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Carnitine/Acylcarnitine Translocase Deficiency

Background

Carnitine/Acylcarnitine Translocase (CACT) Deficiency is a disorder of fatty acid oxidation. Fatty acid oxidation generates ATP in the mitochondria and provides acetyl-CoA for gluconeogenesis. CACT normally acts to transport long-chain acyl-carnitine across the inner mitochondrial membrane into the mitochondrial matrix where β-oxidation occurs. CACT also facilitates the export of free carnitine out of the mitochondria where it can be utilized for formation of acylcarnitines. Deficiency of this transport protein results in impaired long-chain fatty acid oxidation and causes the accumulation of long-chain acylcarnitines outside the mitochondria and in plasma. Short- and medium-chain (C8 and less) fatty acids do not require CACT for entry into the mitochondria and are therefore available for energy metabolism.

Clinical

There are two clinical presentations of CACT Deficiency. The severe form has neonatal onset of acute cardiorespiratory symptoms in the first days of life. If the patients survive the initial illness, they suffer from chronic muscle weakness, cardiac hypertrophy, hypo-glycemia and hyperammonemia. Plasma carnitine is low. Death may occur due to cardio-myopathy complications. These patients have no measurable CACT activity.

A second phenotype may have milder symptoms because they possess some residual CACT activity. These patients exhibit hypoglycemia, which may result in early death, but lack cardiac symptoms. Severe steatosis has been reported in liver, heart and kidneys at autopsy.

Testing

Newborn screening of a dried blood spot using tandem mass spectrometry reveals elevations of several longchain acylcarnitines (i.e. C16, C18, C18:1 and C18:2). These findings are characteristic but not definitive of CACT Deficiency, because Carnitine Palmitoyl Transferase II Deficiency has similar results. Quantitative urine organic acid determination is usually not helpful, as elevations of long chain fatty acids, including dicarboxylic and 3-hydroxy-dicarboxylic acids are inconsistently present. Plasma acyl-carnitine profile testing can confirm elevations of the above acylcarnitines. Definitive diagnosis of CACT Deficiency requires testing cultured fibroblasts or performing DNA mutation analysis of the gene. Prenatal diagnosis can be accomplished using DNA analysis if mutations are identified in the parents.

Treatment

This rare disorder is treated by preventing hypoglycemia and suppressing the need for long-chain fatty acid oxidation. Dietary medium-chain triglyceride oil bypasses the CACT step in fatty acid oxidation and provides safe calories. Aggressive supportive treatment in the newborn period and during intercurrent illnesses is important, since any infection is potentially life threatening.

Because the diagnosis and therapy of CACT 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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