

Methylmalonic Acidemias

Background

Methylmalonic Acidemia (MMA) can result from several different genetic disorders, including Methylmalonic-CoA mutase deficiency and defects of enzymes in cobalamin (vitamin B12) metabolism. Methylmalonic acidemia is one of the most studied metabolic defects, having been first reported in 1967. The incidence is at least 1 in 48,000 births, but is probably higher due to lack of recognition and diagnosis. Multiple DNA mutations for MMA have been identified.

Clinical

Because of the dependence of Methylmalonyl-CoA Mutase activity upon cobalamin metabolism and function, the different defects producing MMA have a similar clinical presentation. The picture of methylmalonic acidemia as recurrent vomiting, dehydration, respiratory distress, muscle hypotonia, and lethargy that can lead to coma and death is often seen in the first week of life. Metabolic acidosis is pronounced. Ketoacidosis, hyperglycinemia, hypoglycemia, and hyperammonemia are often found, along with leukopenia, thrombocytopenia, and anemia. This same scenario can present later in the first month of life, manifesting as failure-to-thrive and mental retardation. All patients are reportedly susceptible to infection. A long-term complication of MMA is renal failure.

Testing

Newborns can be screened for MMA using tandem mass spectrometry analysis of a heel-stick dried blood spot specimen. The finding of elevated three-carbon acylcarnitine (C3) indicates a possible metabolic defect, either MMA or Propionic Acidemia. With MMA, C4-dicarboxylic acylcarnitine may be found as well. To make a diagnosis, further testing is required. Urine organic acid analysis of a patient with MMA will reveal massive elevation of Methylmalonic acid, together with precursor metabolites β -hydroxy-propionate and methylcitrate. These metabolites and others inhibit mitochondrial function. Methylmalonyl-CoA Mutase activity and cobalamin metabolism can be studied in several tissues. A trial of vitamin B12 therapy has diagnostic importance in identifying those patients who have defects in cobalamin metabolism. Prenatal diagnosis is possible by measuring methylmalonic acid in amniotic fluid or maternal urine, and by enzyme activity studies in cultured amniocytes.

Treatment

Treatment of patients with MMA involves reducing protein intake, particularly the branched-chain amino acids Valine and Isoleucine, along with Methionine and Threonine. Special formulas are commercially available for this purpose. All patients should be given a trial of cobalamin supplementation to evaluate a response, since the management of B12-responsive patients is considerably easier and the prognosis is better. Carnitine supplementation has proven beneficial. Oral antibiotics help control infections and hypothetically reduce intestinal bacteria, which produce Propionic acid that can be absorbed through the gut and contribute to methylmalonic acid production. Strict control is most crucial throughout childhood. Several older patients with mild metabolic defects are reported to function untreated.

Because the diagnosis and therapy of MMA is complex, the pediatrician is advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist and dietician. 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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