

**The New Jersey Department of Health and Senior Services
Newborn Screening and Genetic Services**

Fatty Acid Oxidation Disorders

Information for Health Professionals

Description

Fatty acid transport and mitochondrial oxidation is a complex pathway that plays a major role in energy production during times of fasting and metabolic stress. Once free acids are released into the blood they are taken up by the liver and muscle cells and activated to coenzyme A esters. Then they are transported into the mitochondria and oxidized in a cyclic fashion by four sequential reactions that are each catalyzed by one of multiple enzymes. The acyl-CoA dehydrogenases are chain-length specific enzymes. Deficiencies or abnormalities in these result in very long chain acyl-CoA dehydrogenase deficiency (VLCAD), long chain acyl CoA dehydrogenase deficiency (LCAD), medium chain acyl-CoA dehydrogenase deficiency (MCAD), and short chain acyl-CoA dehydrogenase deficiency (SCAD). Any illness may lead to a fasting state that can then lead to the depletion of glucose stores. Once this occurs, fatty acid metabolism becomes the dominant energy source. If there is an abnormality in fatty acid metabolism, then life-threatening episodes of metabolic decompensation can ensue. Relatively simple dietary management may avoid symptoms.

Incidence

MCAD deficiency is the most common of the disorders with an incidence of 1/6000 to 1/10,000. Deficiency of VLCAD, LCAD, and SCAD is rare compared to MCAD.

Clinical Features

Clinically, individuals with one of the fatty acid oxidation disorders may present with hypoglycemia, liver disease, near SIDS, encephalopathy, myopathy, cardiomyopathy, or sudden death. Symptoms may appear at any age from birth to adult life.

Children with MCAD are typically normal at birth and develop episodes of hypoketotic hypoglycemia, vomiting, lethargy, and seizures associated with fasting. The first episode usually occurs between 6 months and two years of age. The plasma acylcarnitine profile is diagnostic and a common gene mutation is found in the majority of patients. Urine organic acids in these patients typically show elevations of dicarboxylic acids, glycine conjugates and acylcarnitines.

Individuals with VLCAD and LCAD are very similar clinically; they can present with SIDS, hypoglycemia, hepatomegaly, myopathy, Reye syndrome, and cardiomyopathy. The plasma acylcarnitine profile in these patients reveals elevated long chain acyl-carnitine esters. Urine organic acids in these patients typically show elevations of dicarboxylic acids. Diagnosis is confirmed by enzyme assay in fibroblasts.

SCAD deficiency presents in the neonatal period with failure-to-thrive, hypotonia, and metabolic acidosis. Hypoglycemia is not a common feature. Hyperammonemia and

lactic acidosis have been reported. The plasma acyl-carnitine profile reveals elevated short chain acyl carnitine esters. Urine organic acids show increased excretion of short chain organic acids ((ethylmalonic acid) and butyrylcarnitine. Diagnosis is confirmed by enzyme assay in fibroblasts.

Screening

The screening tests for the fatty acid oxidation disorders are done by the Inborn Errors of Metabolism Laboratory as part of the standard newborn biochemical screening. The newborn screen assays for plasma acyl carnitine levels by tandem mass spectrometry.

Confirmatory Testing

Diagnosis must be confirmed by molecular analysis. Diagnosis of VLCAD, LCAD and SCAD is confirmed by enzyme assay in fibroblasts.

Treatment

Early diagnosis and treatment is essential for an improved prognosis. If left untreated, these conditions may result in significant disability and, ultimately, death. Most of these conditions are chronic, with life-long episodes of hypoglycemia. For most fatty acid oxidation disorders, including MCAD, management involves long-term monitoring of serum glucose, a low-fat, high-carbohydrate diet, avoidance of fasting, aggressive support during illness, and carnitine supplementation. It is strongly recommended that **infants under age 1 be fed around the clock every 2-4 hours.**

Treatment of SCAD is not effective, but the restriction of fats and supplementation of carnitine has been tried.

Implications for Genetic Testing

All of the disorders of fatty acid oxidation are autosomal recessive and therefore are associated with a 25% recurrence risk in future pregnancies. **If one child is diagnosed with a fatty acid oxidation disorder, their siblings should also be tested, even if the sibling is asymptomatic.**

Interpretations/Recommendations:

Initial Specimens

- **Expected Results:** No elevated markers for C3, C4, C5, C6, C8, C10:1, C14, C14:1, C16 (Acylcarnitine Profile within Acceptable Limits)
- **Equivocal Results:** A fatty acid oxidation disorder or acylcarnitine disorder needs to be ruled out for any reason (e.g., interference); requires a repeat specimen

Recommend: Repeat specimen within 48 hours

Interpretations/Recommendations (cont.):

- **Presumptive Positive Results:** Elevated acylcarnitine markers indicating a possible fatty acid oxidation disorder
 - Possible MCAD (medium chain acyl CoA dehydrogenase deficiency) C6, C8, C10:1, C8/C20, C8/C16
 - Possible SCAD (short chain acyl CoA dehydrogenase deficiency) C4 and C4/C3
 - Possible VLCAD (very long chain acyl CoA dehydrogenase deficiency) C14, C14:1, C14:1/C16

Recommend: Immediate assessment of baby's health status and consultation with metabolic/genetic specialist.

Repeat specimens

- Elevated acylcarnitine levels by tandem mass spectrometry are exactly the same as the initial specimen but do not match an established profile for one of the fatty acid oxidation disorders on the test panel. They might, however, be indicative of some other metabolic disorder.

Recommend: Immediate assessment of the baby's health and consultation with a metabolic/genetic specialist.

This information sheet is based on Information Sheet for Professionals by Joan Pellegrino, M.D.

NOTE: Newborn screening tests are adjuncts to clinical assessment, which is paramount. A fatty acid oxidation disorder should be considered in infants with any of the signs/symptoms regardless of newborn screening results

Additional information:

New England Metabolic Consortium – Newborn Screening Protocols
<http://www.childrenshospital.org/newenglandconsortium/>

Gene Tests/Gene Clinics
<http://www.genetests.org>

U.S. National Newborn & Genetics Resource Center
<http://www.gens-r-us.uthscsa.edu>

For questions, contact:

Inborn Errors of Metabolism Laboratory at (609) 292-3090
Newborn Screening Follow-Up Program at (609) 292-1582

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