ACMG American College of Medical Genetics and Genomics
Translating Genes Into Health®

ACT Sheet

Newborn Screening ACT Sheet

[Elevated Methionine +/- Elevated Homocysteine]

Homocystinuria (Cystathionine beta-synthase deficiency [CBS Deficiency])

Differential Diagnosis: Classic homocystinuria, methionine adenosyltransferase (MAT) I/III deficiency, glycine n-methyltransferase (GNMT) deficiency; adenosylhomocysteine hydrolase deficiency, liver disease, parenteral nutrition, prematurity.

Condition Description: Homocystinuria refers to a group of inherited disorders that result in elevated levels of homocysteine in urine. The amino acid, methionine, derived from ingested protein, is normally converted to homocysteine. In classic homocystinuria, homocysteine cannot be converted to cystathionine. As a result, the concentration of homocysteine and its precursor, methionine, become elevated. In MAT I/III deficiency and the other hypermethioninemias, methionine is increased but homocysteine levels are normal or only slightly increased. Presentation in the neonatal period is rare.

You Should Take the Following Actions:

- Inform family of the newborn screening result.
- Ascertain clinical status (newborns are expected to be asymptomatic).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn with attention to liver disease.
- Initiate confirmatory/diagnostic testing and management, as recommended by the specialist.
- Provide family with basic information about the possible diagnoses and their management.

- Report the final diagnostic outcome to newborn screening program.

Diagnostic Evaluation: Plasma amino acids: Methionine and homocysteine are both elevated in classic homocystinuria (cystathionine-b-synthase deficiency), while methionine alone is elevated in the other disorders. Urine amino acids: Homocysteine is markedly elevated in classic homocystinuria. Total plasma homocysteine is markedly elevated in classic homocystinuria and normal or only slightly increased in the other disorders. Molecular genetic testing may be required to establish the diagnosis.

Clinical Considerations: Neonates with classic homocystinuria are usually asymptomatic. Treatment includes a protein restricted diet and vitamin supplementation. If untreated, later features may include ectopia lentis, developmental delay, abnormalities in long bone formation and an increased risk of thrombosis. MAT I/III deficiency may be benign. Adenosylhomocysteine hydrolase deficiency is a very rare condition associated with developmental delay and hypotonia, and both this disorder and GNMT deficiency can cause liver abnormalities.

Additional Information:

How to Communicate Newborn Screening Results
Emergency Protocols (New England Consortium of Metabolic Programs)
Gene Reviews
Medline Plus
Condition Information for Families- HRSA Newborn Screening Clearinghouse
ClinGen Actionability Report

Referral (local, state, regional, and national:

Find a Genetics Clinic Directory
Genetic Testing Registry