

ACAD9 Deficiency: A New Inborn Error of Fatty Acid Oxidation Presenting as Liver Failure and Sudden Death

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The acyl-CoA dehydrogenases (ACADs) are a group of enzymes that function in the mitochondria in fatty acid oxidation. There are at least nine known members of the ACAD gene family, some of which are also active in amino acid metabolism or fatty acid oxidation. Deficiencies of the ACADs are among the most common inborn errors of metabolism. Seven different ACAD genetic defects have been described in the past. The most frequent signs of fatty acid oxidation defects are low muscle tone and recurrent hypoglycemia with fasting or stress. Clinical symptoms can, however, range from neonatal death to adult onset recurrent muscle break down (rhabdomyolysis). Affected individuals can also remain asymptomatic for life. The variability is great enough to preclude a definitive diagnosis on the basis of clinical symptoms alone.

Of the three long chain specific ACADs, inherited defects have only been identified in very long chain acyl-CoA dehydrogenase (VLCAD). Patients present with recurrent episodes of hypoglycemia with or without rhabdomyolysis, sudden unexplained death, and cardiomyopathy. Recently, tandem mass spectrometry has been used to detect characteristic metabolites in blood spots collected from newborn infants allowing diagnosis of VLCAD deficiency before symptoms develop. Long chain acyl-CoA dehydrogenase (LCAD) was characterized about a decade before VLCAD was discovered, however, its function remains a mystery. Acyl-CoA dehydrogenase 9 (ACAD9) has only recently been recognized and is very similar to VLCAD in many ways. My lab has recently reported the first cases of ACAD9 deficiency presenting with episodic liver dysfunction during otherwise mild illnesses or cardiomyopathy, along with chronic neurologic problems.

The first patient was a 14-year-old male who presented with a Reye-like episode (low blood sugar and high blood ammonia) triggered by ingestion of aspirin during a minor viral illness. He progressed to coma and liver failure, and died of brain swelling in spite of intensive care. On autopsy he had evidence of a stroke in his brain. The second patient is a girl who initially presented with hypoglycemia and liver failure at 4 months of age. Evidence of a mild stroke was present on a brain scan. She has continued to have recurrent episodes of liver dysfunction with hypoglycemia, usually triggered by viral infections though these have improved with age. She is now 10 years old. Another girl, now 2 ½ years old has had similar symptoms. Hypoglycemia in both only developed when they were sick. The final patients were sisters. One died at 4½ year of age of cardiomyopathy (weakness of the heart muscle) first diagnosed at 18 months of age. Her sister died of cardiomyopathy at 22 months of age. Liver abnormalities and hypoglycemia with illness were present in both girls.

Diagnosis of ACAD9 deficiency in these children has been difficult. Abnormalities in the blood acylcarnitine profile and urine organic acids suggested a problem with fatty acid oxidation when they were ill but could not identify the specific defect. These abnormalities disappeared when the patients were well. Acylcarnitine profiles in liver tissue were abnormal in the two patients tested and may prove to be the

most reliable test. DNA testing and special staining of cultured skin cells were useful in all of the cases. The development of rapid liver failure in three of our patients suggests that ACAD9 deficiency should be considered in any child with unexplained liver failure, especially when hypoglycemia or cardiomyopathy are present.

In spite of the high degree of similarity between ACAD9 and VLCAD, it is clear that their functions do not compensate for each other when either is deficient. Rather, our studies of the function of these two enzymes shows that each has a distinct role in metabolism and identifies new functions for fatty acid oxidation in brain metabolism.