

PROTOCOL FOR NEWBORN SCREENING RESULT

Elevated hydroxyacyl carnitine profile (increased 3-OH-C14, -C16, -C18:1, -C18:2 acylcarnitine) associated with Long Chain Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD) or Trifunctional Protein Deficiency (TFPD)

First Newborn screening result

Elevated hydroxyacyl carnitine profile, probable LCHADD/TFPD

Elevated long chain hydroxyacyl carnitine profile, probable LCHADD/TFPD

Long Chain Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD/TFPD) is a defect of fatty acid utilization for energy. Consequently there is decreased tolerance for fasting or hypoglycemic states. Sudden death or permanent organ damage during a metabolic crisis can rapidly ensue.



LCHAD : Long Chain 3-Hydroxyacyl-CoA Dehydrogenase

History and examination

The infant and parent(s) must be seen within the next day or two following notification from the newborn screening lab. A METABOLIC PHYSICIAN MUST BE CONSULTED.

History

The infant may have a normal history. On occasion however, there is a history of neonatal lethargy, hypotonia, cardiomyopathy, muscle weakness, vomiting, seizures, or coma. Since LCHADD is an autosomal recessive genetic disorder, there is a 25% chance that sibs of the identified infant may also have LCHADD. Significant markers in family history includes other children becoming seriously ill, having SIDS or, if the child's mother had the HELLP syndrome during pregnancy (**h**emolysis, **e**levated **l**iver enzymes and **l**ow **p**latelets) or acute fatty liver of pregnancy (AFLP).

Examination

The infant may appear entirely healthy and well. Neonatal signs include hepatomegaly, tachypnea and/or heart failure. Laboratory findings during neonatal illness may include hypoglycemia, metabolic acidosis, hyperammonemia, elevated CPK, elevated lactate,

transaminases and secondary carnitine deficiency. ANY signs of illness must be treated as a medical emergency and treated immediately.

Go to Acute illness protocol, LCHADD.

If the child appears well it is still essential to refer to the metabolic center to ensure that the child and family receive the necessary treatment and guidance to prevent any morbidity.

Contact the metabolic physician for elevated long chain hydroxyacyl carnitine profile

ENSURE THAT THE REPEAT NEWBORN SCREENING SAMPLE IS SENT TO THE NEWBORN SCREENING LABORATORY AND THE RESULT OBTAINED ASAP

(Go to **NNSGRC** for the state labs)

Discussion with parents for elevated long chain hydroxyacyl carnitine profile

Contact metabolic physician for elevated long chain hydroxyacyl carnitine profile

Your local metabolic physician can be found via **metabolic physicians and specialists**

The metabolic physician's role

- Provides you with information on LCHADD/TFPD
- Discusses, in further detail, the meaning of the test result with the family
- Starts appropriate **treatment**
- Provides supportive counseling for the family
- Undertakes **definitive investigations**
- Provides genetic / prenatal counseling
- Hospitalizes, if necessary, in a metabolic unit for acute illnesses. These infants cannot be managed conservatively when they become ill. The threshold should be very low for intravenous 10% dextrose and very close metabolic monitoring by a metabolic physician.

Return to **discussion with parents for elevated long chain hydroxyacyl carnitine profile**

Discussion with parents for elevated long chain hydroxyacyl carnitine profile

Response to a reported newborn screening result must be undertaken in two parts;

1. Initial contact with the family, often by phone, to inform them of the newborn screening result.
2. Meeting with the family at the office.

Initial communication

Many parents want to know what the result is testing positive for and are reassured if their doctor has knowledge of Long chain hydroxyacyl-CoA Dehydrogenase Deficiency

(LCHADD) or has taken the time to find out about the condition when informing the family (see **commonly asked questions**).

A highly elevated long chain hydroxyacyl carnitine profile probably means that the infant has LCHADD or TFPD (which is generally milder than LCHADD).

LCHADD is a disease in which fat cannot be properly utilized for energy. Treatment can be very effective. However, if not treated preventatively, children can become ill very rapidly if their blood sugar drops too low and death or damage to the heart and/or liver can occur. The mainstay of treatment is prevention and amelioration. It is essential that parents arrange to see a metabolic doctor as soon as possible.

In the office

Many parents do not understand newborn screening or the need to treat their apparently healthy baby.

Parental anxiety will be high and it is important to reassure them that

- Treatment is available.
- But note that failure to treat a baby with LCHADD may result in life threatening illness that could produce mental retardation, heart failure, hepatic failure, muscular weakness, or death.

Treatment for LCHADD is based on ensuring that hypoglycemia through fasting or the increased energy requirement of the body when sick is avoided. Therefore, if not ill, the baby should initially be fed every 4 hours around the clock. If the infant becomes ill, supplemental glucose as 10% dextrose given intravenously is often required to maintain energy levels and avoid life threatening energy deficit. When this happens, the metabolic doctor must be contacted and involved to ensure that all the necessary metabolic tests and measures are carried out.

Further counseling, treatment and a more detailed assessment and testing of the infant is required; therefore

contact metabolic physician for elevated long chain hydroxyacyl carnitine profile

Commonly asked questions

1. What is LCHADD?

LCHADD, also known as Long chain hydroxyacyl-CoA Dehydrogenase Deficiency, is a fatty acid oxidation disorder (FAOD). It is a defect in one of the enzymes responsible for converting fats to fuel that can be used by the body. It becomes very important when the body is low on glucose or needs additional fuel (e.g. when the child has not eaten for a period of time, during infections and other illnesses, during operations and when exercising vigorously).

