropriate.
- Initiate confirmatory/diagnostic tests in consultation with metabolic specialist.
- Initial testing: plasma quantitative amino acids and plasma total homocysteine.
- Repeat newborn screen if second screen has not been done.
- Educate family about homocystinuria and its management as appropriate.
- Report findings to newborn screening program.

Diagnostic Evaluation: Quantitative plasma amino acids will show increased homocysteine and methionine in classical homocystinuria, but only increased methionine in the other disorders. Plasma homocysteine analysis will show markedly increased homocysteine in classical homocystinuria and normal or only slightly increased homocysteine in the other disorders. Urine homocysteine is markedly increased in classical homocystinuria.

Clinical Considerations: Homocystinuria is usually asymptomatic in the neonate. If untreated, these children eventually develop mental retardation, ectopia lentis, a marfanoid appearance, including arachnodactyly, osteoporosis, other skeletal deformities, and thromboembolism. MAT I/III deficiency may be benign. Adenosylhomocysteine hydrolase deficiency has been associated with developmental delay and hypotonia, and both this disorder and GAMT deficiency can cause liver abnormalities.

Additional Information:

http://www.childrenshospital.org/newenglandconsortium/NEWBS/met/met_protocol.htm

Gene Tests/Gene Clinics

Genetics Home Reference
http://www.newbornscreening.info/Pro/aminoaciddisorders/CBS.html
http://www.newbornscreening.info/Parents/aminoaciddisorders/CBS.html

Disclaimer: This information is adapted from American College of Medical Genetics website ACT sheets. http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm 10/06
What is HCY?
HCY is a type of amino acid disorder. People with HCY can’t break down an amino acid called methionine from the food they eat.

What Causes HCY?
Enzymes help start chemical reactions in the body. HCY happens when an enzyme called “cystathionine beta-synthase” (CBS) is missing or not working right. This enzyme breaks down methionine. When the CBS enzyme is not working right, methionine and homocysteine (another amino acid) build up in the blood and cause problems.

What Symptoms or Problems Occur with HCY?
[B]Symptoms are something out of the ordinary that a parent notices.[/B] Babies look healthy and normal at birth. If untreated, HCY can cause growth and learning delays. It can also affect the eyes, bones, heart, and blood vessels.

Growth, learning and behavior – Delays in growth and learning are often noticed between ages one and three. Common problems include:

- poor growth
- problems gaining weight
- delays in crawling, walking, and talking
- behavior and emotional problems (such as crying for no reason)
- serious learning disabilities or mental retardation

Eyes – Children with HCY usually start to develop severe nearsightedness after age one. If this isn’t treated, the lens of the eye can get loose and move out of place. This is called “lens dislocation.” It often happens between ages two and eight. Glaucoma is a condition caused by increased eye pressure. This can happen over time if the lens dislocation is not treated. Untreated glaucoma can cause blindness.

Bones and skeleton – Teens and adults with HCY are often tall and slender. They may have very long arms, legs, and fingers. About half have thinning of the bones, called osteoporosis. Some children will have muscle weakness, especially in the legs.

Heart and blood vessels – HCY can cause blood clots resulting in heart disease or stroke if not treated. Stroke and heart disease are the main causes of early death in people with untreated HCY.

Other – Children who are not treated often have pale hair and skin. Some will have periods of pancreatitis (inflammation of the pancreas gland), which causes severe pain.

What is the Treatment for HCY?
Your baby’s primary doctor will work with a metabolic doctor and dietitian to care for your child. Dietitians know what are the right foods to eat.

The following are treatments often used for children with HCY:

- Low-methionine diet
- Special medical formula
- Blood and urine tests
  - Vitamin B6
  - Betaine
  - Vitamin B12
  - Folic Acid
  - L-cystine

Things to Remember
With treatment all life long, 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. Even when treated, some people still develop lens dislocation. This can often be fixed by surgery or other methods.

Children who begin treatment later in life may have mental retardation and behavior problems.