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GENOMICS

Isobutyryl-CoA Dehydrogenase Deficiency

Background

Isobutyryl-CoA Dehydrogenase (IBD) is an enzyme involved in the metabolism of Valine, a branched-chain amino acid. Deficiency of IBD was recently described and only a few patients have been identified. The gene for IBD (ACAD8), located on chromosome 9, has been cloned and mutations have been identified in several patients.

Clinical

The clinical features of IBD deficiency are poorly defined and may have a highly variable presentation. The first patient described with this disease had failure to thrive and developed dilated cardiomyopathy associated with anemia at 11 months of age. Plasma carnitine levels were profoundly decreased. Several other patients have been identified by newborn screening and appear "asymptomatic". Long-term clinical follow-up, however, is lacking and the true clinical spectrum of the disease is yet to be determined.

Testing

Newborns can be screened for IBD deficiency using tandem mass spectrometry analysis of a dried blood spot. The finding of elevated 4-carbon acylcarnitine (C4) indicates either IBD deficiency or short-chain acyl-CoA dehydrogenase deficiency. C4-acylcarnitine may also be seen in Multiple Acyl-CoA Dehydrogenase Deficiency (MADD), but this is usually accompanied by other acylcarnitine metabolites. To differentiate and make a diagnosis of IBD deficiency, further testing with urine organic acid analysis is required. Urine from a patient suspected of IBD deficiency may reveal an elevation of isobutyryl-glycine or be normal, whereas patients with Short-Chain Acyl-CoA Dehydrogenase deficiency (SCAD) excrete ethylmalonic acid. Plasma free carnitine levels may be low. Identification of mutations in the ACAD8 gene should permit genetic counseling and prenatal diagnosis.

Treatment

The proper treatment of IBD deficiency is not yet established, because of the wide variation in clinical phenotype and lack of long-term follow-up. Asymptomatic patients may not require specific treatment, whereas those patients who are symptomatic and have low plasma carnitine may benefit from carnitine supplementation.

Because the diagnosis of IBD 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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