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Multiple Acyl-CoA Dehydrogenase Deficiency

Background

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) is also known as Glutaric Acidemia Type II (GA-II). It is associated with deficiency of several mitochondrial dehydrogenase enzymes that utilize Flavin Adenine Dinucleotide (FAD) as cofactor, at least nine of which are known. These include the acyl-CoA dehydrogenases of fatty acid β-oxidation, and enzymes that degrade glutaric acid, isovaleric acid, and sarcosine (a precursor to glycine). During these dehydrogenation reactions, reduced FAD contri-butes its electrons to the oxidized form of Electron Transfer Flavoprotein (ETF) and subsequently to the respiratory chain to produce ATP. The reduced form of ETF is recycled to oxidized ETF by action of ETF- ubiquinone oxidoreductase (ETF-QO, also known as ETF dehydrogenase). Deficiency of ETF or ETF-QO therefore results in decreased activity of many FAD-dependent dehydrogenases and the combined metabolic derangements seen in MADD. Some MADD patients have had normal ETF and ETF-QO, suggesting the existence of genetic defects in other unidentified proteins.

Clinical

Three clinical presentations are reported for MADD. Two newborn presentations are seen – one with congenital anomalies, and one without. Those with congenital anomalies are often premature, and develop symptoms in the first 24-48 hours consisting of hypotonia, hepatomegaly, severe nonketotic hypoglycemia, metabolic acidosis and variable body odor of sweaty feet. Dysmorphic facial features and dysplastic, cystic kidneys are present. Plasma carnitine levels are low. Those patients with no congenital anomalies have similar symptoms and metabolic abnormalities. With both neonatal presentations, most patients do not live past a few weeks, though some older survivors succumb at a few months of age from hypertrophic cardiomyopathy. Heart, liver and kidneys are infiltrated with fat. The third cohort of patients has a mild and/or later onset with variable symptoms including lipid storage myopathy.

Testing

Newborn screening using a dried blood spot has identified MADD patients by detecting elevated acylcarnitine (C4, C5, C8, C10, and C16). Severe hypoglycemia without ketosis is a cardinal finding. Analysis of the urine for abnormal organic acids in a suspected patient usually reveals elevated glutaric acid, and always shows elevated 2-hydroxy-glutaric acid which is pathognomonic. Plasma and urine sarcosine levels are elevated in the milder patients, but not in the severe neonatal cases. Cultured fibroblasts and amniocytes have been used to measure dehydrogenase substrate oxidation. Mutations have been identified in the genes for ETF and ETF-QO. Prenatal diagnosis has been performed by finding elevated glutaric acid and elevated acylcarnitines in amniotic fluid. Prenatal diagnosis by DNA analysis is restricted to those families in which the mutation(s) is known.

Treatment

There is no effective treatment for the severe forms of MADD that present in the neonatal period. Patients with later onset less severe symptoms may respond to riboflavin (a precursor to FAD) and L-carnitine upplementation. Dietary restriction of fats and protein has had variable results.

Because the diagnosis and therapy of MADD 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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