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GENOMICS

Mitochondrial Acetoacetyl-CoA Thiolase Deficiency

Background

Mitochondrial Acetoacetyl-CoA Thiolase (commonly called β-Ketothiolase) is an enzyme with a dual function in metabolism. It acts in the breakdown of acetoacetyl-CoA generated from fatty acid oxidation and regulates production of ketone bodies. It also catalyzes a late step in the breakdown of the amino acid Isoleucine. β-Ketothiolase Deficiency was first described in 1971 and more than 40 cases have been reported.

Clinical

β-Ketothiolase Deficiency has a variable presentation. Most affected patients present between 5 and 24 months of age with symptoms of severe ketoacidosis. Symptoms can be initiated by a dietary protein load, infection or fever. Symptoms progress from vomiting to dehydration and ketoacidosis. Neutropenia and thrombocytopenia may be present, as can moderate hyperammonemia. Blood glucose is typically normal, but can be low or high in acute episodes. Developmental delay may occur, even before the first acute episode, and bilateral striatal necrosis of the basal ganglia has been seen on brain MRI. Some patients may develop cardiomyopathy. An exaggerated ketogenic response to fasting or illness should raise suspicion of this disease.

Testing

Newborns can be screened for β-Ketothiolase Deficiency using tandem mass spectrometry analysis of a dried blood spot. The finding of elevated five-carbon acylcarnitine (C5) suggests the metabolic defect. To make a diagnosis, further testing is required. Urine organic acid analysis of a patient with β-Ketothiolase Deficiency will find elevations of 2-methyl-3-hydroxybutyric acid, tiglic acid, and tyglylglycine. A diagnosis should be confirmed by measuring enzyme activity in fibroblasts or leukocytes. Prenatal diagnosis is possible by measuring enzyme activity in cultured amniocytes or chorionic villus cells.

A variety of mutations have been identified in patients with β-Ketothiolase Deficiency. There are no common mutations, however, that would permit rapid screening. The potential for prenatal diagnosis exists if the mutations are known in a family.

Treatment

The acute acidosis of β-Ketothiolase Deficiency should be treated aggressively with sodium bicarbonate, keeping in mind the possibility of iatrogenic hypernatremia. Plasma levels of glucose, electrolytes, and ammonia should be normalized. Carnitine supplementation may be helpful.

For the long-term, affected patients should avoid fasting, eat frequently, and restrict protein intake. Intravenous glucose can be used when the patient is febrile or vomiting. Carnitine supplementation is reasonable. With appropriate monitoring and therapy, there is a good prognosis for normal development.

Because the diagnosis and therapy of β-Ketothiolase Deficiency 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

Henry, C.G., Strauss, A.W., Keating, J.P., and Hillman, R.E. Congestive cardio-myopathy associated with beta-ketothiolase deficiency. J Pediatrics 99:754, 1981.

Mitchell, G. and Fukao, T. Inborn Errors of Ketone Body Metabolism. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al., ed., McGraw-Hill. Chapter 102:2327-2356.

Sweetman, L. and Williams, J.C. Branched Chain Organic Acidurias. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al., ed., McGraw-Hill. Chapter 93:2125-2163.