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Propionic Acidemia (PA)

Background

Propionic Acidemia (PA) is characterized by the accumulation of propionic acid due to a deficiency in Propionyl CoA Carboxylase, a biotin dependent enzyme involved in amino acid catabolism. Propionic acid may also accumulate in Multiple Carboxylase deficiency and Methylmalonic Acidemia. Multiple mutations for PA have been identified.

Clinical

Patients with PA typically present in the first days of life with dehydration, lethargy, hypotonia, vomiting, ketoacidosis, and hyperammonemia. Seizures, neutropenia, thrombocytopenia, and hepatomegaly may be present. Untreated patients can progress to coma and die. Most patients who survive the neonatal period have episodes of metabolic acidosis precipitated by infection, fasting, or a high protein diet. In some cases, episodic hyperammonemia seems to predominate over the metabolic acidosis. Psychomotor retardation is a life-long complication. Some patients have first presented later in infancy with encephalopathy and associated ketoacidosis, or developmental delay.

Testing

Newborns can be screened for PA using tandem mass spectrometry analysis of a heel-stick dried blood spot. The finding of elevated three-carbon acylcarnitine (C3) indicates a possible metabolic defect, either PA, Methylmalonic Acidemia, or less likely a defect in biotin metabolism. With Methylmalonic Acidemia, C4-dicarboxylic acylcarnitine may also be found, helping distinguish this disorder from PA. To make a diagnosis, further testing is required. Urine organic acid analysis of a patient with PA will demonstrate massive elevations of propionic acid and related compounds such as methylcitrate, propionylglycine, β-hydroxypropionate, and tiglic acid. In PA, carnitine deficiency due to increased renal excretion of propionyl carnitine is often seen.

Treatment

Treatment of PA involves reducing protein intake, particularly the amino acids Valine, Isoleucine, Methionine, and Threonine that feed into the defective pathway. This requires placing the infant on a special metabolic formula depleted in these amino acids. Until the diagnosis of PA is clearly established, all patients should be given a trial of cobalamin and biotin to evaluate a response. Carnitine supplementation has proven beneficial. Oral antibiotics help control infections and hypothetically reduce intestinal bacteria, which produce propionic acid that can be absorbed through the gut and contribute to metabolic stress. Prevention of constipation is important. Strict control is most crucial throughout childhood. Rarely, older patients with mild forms of PA are reported to function untreated.

Because the diagnosis and therapy of metabolic disorders like PA 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

Fenton, W.A., Gravel, R.A. and Rosenblatt, D.S. Disorders of Propionate and Methylmalonate Metabolism. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al. McGraw-Hill.

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