

PROTOCOL FOR NEWBORN SCREENING RESULT

Elevated C16 & C18:1 acylcarnitine, (hydroxyhexadecanoyl- and hydroxyoctadecanoyl-carnitines), associated with

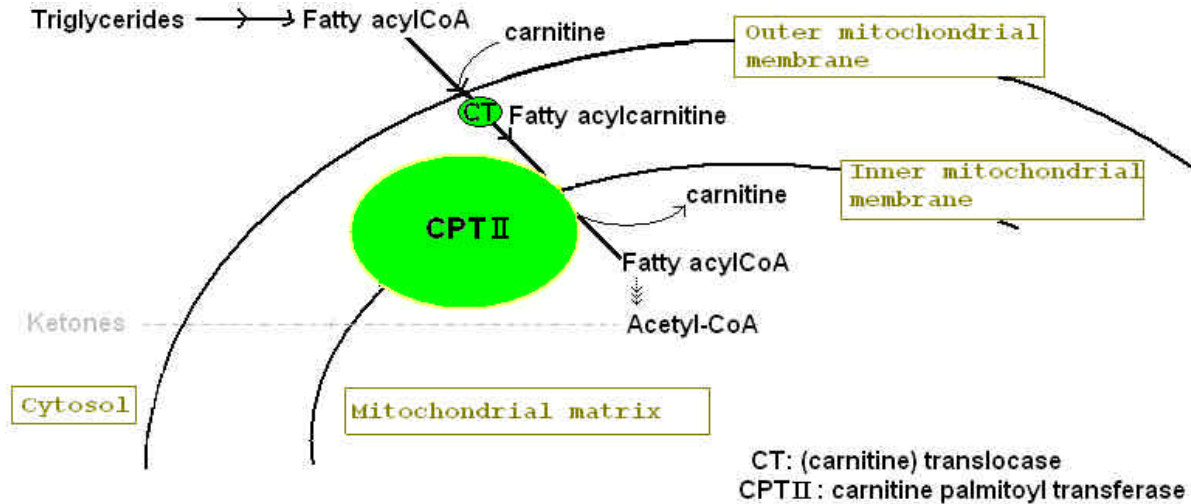
Carnitine Palmitoyltransferase II (CPT II) Deficiency (or Carnitine Translocase Deficiency)

First Newborn screening result

C16 & C18:1 markedly elevated, probable CPT II deficiency (or Translocase deficiency)

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Carnitine palmitoyltransferase II (CPT II) is an enzyme that catalyzes the release of fatty acids from the fatty acylcarnitine transported across the mitochondrial bi-membrane layer by the translocase. These two enzymes complete the transport of fatty acids into mitochondria where they are oxidized and thus utilized for energy. In CPT II deficiency and translocase deficiency states the fatty acylcarnitine produced from the extramitochondrial fatty acids by CPT I cannot be transported and converted into utilizable fuel in the mitochondrial matrix. Consequently there is decreased tolerance for fasting or any hypoglycemia state wherein energy must be supplied from fats. Death during a metabolic crisis can ensue.



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

For CPT II deficiency the infant may have a normal history. In the neonatal form of CPT II deficiency and CT deficiency, there is a history of neonatal lethargy, cardiomyopathy, seizures or coma. Since both these conditions are autosomal recessive genetic disorders, there is a 25% chance that sibs of the identified infant may also have CPT II deficiency or translocase deficiency. A family history of other children becoming seriously ill particularly with liver failure, hypertrophic cardiomyopathy, arrhythmias or sudden death is very significant. Translocase deficiency is extremely rare and presents with severe metabolic decompensation in the early neonatal period. CPT II deficiency has neonatal, infantile and adult onset variants.

Examination

The infant may appear entirely well. Neonatal signs include dysmorphic features, renal dysplasia, neurocortical defects, respiratory distress, hypoglycemia, seizures, hepatomegaly, arrhythmias and cardiomegaly. Laboratory findings during neonatal illness include hypoglycemia, metabolic acidosis, marked hyperammonemia and low free & total carnitine. Mortality is very high for neonatal onset cases. ANY signs of illness must be treated as a medical emergency and treated immediately by a metabolic physician.