2. How and when will we know if my baby has LCHADD?

If your baby's newborn screening result showed an elevated long chain hydroxyacyl carnitine profile he or she probably has LCHADD (or TFPD). If the result was less elevated your baby either could still have LCHADD or it may have been a false positive result. The newborn screening test will be repeated and additional tests will be undertaken to help determine if your baby has LCHADD or not. Typically the results of these tests take up to 4 days to come back. Depending on the test results, additional

testing can take a variable amount of time to confirm the diagnosis. In a very small minority of cases, it can be difficult to determine whether a child is affected or not.

3. How did my baby get this?

LCHADD is an autosomal recessive disorder. This means that your baby has two mutated LCHAD genes, one from the mother and one from the father. Having only one mutated LCHAD gene (a carrier) does not affect a person at all.

4. What does it mean for my child?

If your baby has LCHADD, he or she will have to be fed regularly on a fat modified/decreased diet and cannot be allowed to miss a meal. Some children also take carnitine, a mild supplemental medicine, but your metabolic physician will be able to let you know if this is appropriate for your child. If he or she becomes ill, it may well be necessary early in the illness (i.e. when it might be considered mild), to provide extra energy in the form of glucose through addition to food or, if necessary, by intravenous drip.

5. What is the treatment? Does it work? Is the diet difficult to do/expensive?

LCHADD is primarily treated by a high carbohydrate and fat modified/decreased diet that is given at regular defined intervals around the clock. As the diet is essentially normal it should not be a financial burden. However, ensuring that you and the baby wake up, initially every 4 hours, can be physically exhausting over time. If possible you should anticipate this and try and ensure that you have support from your spouse or other close contacts to assist you so that you may enjoy your time with your baby.

6. What about my other children/future children?

As LCHADD is an inherited condition it is essential to have your other children tested. Children from the same father and mother as the affected infant have a 1 in 4 (25%) chance of having LCHADD. Your other children can appear healthy and still have LCHADD. If they have LCHADD, successfully having weathered illnesses in the past is no guarantee that an illness in the future will not have serious consequences.

Since there is a risk for having a future child with LCHADD it is important to let your obstetrician and pediatrician know that you have a child with LCHADD if you are planning future pregnancies so that they may discuss the options with you and prepare accordingly. The obstetrician should furthermore be alerted to the association between LCHADD and the HELLP and AFLP syndromes to the mother during pregnancy (see "History and Examination section" above).

Definitive Investigations

1. Quantitative urine organic acids

In symptomatic patients high elevations of C6-C14 hydroxydicarboxylic acids, and on occasion medium chain C6-C10 dicarboxylic acids are also seen. Nevertheless, standard urine organic acid profiles may be normal within the first day or two of life or uninformative when those with LCHADD are stable and are not fasting.

2. Plasma acylcarnitines

The profile of patients with LCHADD is characterized by accumulation of 3-OH-C16, -C18:1 & -C18:2. A potential pitfall of acylcarnitine analysis in the diagnosis of LCHADD is the possibility that patients with secondary carnitine deficiency may not show a significant elevation of acylcarnitines.

3. Acute illness labs

Hypoketotic hypoglycemia at all ages is suggestive of a fatty acid oxidation disorder.
NBS LCHAD results protocol 02/03

CPK and liver function tests should be assayed. Decreased carnitine, anemia and thrombocytopenia may be present.

The lab tests may not be informative when the infant is well, therefore these tests are most valuable at times of acute illness. Labs ideally obtained for diagnostic purposes during acute illness in order of priority include plasma glucose, urinalysis, plasma acylcarnitines, plasma amino acids, and urine for organic acids. However, treatment should **NEVER** be delayed to obtain these labs and acute management labs should take priority (see [Acute illness protocol, LCHADD.](#))

4. Enzyme assay

LCHAD enzymatic activity can be measured in cultured fibroblast cells from e.g. skin biopsy. As LCHAD is caused by a defect in the LCHAD component of a trifunctional protein. In trifunctional protein deficiency all three components (LCHAD, long chain oxoacyl-CoA thiolase and 2-enoyl-coA hydratase) are affected. [Go to genetests](#)

Molecular testing

Mutation testing of the gene is helpful, particularly for the C1528G mutation, which is present in the homozygous form (i.e. both copies of the gene) in 70% or more of cases of LCHADD. [Go to genetests](#)

Treatment

Diet

The mainstay in the treatment of LCHADD is avoidance of fasting. Infants require frequent feedings, initially every 4 hours. A relatively high carbohydrate modified fat diet is helpful. Medium chain triglyceride (MCT) oil may be helpful. BUT, MCT oil should only be initiated by the metabolic physician following comprehensive workup as it will worsen other fatty acid oxidation defects including medium chain acyl-CoA, short chain acyl Co-A and glutaric acidemia type II.

Carnitine

It is unclear that carnitine (or riboflavin, which has also been used) is helpful.

Acute illness treatment

Any time the child is sick an evaluation should be made and the child's metabolic physician contacted. Prophylactic intravenous 10% glucose should be given if the child is unable to eat, vomiting or physiologically stressed, even mildly. The threshold for aggressive treatment should be very low.

All patients should be provided with an up to date personalized "emergency" letter to give to ER, or other doctors, who are probably not familiar with LCHADD. This letter should include management issues and emphasize the importance of preventive measures (e.g., IV 10% glucose regardless of "normal" laboratory results and the telephone numbers of the patient's metabolic specialist who needs to be contacted to discuss management). See [Acute illness protocol.](#)