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Neonatal Carnitine Palmitoyl Transferase Deficiency-Type II (CPT-II)

Background

Carnitine Palmitoyl Transferase II (CPT II) Deficiency is a disorder of mitochondrial fatty acid oxidation. Fatty acid oxidation normally generates ATP inside the mitochondria and provides acetyl-CoA for gluconeogenesis. Long-chain fatty acids require carnitine for transport into the mitochondria as long-chain acyl-carnitine esters (i.e. carnitine esterified to a fatty acid). CPT II is located on the inner mitochondrial membrane and acts to convert long-chain acyl-carnitine substrates that are transported across the outer mitochondrial membrane to acyl-CoAs for subsequent β-oxidation. Deficiency of CPT II results in the accumulation of long-chain acylcarnitines inside the mitochondria and in the plasma. Medium- and short-chain (C8 and shorter) fatty acids do not require CPT II and are metabolized normally. Muscle is particularly dependent on fatty acid oxidation for energy production.

Clinical

There are three clinical presentations of CPT II Deficiency. The classic form has adult onset of exercise-induced muscle weakness, often with rhabdomyolysis and myoglo-binuria that can be associated with acute renal failure. CK levels are found to be elevated only during a symptomatic period. Carnitine levels are normal.

A second phenotype is often fatal in the period from 3 to 18 months of age. Presentation can be onset of seizures with hepatomegaly, non-ketotic hypoglycemia, cardiomyopathy, hypotonia, and muscle weakness. Plasma free carnitine levels are low and acyl-carnitine high.

A severe form presents in the newborn period with non-ketotic hypoglycemia, cardiomyopathy, muscle weakness, and renal dysgenesis in some patients. All of these patients have expired within days of birth.

These different clinical presentations appear to be correlated with residual CPT II enzyme activity. Adult onset patients are found to have approximately 25% of normal activity while the other clinical groups have less than 15%.

Testing

Newborn screening of a dried blood spot using tandem mass spectrometry detects elevations of several long-chain acylcarnitines (i.e. C16, C18, C18:1 and C18:2). These findings are characteristic but not definitive of CPT II Deficiency, because Carnitine/ Acylcarnitine Translocase Deficiency has similar findings. Quantitative urine organic acid determination is usually not helpful, as elevations of long chain fatty acids, including dicarboxylic and 3-hydroxy-dicarboxylic acids, are not always present. Plasma acylcarnitine profile results confirm the findings on a dried blood spot. Definitive testing is performed by direct enzyme testing in fibroblasts, leukocytes, liver, or muscle biopsy.

Treatment

CPT II deficiency varies with the clinical type. Patients with adult-onset muscle form of the disease must alter their lifestyle and refrain from rigorous exercise. It is probably prudent to avoid prolonged fasting. Medium-chain triglyceride oil may be beneficial for all patients, because it bypasses the need for CPT II activity. Aggressive treatment of acutely ill infants with IV glucose and cardiac support is critical. L-Carnitine supple-mentation should be instituted. Any intercurrent infection or illness will be life threat-ening to patients affected with the childhood form.

Because the diagnosis and therapy of CPT II 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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