

Carnitine Palmitoyl Transferase Deficiency Type I

Background

Mitochondrial β -oxidation plays a major role in energy production and glucose homeo-stasis, especially during periods of fasting. Fatty acids are mobilized from adipose stores and released into the circulation to be taken up by the cell and quickly activated to their acyl-CoA esters. To be subsequently oxidized in mitochondria, the fatty acyl-CoAs must be converted to acyl-carnitine esters, a reaction that is catalyzed by Carnitine Palmitoyl Transferase I (CPT I), which is bound to the outer mitochondrial membrane. The acyl-carnitines are then transported across the inner mitochondrial membrane for subsequent fatty acid β -oxidation. In liver, CPT I is inhibited by malonyl-CoA, which provides a mechanism for regulation of fatty acid oxidation. Deficiency of CPT I prevents fatty acids from being transported into mitochondria and disrupts the normal regulation of fatty acid oxidation. There are three isoforms of CPT I and each tends to be more specific for the liver (CPT IA), muscle (CPT IB) or brain (CPT IC), but only the hepatic CPT I has been found to be deficient in patients identified so far. Hepatic CPT I deficiency has been described in patients with a wide range of ethnic origins.

Clinical

Patients with hepatic CPT I deficiency usually present after the newborn period with episodic, life-threatening symptoms associated with a viral illness and prolonged fasting. Among the signs most commonly observed in patients are lethargy, hepatomegaly, and seizures progressing to coma. Laboratory tests reveal hypoketotic hypoglycemia, mild metabolic acidosis with or without lactic acidemia, elevated transaminases, and hyper-ammonemia. Urinary ketones are conspicuously absent. Chronic muscle weakness and cardiomyopathy are not typical of this disease. Unlike many other defects in fatty acid oxidation, plasma carnitine levels are normal or elevated, and urinary dicarboxylic acids are absent.

Testing

Newborn screening of the heel stick dried blood spot using tandem mass spectrometry finds elevation of free carnitine and reduction of long-chain acylcarnitines (i.e. C16:0 and C18:0), resulting in an increased ratio of free carnitine to C16:0 and C18:0 acyl-carnitines. The definitive diagnosis of CPT I deficiency is made by measuring enzyme activity in fibroblasts, leukocytes, or liver. A variety of mutations have been detected in the gene for hepatic CPT I, but no common mutations have been found to allow easy DNA diagnosis.

Treatment

Any intercurrent infection or illness is potentially life threatening to affected patients. CPT I deficiency is treated by preventing prolonged fasting and administering IV glucose during acute episodes to prevent hypoglycemia and suppress release of fatty acids from adipose stores. Medium-chain fatty acids bypass the metabolic block, because they do not require conversion to acylcarnitine esters in order to enter the mitochondria. Medium-chain triglyceride oil may therefore be beneficial to patients.

Because the diagnosis and therapy of CPT I 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

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