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International Network for Fatty Acid Oxidation Research and Management

ACAD9

Acyl-CoA dehydrogenase 9 (ACAD9) is a member of the fatty acid acyl-CoA dehydrogenase (ACAD) protein family that for years had no clearly identified function. Like other members of the ACAD family, it resides within cells in the energy generating part called mitochondria and contributes to breaking down fats. It is found at high concentrations in certain organs like the liver and heart and in specific cell types in the lung and kidney. ACAD9 has a second important role in the assembly or stabilization of Complex 1 in the mitochondrial respiratory chain. The mitochondrial respiratory chain frees energy to do the body's work, including that from the fat breakdown pathways. The best guess at present is that ACAD9 is a dual function protein involved in essential functions for life.

Signs and symptoms

ACAD9 patients classically present with poor heart function due to an enlarged heart (hypertrophic cardiomyopathy), as early as the newborn period, but they can have a wide spectrum of presentations. Other common features include liver disease, large head (macrocephaly), and a progressive neurologic syndrome called Leigh's (Robinson et al. 1998). Leigh's syndrome is caused by the reduction of Complex 1 activity, making patients unable to generate sufficient energy to keep their cells healthy. The signs include poor suck; loss of head control and motor skills; loss of *appetite*; *vomiting*; and seizures. As the condition progresses, symptoms may include *weakness* and lack of *muscle* tone; extreme muscle tightness (*spasticity*); movement disorders; specific inability to coordinate joints and even eyes (*cerebellar ataxia*); and loss of nerve function in feet and legs and even fingers (peripheral neuropathy). Because these patients always function with inadequate energy, even a mild illness can precipitate Leigh's syndrome.

If the protein defect is located in the portion that is involved in fat breakdown, the patients tend to have more severe symptoms. Vitamin B2 (riboflavin) responsive mutations have been reported. One 36-year-old patient has been reported with a mild ACAD9 presentation. She had a lifetime history of exercise intolerance with lactic acidosis (clinical test) resulting in nausea and vomiting.

Diagnosis

Just as ACAD9 is a disorder with a varied presentation, there are no consistent specific biochemical markers in blood or urine of patients with ACAD9 deficiency. In some cases, especially those with a fatty acid oxidation defect-like presentation, the liver profile of the fat product acylcarnitine may be abnormal with an excess of unsaturated compared to saturated species. If the clinical presentation is more like that of a complex 1 defect, then the diagnosis becomes very difficult since there are over 100 genes that if defective can cause complex 1 dysfunction. Complex 1 activity may be low or occasionally normal(ref). Unlike most of the fatty acid oxidation disorders, ACAD9 deficiency is not identified by newborn screening, and there is no test for protein activity, as with many other ACAD defects. Most recent patients have been identified through whole exome sequencing, a method to look for mistakes at the gene expression level.

Genetics:

ACAD9 deficiency occurs when an individual inherits one change (mutation) in the gene for ACAD9 from each parent (autosomal recessive). Because ACAD9 is difficult to diagnose, there is no information as to its incidence. Parents of patients are carriers of the disease and have no symptoms. With each pregnancy, the parents have a 25% risk (1 in 4) chance to have another child with ACAD9 deficiency. Many different mutations in ACAD9 have been reported (249), but there is no common mutation to date. There have been no reported cases of prenatal diagnosis.

Treatment

Treatment of ACAD9 deficiency should focus on the defect in complex 1. If low blood sugar (hypoglycemia) is present, it should be corrected, but care must be taken not to induce a secondary lactic acidosis due to excess pyruvate production. VitaminB2 (riboflavin) at 100 mg/kg/day should be provided due to reports of its stabilization of some mutant ACAD9 variants. Cardiomyopathy should be treated aggressively medically.