

PROTOCOL FOR NEWBORN SCREENING RESULT

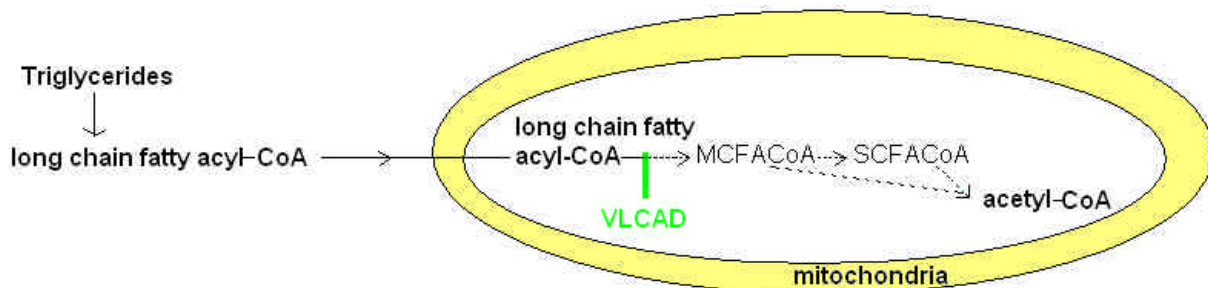
Elevated C14, C14:1 acylcarnitine (tetradecanoylcarnitine); Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD)

First Newborn screening result

C14 C14:1 markedly elevated, probable VLCADD

C14, C14:1 markedly elevated, probable VLCADD

Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD) is a defect of very long chain fatty acid utilization for energy. Consequently there is little or no tolerance for fasting or hypoglycemic states. Sudden death or permanent neurologic damage during a metabolic crisis can rapidly ensue.



VLCAD: very long chain acyl-CoA dehydrogenase
MCFACoA : medium chain fatty acyl-CoA
SCFACoA : short chain fatty acyl-CoA

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, irritability, feeding difficulties, vomiting, seizures, or coma. Since VLCADD is an autosomal recessive genetic disorder, there is a 25% chance that sibs of the identified infant may also have VLCADD. A family history of other children in the family becoming seriously ill, having cardiomyopathy or SIDS is very significant.

Examination

The infant will may appear entirely healthy and well. If ill, the neonatal signs include hepatomegaly, tachypnea, lethargy and, later in infancy, cardiomyopathy. Laboratory findings during neonatal illness may include hypoglycemia, wide anion gap, metabolic acidosis, hyperammonemia, elevated CPK, transaminases and secondary carnitine deficiency. **ANY** signs of illness must be treated as a medical emergency and treated immediately.

Go to Acute illness protocol, VLCADD.

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 markedly elevated C14, C14:1

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 markedly elevated C14, C14:1

Contact metabolic physician for markedly elevated C14, C14:1

Your local metabolic physician can be found via [metabolic physicians and specialists](#)

The metabolic physician's role

- Provides you with information on VLCADD.
- 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 can not 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 markedly elevated C14, C14:1](#)

Discussion with parents for markedly elevated C14, C14:1

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 Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD) or has taken the time to find out about the condition when informing the family (see [commonly asked questions](#)).

Highly elevated C14 and C14:1 acylcarnitines (tetradecanoylcarnitine, also known as myristoylcarnitine) levels of > 0.76 and >0.43 $\mu\text{mol/L}$ respectively, usually means that the infant has VLCADD.

VLCADD is a disease in which fat cannot be properly utilized for energy. It is TREATABLE. However, if not treated preventatively, children can become ill very rapidly if their blood sugar drops too low and sudden death can occur. The mainstay of treatment is prevention and early aggressive treatment for illness. 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 to help treat the condition.
- But note that failure to treat a baby with VLCADD may result in life threatening illness that could produce mental retardation, heart failure or sudden death.

Treatment for VLCADD is based on ensuring that hypoglycemia through fasting or the increased energy requirement of the body when sick is avoided. Therefore, when well the baby should initially be fed every 4 hours around the clock with no exceptions. Once the diagnosis is confirmed, AND other fatty acid oxidation defects are ruled out (but not before), medium chain triglyceride (MCT) oil may be given. 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 markedly elevated C14, C14:1](#)

Commonly asked questions

1. What is VLCADD?

VLCADD, also known as Very Long Chain Acyl-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 such as when the child has not eaten for a period of time, during infections and other illnesses, during operations, or when exercising vigorously.

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

If your baby's newborn screening result showed a markedly elevated C14 & C14:1 levels, he or she probably has VLCADD. If the result was less marked your baby either could still have VLCADD 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 whether or not your baby has VLCADD. 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 or not a child is affected.

3. How did my baby get this?

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

4. What does it mean for my child?

If your baby has VLCADD, he or she will have to be fed regularly on a fat modified 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?

VLCADD is primarily treated by a high carbohydrate and fat modified diet that is given at regular defined intervals around the clock. As the diet is essentially normal it should not be a major additional 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 VLCADD 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 VLCADD. Your other children can appear healthy and still have VLCADD. If they have VLCADD, 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 VLCADD it is important to let your obstetrician and pediatrician know that you have a child with VLCADD if you are planning future pregnancies so that they may discuss the options with you and prepare accordingly.

Definitive Investigations

1. Quantitative urine organic acids

In symptomatic patients, saturated and unsaturated dicarboxylic aciduria will be present. Hypoketotic hypoglycemia at any age is suggestive of a fatty acid oxidation disorder. Nevertheless, standard urine organic acid profiles may be uninformative when those with VLCADD are stable and are not fasting.

2. Plasma acylcarnitines

The profile of patients with VLCADD is characterized by accumulation of C14, C14:1 and C16 species, with C14:1 (myristoylcarnitine) as the most prominent abnormality. A potential pitfall of acylcarnitine analysis in the diagnosis of VLCADD is the possibility that patients with secondary carnitine deficiency may not show a significant elevation of acylcarnitines.

3. Acute illness labs

As can be seen from above, many of the lab tests can be not 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, VLCADD.](#))

4. Enzyme assay. [Go to genetests](#)

VLCAD enzymatic activity can be measured in cultured fibroblast cells (e.g. from skin biopsy). The ratio of C16 to C12 in cells incubated with H₃-palmitate can help to predict whether the infant will be more likely to have the cardiomyopathic or milder hypoglycemic form.

5. Molecular testing

Mutation testing of the gene is available. V243A is the most frequent mutation. [Go to genetests](#)

Treatment

Diet

The mainstay in the treatment of VLCADD 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, which is metabolized after the enzyme block, appears to be very helpful. BUT MCT oil should only be given after an unequivocal diagnosis of VLCADD has been made 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

Oral supplementation with 100 mg/kg/day of carnitine is used in both the cardiac and non-cardiac forms of VLCADD.

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 VLCADD. 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](#).