PerkinElmer
For the Better

PerkinElmer
GENOMICS

Homocystinuria (Hypermethioninemia)

Background

The finding of elevated Methionine in a dried blood spot upon newborn screening suggests one of two metabolic defects: 1) Homocystinuria due to Cystathionine β-Synthase (CBS) deficiency or 2) hepatic methionine adenosyltransferase deficiency. The most likely defect is a deficiency of CBS, which causes a connective tissue disease with several manifestations. Many patients with homocystinuria have been described since the deficiency was first reported in 1962. Methionine accumulates at the beginning of a metabolic pathway that sequentially converts this amino acid to Homocysteine, Cysta-thionine and Cysteine. The step in the pathway that converts Homocysteine to Cysta-thionine is catalyzed by CBS. Although it is highly elevated, Homocysteine is not detected with newborn screening because of its reactive nature with many components in blood, including itself with the formation of the dimer Cystine. The elevation of Methionine, therefore, is used to detect this disorder in newborn screening. The incidence of CBS deficiency is about 1 in 60,000, although several investigators believe this disease is more common.

Clinical

While the metabolic defect is present at birth, initial symptoms of homocystinuria usually have onset later in infancy and childhood. Developmental delay may be the first sign and is a harbinger of mental retardation, but is not obligate. An early and distinctive finding is dislocation of the lens of the eye (ectopia lentis). Patients are at high risk for developing thromboembolism that may occur at any age. These may lead to stroke, seizures, permanent neurologic sequela and death. Increased clotting ability makes surgery a risk. Osteoporosis is a long-term complication of homocystinuria.

Testing

Newborn screening of a dried blood spot using tandem mass spectrometry reveals elevated levels of methionine, which should prompt testing plasma for amino acids, including homocysteine. Elevated methionine and homocysteine in plasma indicate CBS deficiency, while an isolated increase in methionine suggests hepatic methionine adenosyltransferase deficiency. In affected patients, the presence of homocystine in the urine is a consistent finding, especially after early infancy. CBS enzyme activity can be measured in many tissues, including fibroblasts, lymphocytes, liver, amniocytes, and chorionic villi (biopsy or cultured cells). Deficient enzyme activity may be followed with DNA mutation analysis for the several known mutations in the CBS gene.

Treatment

Treatment of CBS deficiency usually begins with a trial of oral vitamin B6 (pyri-doxine) 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 identi-fied through newborn screening. This pyridoxine response usually coincides with the presence of some residual enzyme activity. Dietary restriction of Methionine in conjunc-tion 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.

Inheritance

This disorder most often follows an autosomal recessive inheritance pattern. With recessive disorders affected patients usually have two copies of a disease gene (or mutation) in order to show symptoms. People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder.

References

Applegarth, D.A., Hardwick, D.F., et al. Excretion of S-adenosylmethionine and S-adenosylhomocysteine in Homocystinuria. New England J. Med. 285:1265, 1971.

Mudd, S.H., Levy, H.L., and Kraus, J.P. Disorders of Trans-sulferation. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al. McGraw-Hill. Chapter 88, pg. 2007-2046.

Wong, P.W.K., Justice, P., et al. Folic acid non-responsive homocystinuria due to methylenetetrahydrofolate reductase deficiency. J Pediatrics 58:749-756, 1977.