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3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC Deficiency)

Background

3-Methylcrotonyl-CoA Carboxylase (3-MCC) Deficiency has been recognized since 1984. It is a defect in the degradation of the amino acid Leucine. As a carboxylase enzyme, 3-MCC requires biotin for activity. There are four carboxylases in man that utilize biotin and each can be deficient singly or together. If biotin metabolism is defective, activities of all four carboxylases will be low, resulting in Multiple Carboxylase Deficiency. Some of the biochemical findings in 3-MCC Deficiency overlap with those seen in Multiple Carboxylase Deficiency, necessitating careful testing to distinguish the two disorders.

Clinical

The clinical presentations of 3-MCC deficiency range from severe to benign. The age of onset of symptoms is usually during the first several years of life, but later onsets and even asymptomatic adults have been reported. Symptoms often have onset with an infection, illness, or prolonged fasting. Patients with 3-MCC deficiency can lapse into catabolic stress leading to vomiting, lethargy, apnea, hypotonia, or hyperreflexia and seizures. Patients may have profound hypoglycemia, mild metabolic acidosis, hyperammonemia, elevated liver transaminases, and ketonuria. Plasma free carnitine levels may be very low. Other patients may present with failure to thrive beginning in the neonatal period or developmental delay. Some individuals with 3-MCC deficiency have no apparent symptoms. Asymptomatic women with 3-MCC deficiency may pass along the 3-MCC metabolite transplacentally to their infants, who are then found to have elevated 3-MCC by newborn screening with tandem mass spectrometry, but who themselves do not have the disease.

Testing

Newborn Screening using tandem mass spectrometry reveals an elevation of C5-hydroxy acylcarnitine from the dried blood spot of an affected patient. Diagnosis of 3-MCC deficiency then requires further testing. Urine organic acid analysis finds elevation of 3-hydroxyisovaleric acid and usually 3-methylcrotonylglycine. Following carnitine supplementation, 3-hydroxyisovalerylcarnitine is usually elevated in an acylcarnitine profile using tandem mass spectrometry. If C3 acylcarnitine is elevated, the disorder is multiple carboxylase deficiency. To further confirm isolated 3-MCC deficiency, the enzyme activity should be assayed in fibroblasts or leukocytes, along with at least one other carboxylase having normal enzyme activity. 3-MCC activity can also be measured in chorionic villus specimens. Mothers of all infants found to have elevated 3-MCC with newborn screening should be tested with a blood acylcarnitine profile to determine whether they have 3-MCC deficiency rather than their infant. The testing should also extend to other family members.

Treatment

Treatment of 3-MCC deficiency involves reducing dietary Leucine intake using a special leucine-depleted formula or instituting a general protein restricted diet. With onset of illness, IV glucose is needed and the acidosis must be corrected. Both carnitine and glycine supplementation have proven beneficial. Patients should undergo an early trial of biotin supplementation on the possibility that the defect is with biotin metabolism rather than isolated 3-MCC; biotin may be discontinued if there is no response.

Because the diagnosis and therapy of 3-MCC 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.

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