**Fatty Acid Oxidative Disorders**

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**Definition:** Fatty acid oxidation disorders are inherited conditions that affect the way a person’s body breaks down certain fats (fatty acids). A person with a fatty acid oxidation disorder cannot breakdown their stored fat for energy. Consequently, the body begins to fail once food the person has eaten runs out. In addition, fatty acids build up in the blood. In the case of fatty acid oxidation disorders, the inability to break down fats for energy and the build up of fatty acids can cause serious health problems.

**Outcomes without screening:** The symptoms of these conditions vary and depend on the type of fatty acid oxidation disorder. Some present in the newborn period with hypoketotic hypoglycemia, signs of liver failure, hyperammonemia; accumulation of toxic long chain acyl carnitines causing lactic acidosis, cardiomyopathy, and hepatopathy; others affecting long chain FAOD may present as chronic weakness, rhabdomyolysis, and cardiomyopathy; and renal excretion may cause Carnitine deficiency. Without treatment, children with a fatty acid oxidation disorder may experience periods of poor feeding, lack of energy, difficulty breathing, low blood glucose (sugar) and vomiting. These episodes can become serious enough to lead to developmental delay, seizures, coma and even sudden death.

**Incidence:** Most FAODs are rare disorders in the general population but some ie MCAD have incidences of 1/10,000 to 1/15,000.

**Outcomes with screening:** The first step of newborn screening is to identify all infants with elevated metabolite levels. The next steps are to quickly confirm the suspected disorder, assess the need for glucose, carnitine, modified diet and cofactor therapy and begin treatment immediately. Each of these disorders is rare, and there have been only a few years of experience with children identified by a newborn screen. However, evidence is accumulating that early detection and treatment can lessen the symptoms in the classic early onset cases and protect the milder cases from the repercussions of metabolic insult.

**Causes of fatty acid oxidative disorders:** Fatty acid oxidation disorders are genetic conditions caused by changes in certain genes. These genes are responsible for making enzymes. Enzymes deficient in FAODs are responsible for breaking down fatty acids. When there is an alteration in these genes, enzyme levels go down and fatty acids build up in the blood. Fatty acid oxidation disorders are inherited in an autosomal recessive pattern, which means two copies of a gene must be changed for a person to be affected with a fatty acid oxidation disorder. Most often, the parents of a child with an autosomal recessive condition are not affected because they are “carriers”, with one copy of the changed gene and one copy of the normal gene. When both parents are carriers, there is a one-in-four (or 25%) chance that both will pass a changed gene on to a child, causing the child to be born with the condition. There also is a one-in-four (or 25%) chance that they will each pass on a normal gene, and the child will be free of the condition. There is a two-in-four (or 50%) chance that a child will inherit a changed gene from one parent and a normal gene from the other, making it a carrier like its parents. These chances are the same in each pregnancy for the same parents.

**Screening test and confirmation:** Babies can be tested (newborn screening) for fatty acid oxidation disorders before they leave the hospital. The baby’s heel is pricked and a few drops of blood are taken. The blood is sent to the state laboratory to find out if it has more than a normal amount of fatty acids.
Some states screen newborns for fatty acid oxidation disorders. The metabolites that are related to specific disorders are detected by tandem mass spectrometry. Due to the natural variation in the metabolic function of newborn infants, some infants will be reported with elevated levels of metabolites that are only temporary. Thus follow-up diagnostic tests are required to identify the infants truly affected by an organic acid disorder.

There are various types of fatty acid oxidation disorders. The following is a list of fatty acid oxidation disorders that can be screened for:

- 2, 4 Dienoyl CoA Reductase deficiency
- Carnitine/Acylcarnitine Translocase deficiency (CAT)
- Carnitine Palmitoyl Tranferase deficiency Type I (CPT-I)
- Carnitine Palmitoyl Tranferase deficiency Type II (CPT-2)
- Carnitine Uptake Defect (CUD)
- Long/Very Long Chain Acyl CoA Dehydrogenase deficiency (LCAD/ VLACD)
- Long Chain Hydroxy Acyl CoA Dehydrogenase deficiency (LCHAD)
- Medium Chain Acyl CoA Dehydrogenase deficiency (MCAD)
- Multiple Acyl CoA Dehydrogenase deficiency (GA-II)
- Short Chain Acyl CoA Dehydrogenase deficiency (SCAD)
- Trifunctional Protein deficiency (TFP)

**Treatment:** In many cases, therapy with a special diet and/or prescription medication is used. Children and adults with a fatty acid oxidation disorder require follow-up care at a medical center or clinic that specializes in this condition.

**Special concerns and issues:** Confirmation may require analysis of urine organic acids, blood acyl carnitine profiles, enzymatic and molecular studies.

