



3-Hydroxy Long Chain Acyl-CoA Dehydrogenase Deficiency (LCHAD)

Background

Long-chain-3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is a disorder of mitochondrial fatty acid β -oxidation. LCHAD is one of two enzymes that carry out the third step (of four) in the β -oxidation of fatty acids – the other enzyme being short-chain hydroxyacyl-CoA dehydrogenase (SCHAD), which acts on shorter-chain substrates. LCHAD activity resides on the Mitochondrial Trifunctional Protein, which acts to catalyze three sequential steps in β -oxidation. LCHAD deficiency occurs as an isolated defect (described here) or together with deficiency of the other two enzymes in Mitochondrial Trifunctional Protein deficiency. LCHAD deficiency impairs oxidation of dietary and endogenous fatty acids of long-chain length (16 carbons and longer).

Clinical

LCHAD deficiency can present clinically from day one to three years of age. Two clinical scenarios have been described. One group of LCHAD deficiency patients presents with symptoms of cardiomyopathy, which may lead to death. Several cardiac problems have been described, including cardiomegaly, left ventricular hypertrophy, and poor contractility. Onset may be acute or chronic. A second group of patients presents, usually following fasting, with non-ketotic hypoglycemia, vomiting, hypotonia, and hepatomegaly. Rhabdomyolysis may occur. Both presentations are highly variable and may have overlapping features. Symptoms may be initiated by a seemingly innocuous illness (a cold or otitis media), leading to prolonged fasting. Symptoms often precede onset of hypoglycemia. Hypoglycemia occurs from an inability to meet gluconeogenic requirements during fasting despite activation of an alternate pathway of substrate production – proteolysis. Physical examination of the acutely ill child may find mild to moderate hepatomegaly and muscle weakness. Laboratory examination of blood may reveal hypoglycemia, elevated CK and abnormal transaminases. Unique among the fatty acid oxidation disorders, LCHAD patients may develop a sensorimotor peripheral neuropathy and pigmentary retinopathy over time. Fatty liver is noted at autopsy, often leading to a misdiagnosis of Reye's syndrome or Sudden Infant Death Syndrome (SIDS) in an infant.

A complication of pregnancy, HELLP Syndrome (hemolysis, elevated liver enzymes, and low platelets), has been described in women carrying a fetus affected with LCHAD deficiency.

Testing

Newborn screening using tandem mass spectrometry of a dried blood spot identifies elevated levels of several long chain hydroxyacylcarnitines (C16:OH, C16:1-OH, C18:OH, C18:1-OH, C18:2-OH, and generalized C12 through C14 species). Biochemical testing of blood and urine for carnitine, acylcarnitines, acylglycines, and organic acids is diagnostic for this disorder. Dicarboxylic and hydroxydicarboxylic acids are usually found with urine organic acid analysis, but may be "normal" when the patient is not acutely ill. Analysis of LCHAD activity in fibroblasts can reveal affected individuals compared to heterozygous carrier and normal fibroblast lines. LCHAD activity should be assayed after antibody precipitation of SCHAD activity, due to the overlap in substrate recognition.

LCHAD patients have a common mutation (1528G>C) in the β -subunit of mitochondrial trifunctional protein. Detection of mutations in the DNA of affected individuals allows for confirmation of biochemical test results and accurate detection of asymptomatic carriers among other family members. Prenatal diagnosis is possible by enzyme assay of cultured amniocytes or by in vitro probe of the β -oxidation pathway. DNA analysis can also be used for prenatal diagnosis of affected fetuses in at-risk pregnancies when both parents carry a known mutation.

Treatment

Fundamental to the medical management of LCHAD is the avoidance of fasting, particularly during periods of high metabolic stress, such as illness. Overnight fasts should last no longer than twelve hours and infants should receive late evening feedings to reduce this period. The addition of food-grade uncooked cornstarch mixed in liquid at bedtime has helped some infants decrease the frequency of morning hypoglycemia. A diet high in natural fat should be avoided. Medium-chain triglyceride supplementation bypasses the metabolic block and provides safe calories. Supplementation with oral L-Carnitine has not been shown to be beneficial in avoiding or ameliorating clinical symptoms.

High carbohydrate intake should be encouraged during illness, with initiation of intra-venous glucose supplementation if the child is unsuccessful in keeping down fluids, or unable to take adequate oral feedings. For individuals with LCHAD deficiency, it is imperative that the lethargic patient receive parenteral dextrose to avoid hypoglycemia during evaluation.

Because the diagnosis and therapy of LCHAD 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 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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