

HOMOCYSTINURIA

The term "homocystinuria" designates a biochemical abnormality, not a specific disease entity. There are many causes of homocystinuria. All affect one of the transsulfation pathways that convert the sulfur atom of methionine into the sulfur atom of cysteine. This pathway is the chief route of disposal of methionine. The most common defect, cystathionine β -synthase (CBS) deficiency (OMIM database No. 236200),⁹⁶ results in high concentrations of serum methionine. One form of CBS deficiency is responsive to vitamin B₆.⁹⁷ Other metabolic variants of homocystinuria include defects of vitamin B₁₂ uptake or activation and tetrahydrofolate reductase deficiency (OMIM database No. 236250).

Incidence

Although homocystinuria is a rare disorder, carriers of the condition represent a much larger population. If one assumes a worldwide incidence of 1 in 300000 individuals, the expected carrier frequency is 1 in 135. Because carriers are more prone to thromboembolic events, ascertainment of these individuals via identification of an affected person needs to be emphasized to primary health care professionals.⁹⁸

Clinical Manifestations

Clinical problems include multiple, recurrent thromboemboli.⁹⁹ Arterial or venous thromboses may involve the cerebral, pulmonary, renal, and myocardial circulation.¹⁰⁰ Patients may also exhibit ectopia lentis, glaucoma, cataracts, developmental delays/mental retardation, seizures, psychiatric disturbances, osteoporosis with bone deformities, scoliosis, high palatal arch, muscle weakness with a shuffling gait, and a marfanoid habitus. Death has been reported within the first year of life. Approximately 50% of untreated individuals die by 25 years of age; death is frequently a result of thromboembolic events. Developmental delay is reported in 65% to 80% of untreated individuals.¹⁰¹

Pathophysiology

Two mechanisms probably explain most of the clinical symptoms seen: (1) abnormal (hyper) coagulation because of "sticky" platelets; and (2) direct toxicity of homocystine and its metabolites, causing endothelial cell damage.

Inheritance

The specific enzymatic defect should be ascertained. However, all heritable forms of homocystinuria exhibit autosomal recessive inheritance. Prenatal diagnosis is available for CBS deficiency using cultured chorionic villus cells or amniotic fluid cells to measure the activity of this enzyme. The chromosome map location is 21q22. The incidence in Ireland, Australia, Great Britain, and New England is 1 in 50000, the incidence in Japan is 1 in 1 million, and the worldwide incidence is 1 in 250000.

More than 90 different disease-associated mutations of the *CBS* gene have been identified. The vast majority of these mutations are "private" mutations that occur in only a single or a very small number of families. The most prevalent mutations are the G307S and I278T mutations.¹⁰² Affected patients vary widely in the extent to which they manifest clinical abnormalities, suggesting considerable genetic heterogeneity. Some of the variability is accounted for by the relative reduction of enzymatic activity. Absent to relatively low residual activity (up to 10%) of CBS has been noted among different families. However, there are reports of individuals with the identical genotype resulting in a different phenotype within the same family.

Rationale for and Benefits of Newborn Screening

The potential for early clinical diagnosis is limited. Ocular abnormalities, because of their distinctive lens displacement, may lead to the diagnosis. The diagnosis should be considered in any child or young adult with thromboembolism affecting both the large and small arteries as well as the veins, particularly in association with developmental disabilities, mental retardation, or skeletal findings. Most patients, however, have nonspecific features so that definitive testing involving the measurement of serum or urine amino acids is not accomplished before the expression of more severe clinical symptoms. Treatment seems to reduce the risk of thromboembolic episodes. Because this is the major cause of mortality and morbidity in these patients, the survival rate may improve with early, effective treatment. The incidence of mental retardation may be prevented or reduced.¹⁰³ For patients with classic (homozygous) homocystinuria, early treatment with good biochemical control (lifetime plasma-free homocystine < 11 $\mu\text{mol/L}$) seems to prevent mental retardation,¹⁰⁴ ectopia lentis seems to be delayed, and the incidence of seizures is reduced.

Screening

The bacterial inhibition assay (BIA) test may be used to detect increased concentrations of blood methionine.¹⁰⁵ Normal values for serum methionine concentration are noted to be less than 2 mg/dL. Newer methods include direct methionine assay by MS/MS.¹⁰⁶ The false-negative rate seems to correlate with the time that the specimen was obtained and the level of residual CBS activity present (ie, the B₆-responsive form). The false-negative rate increases with earlier newborn discharges. Approximately 1 in 5000 infants is found to have blood methionine concentrations more than 2 mg/dL. The use of a reduced cutoff level (1 mg/dL) increases the false-positive rate from 0.006% to 0.03%.¹⁰⁷ However, use of this cutoff should identify affected infants who have only slightly increased concentrations of methionine and reduce the frequency of false-negative results. It has been suggested that the increased false-positive rate does not represent an undue burden in terms of requests for repeat analysis.

Follow-up and Diagnostic Testing

Quantitative serum or plasma amino acid determination is used for diagnosis of homocystinuria. Plasma amino acids show increased methionine and homocystine concentrations with reduced concentrations of cystine and absent cystathionine. A urine organic acid profile with gas chromatography and MS/MS may be used to determine the presence or absence of methylmalonic acid.

Brief Overview of Disease Management

Treatment depends on the underlying cause of homocystinuria. As a first step, pyridoxine (vitamin B₆) responsiveness should be ascertained, because approximately 50% of patients respond to large doses of this vitamin. Nonresponsive patients with CBS deficiency should be treated with a methionine-restricted, cystine-supplemented diet. Folic acid and betaine therapy may also be helpful with all patients. In the disorders of cobalamin metabolism and transport in which methylmalonic acid and homocystine appear in the urine, hydroxycobalamin treatment (vitamin B₁₂, not cyanocobalamin) may be beneficial. Aspirin and dipyridamole have also been used to decrease the occurrence of thromboembolic phenomena. Clinical variability remains despite therapy. Not all affected individuals have increased methionine concentrations. The relationship between variability and the underlying metabolic processes or compliance has not yet been completely ascertained. One described mutation, G307S, is typically a pyridoxine-nonresponsive mutation, and individuals homozygous for the I278T mutation are usually responsive to pyridoxine therapy. The presence of some activity of the enzyme seems necessary for a clinical response to pyridoxine (vitamin B₆) administration. Individuals who are clinically responsive to pyridoxine generally have milder or more slowly progressive disease.

Current Controversies

Increased concentrations of methionine may be minimal during the first 3 days of life until there is adequate protein intake (milk feedings). This is especially true in patients who are responsive to vitamin B₆, who usually have some residual enzyme activity. This minimal increase probably accounts for the difference in screening frequencies between the United States and United Kingdom, where screening specimens are obtained at 5 to 7 days. It may be preferable to screen for this disorder at 2 to 4 weeks of age. Early discharge at 24 or even 18 hours results in many missed cases and decreases screening effectiveness.

Programs continue to evaluate the efficacy of screening and early treatment. Improvement in screening to decrease the numbers of missed cases is important. Recent evidence has shown that carriers (heterozygotes) for homocystinuria have an increased risk of thromboembolic events. Therefore, genetic counseling and screening should be offered to relatives of persons with homocystinuria.

Special Issues/Concerns

Specialized care is required that includes the ability to monitor amino acids and provide nutritional assessment and planning. Doses of pyridoxine higher than 900 mg have been associated with neuropathy; however, these higher doses are usually not required for adequate treatment. Thromboembolic phenomena are more prone to occur during anesthesia, surgical procedures, and prolonged immobilization.

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