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GENOMICS

Short Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)

Background

Short-Chain Acyl-CoA Dehydrogenase (SCAD) Deficiency is a disorder of fatty acid β-oxidation. The defect involves short-chain (butyryl) acyl-CoA dehydrogenase, one of four mitochondrial acyl-CoA dehydrogenases that carry out the initial dehydrogenation step in the β-oxidation cycle. SCAD deficiency impairs oxidation of fatty acids of short-chain length (4 carbons).

Clinical

SCAD deficiency usually has clinical onset between the second month and second year of life, although presentations as early as two days and as late as adulthood have been reported. Clinical presentation is highly variable with patients having constant symptoms marked by episodic deterioration. Patients have hypotonia, progressive muscle weakness, developmental delay and, possibly seizures. Failure to thrive, vomiting, and hypoglycemia may be seen. Symptoms may be worsened by a seemingly innocuous illness (a cold or otitis media) that is associated with prolonged fasting, which may lead to lethargy, coma, apnea, cardiopulmonary arrest, or sudden unexplained death. Physical examination of the acutely ill child may reveal mild to moderate hepatomegaly. Symptoms often precede the onset of hypoglycemia, which occurs from an inability to meet gluconeogenic requirements during fasting despite activation of an alternate pathway of substrate production – proteolysis. Cerebral edema and fatty liver and muscle are noted at autopsy, often leading to a misdiagnosis of Reye's Syndrome or Sudden Infant Death Syndrome (SIDS). SCAD deficiency accounts for about one of every 100 SIDS deaths. Older patients who present chiefly with progressive muscle involve-ment may respond to riboflavin (Vitamin B2) supplementation and have a generalized multiple acyl-CoA dehydrogenase deficiency. SCAD enzyme is the most vulnerable dehydrogenase to low riboflavin levels.

Testing

Newborn screening by tandem mass spectrometry of a dried blood spot identifies elevated levels of butyrylcarnitine (C4 acylcarnitine), usually with an elevated C4/C2 ratio. These results can be seen with another metabolic genetic defect (Isobutyryl-CoA Dehydrogenase Deficiency – IBDH) and therefore require further testing. Laboratory examination of blood may reveal hypoglycemia, mild metabolic acidosis, mild lactic acidosis, hyperammonemia, elevated BUN, and high uric acid levels. Liver function tests are often abnormal. Examination of the urine may show ketones, and urine organic acids often have elevated ethylmalonic acid. Plasma carnitine may be normal or low. Analysis of fibroblasts for the activity of SCAD identifies affected individuals, while heterozygous carriers for the defect usually have intermediate levels of activity, but are otherwise clinically and biochemically unaffected. SCAD activity should be assayed after antibody precipitation of MCAD activity, due to the overlap of substrate recognition.

Detection of mutations in the SCAD gene on chromosome 12 in affected individuals allows for confirmation of biochemical testing and detection of asymptomatic carriers in other family members. In addition to disease-causing mutations, the gene has two common polymorphisms, which may interact to cause reductions in SCAD activity and complicate the genetic analysis. DNA analysis of postmortem tissue is possible when plasma and urine samples are not available. Prenatal diagnosis is possible from cultured amniocytes using direct enzyme assay. DNA analysis in amniocytes or chorionic villi can also be helpful in the diagnosis of affected fetuses in pregnancies at risk where both parents carry a known mutation.

Treatment

Fundamental to the medical management of SCAD deficiency is to avoid fasting, particularly during periods of high metabolic stress, such as illness. Overnight fasts should be managed with nighttime or late evening feedings where appropriate. The addition of food-grade uncooked cornstarch mixed in liquid for a bedtime feeding has helped to decrease the frequency of morning hypoglycemic episodes in several patients. High carbohydrate intake should be encouraged during illness, with initiation of intravenous glucose supplementation if the child is unsuccessful in keeping down fluids, or unable to take adequate oral feedings. The preventive efficacy of a low fat diet versus a normal fat diet is unclear, but high intake of long and medium chain fatty acids should be avoided. Supplementation with oral L-Carnitine may be indicated during acute illness. For individuals with SCAD deficiency, it is imperative that the lethargic patient receives parenteral dextrose to avoid hypoglycemia during evaluation.

Because the diagnosis and therapy of SCAD 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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