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 C16 & C18:1

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 C16 & C18:1

Contact metabolic physician for markedly elevated C16 C18:1

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

The metabolic physician's role

- Provides you with information on CPT II deficiency (and translocase deficiency).
- 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 markedly elevated C16 & C18:1](#)

Discussion with parents for markedly elevated C16 & C18:1

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 deficiency or has taken the time to find out about the condition when informing the family (see [commonly asked questions](#)).

A highly elevated C16 & C18:1 acylcarnitine (hydroxyhexadecanoyl- and hydroxyoctadecanoyl-carnitine, also known as myristoylcarnitine) probably means that the infant has CPT II deficiency though very rarely the child may have carnitine translocase deficiency (which owing to the extreme rarity and acute severe neonatal presentation will not be discussed further here).

CPT II deficiency is a disease in which fat cannot be properly utilized for energy. Treatment can help. However, if not treated preventatively, children can become ill very rapidly if their blood sugar drops too low. Rhabdomyolysis is a risk. Death can also occur. The mainstay of treatment is prevention. 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 CPT II deficiency may result in life threatening illness or death.

Treatment for CPT II deficiency 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 or may even require continuous nasogastric drip-feeding. 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 C16 & C18:1](#)

Commonly asked questions for CPT II deficiency

1. What is CPT II deficiency?

CPT II deficiency, also known as carnitine palmitoyltransferase deficiency, is a fatty acid oxidation disorder (FAOD). It is a defect in one of the enzymes involved in the deployment of 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 and when exercising vigorously.

2. How and when will we know if my baby has CPT II deficiency?

If your baby's newborn screening result showed a markedly elevated C16 & C18:1 level, he or she probably has CPT II deficiency. If the result was only mildly elevated your baby either could still have CPT II deficiency 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 CPT II deficiency 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?

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

4. What does it mean for my child?

If your baby has CPT II deficiency, he or she will have to be fed regularly on a carbohydrate rich fat modified/decreased diet and can not be allowed to miss a meal. Medium chain triglyceride supplementation is used to provide fat energy past the enzyme block. 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?

CPT II deficiency is primarily treated by a high carbohydrate and fat modified/decreased diet that is given at regular defined intervals around the clock or even, in some cases, during the initial period by continuous nasogastric feeding. As the diet is essentially normal it should not be a financial burden. However, ensuring that you and the baby awake, 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 CPT II deficiency 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 CPT II deficiency. Your other children can appear healthy and still have CPT II deficiency. If they have CPT II deficiency, 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 CPT II deficiency it is important to let your obstetrician and pediatrician know that you have a child with CPT II deficiency 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 a dicarboxylic aciduria is seen. Nevertheless, standard urine organic acid profiles may be uninformative when those with CPT II deficiency are stable and are not fasting.

2. Plasma acylcarnitines

The profile of patients with CPT II deficiency is characterized by accumulation of C16, & C18:1. A potential pitfall of acylcarnitine analysis in the diagnosis of CPT II deficiency 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. CPK and liver function tests should be assayed as well as free and total carnitine. 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 .

5. Enzyme assay

CPT II is ubiquitous in human tissues and enzymatic oxidation of radiolabelled long chain fatty acids can be measured in cultured fibroblast cells. Levels in infantile/neonatal variants of CPT II are typically 5-25% of control values. [Go to genetests](#)

Molecular testing

Mutation testing of the gene is helpful particularly for the common C338T and C149A mutations found in the European populations or for the Ashkenazi Jewish 1238-9 delAG & T1342C mutations. There are numerous other less common recognized mutations and for some mutations it is possible to make a genotype : phenotype correlation. [Go to genetests](#)

Treatment

Diet

The mainstay in the treatment of CPT II deficiency is avoidance of fasting. Infants require frequent feedings, initially every 4 hours and in some cases may even initially require continuous nasogastric infusion. A relatively high carbohydrate modified fat diet is helpful. Medium chain triglyceride (MCT) oil is 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

Carnitine may be helpful in severe cases.

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 CPT II deficiency. 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). As CPT II deficiency can require additional measures it is essential that emergency treatment involves a metabolic physician.