

Increased Methionine Homocystinuria (CBS Deficiency) / Hypermethioninemia (MET)

Differential Diagnosis: Classical homocystinuria (cystathionine β -synthase (CBS) deficiency); hypermethioninemia (MET) due to methionine adenosyltransferase I/III MAT I/III deficiency; glycine n-methyltransferase GNMT 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 hypermethioninemias, 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: Plasma quantitative 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. These children eventually develop intellectual disabilities, ectopia lentis, a marfanoid appearance, including arachnodactyly, osteoporosis, other skeletal deformities, and thromboembolism if left untreated. MAT I/III deficiency may be benign. Adenosylhomocysteine hydrolase deficiency has been associated with developmental delay and hypotonia, and both this disorder and GNMT deficiency can cause liver abnormalities.

Additional Information:

American College of Medical Genetics and Genomics
<https://www.acmg.net/StaticContent/ACT/Methionine.pdf>

Genetics Home Reference
<http://ghr.nlm.nih.gov/condition=homocystinuria>

STAR G FELSI
<http://www.newbornscreening.info/Pro/aminoaciddisorders/CBS.html>
<http://www.newbornscreening.info/Parents/aminoaciddisorders/CBS.html>