**Examples:**

**Medium Chain Acyl CoA Dehydrogenase deficiency (MCAD)**

*Introduction:* MCADD is an autosomal recessive disorder of fatty acid oxidation occurring in 1:10-15,000 live births. MCADD results in an inability to break down fatty acids of medium chain length for ketone and ATP synthesis (see figure).

*Clinical Features:* Affected individuals can be completely normal until prolonged fasting or infection leads to metabolic decompensation. This typically presents with hypoketotic hypoglycemia, seizures, vomiting, lethargy and coma. About 20% of infants with MCADD die during an acute episode when the diagnosis is not yet suspected. Survivors may suffer from neurological sequelae such as developmental delay, seizures, attention deficit hyperactive disorder or other behavioral abnormalities.

*Diagnosis:* Newborn screening by tandem mass spectrometry identifies elevations in medium chain acylcarnitines, most notably octanoylcarnitine (C8-carnitine).

*Treatment:* The basic treatment for MCADD is the avoidance of fasting. This involves regular feeding during the day and limitation of overnight fasting. The duration of overnight fasting depends on the age of the child. Infants and young children may be more subject to sudden death than older children and should not go without food intake longer than 4 hours for the first 4 months of life, no longer than 6 hours for ages 4-8 months and no longer than 8 hours thereafter. Restriction of dietary fat is controversial but it is reasonable during intercurrent infections. Carnitine administration may be provided in the case of a low blood carnitine level.
Very Long chain Acyl-CoA Dehydrogenase Deficiency

Introduction: Very long-chain acyl-CoA Dehydrogenase Deficiency (VLCADD) is an autosomal recessive disorder of fatty acid oxidation resulting in an inability to breakdown long-chain fatty acids for ketone and ATP synthesis (see figure). Clinical symptoms are often triggered by prolonged fasting, infection or exercise. It is treated with diet and supplemental carnitine.


Diagnosis Newborn screen: Tandem mass spectrometry diagnosis on the basis of elevated long-chain acyl carnitines, notably C14-carnitine and C16-carnitine.

Confirmation: Repeat newborn screen, plasma or blood acylcarnitines (elevated long-chain acylcarnitine), urinary organic acids (dicarboxylic aciduria) and reduced palmitoyl-CoA dehydrogenase activity in cultured fibroblasts.

Treatment: Treatment for VLCADD includes a low fat, high carbohydrate diet supplemented with medium chain triglyceride (MCT) oil and avoidance of fasting by regular feeding during the day and limitation of overnight fasting, corn starch is often mixed into the evening formula or milk. The duration of overnight fasting depends on the age of the child. Infants and young children may be more subject to sudden death than older children and should not go without carbohydrate intake longer than 4 hours for the first 4 months of life, no longer than 6 hours for ages 4-8 months and no longer than 8 hours thereafter. Adequate treatment can prevent or reverse the clinical symptoms in VLCADD, including the cardiomyopathy. Carnitine administration may be provided in the case of a low blood carnitine level. Some centers treat with carnitine regardless of the blood level. No side effects of carnitine are known other than a fishy odor and some loosening of stools when given in very high doses (usually not necessary in VLCADD).

Short Chain Acyl CoA Dehydrogenase Deficiency

Introduction: Short chain acyl-CoA Dehydrogenase Deficiency (SCADD) is a rare autosomal recessive disorder of fatty acid oxidation. Reported individuals have shown extremely variable phenotypes.


Diagnosis Newborn screen: Tandem mass spectrometry diagnosis on the basis of elevated short chain acyl carnitines, notably C4-carnitine (butyrylcarnitine)

Confirmation: Plasma acylcarnitines (elevated butyryl-acylcarnitine), urinary acylglycines (elevated butyrylacylglycine), urinary organic acids (elevated ethylmalonic acid and other short chain acyl CoA metabolites) and enzyme assay of cultured fibroblasts

Treatment: The basic treatment for SCADD is the avoidance of fasting. This involves regular feeding during the day and limitation of overnight fasting. The duration of overnight fasting depends on the age of the child. Infants and young children may be more subject to sudden death than older children and should not go without food intake longer than 4 hours for the first 4 months of life, no longer than 6 hours for ages 4-8 months and no longer than 8 hours thereafter. Restriction of dietary fat is controversial but it is reasonable during intercurrent infections. Carnitine administration may be provided in the case of a low blood carnitine level. Some centers treat with carnitine regardless of the blood level. No side effects of carnitine are known other than a fishy odor and some loosening of stools when given in very high doses (usually not necessary in SCADD). However routinely treating with carnitine remains a topic of debate in the metabolic community.