

**Elevated C8 acylcarnitine, (octanoylcarnitine) Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)**

**First Newborn screening result**

**C8 markedly elevated, > 2 µmol/L, probable MCADD**

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) is a defect of medium 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 crises can rapidly 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**

The infant is most likely to have a normal history. On occasion however, there is a history of neonatal lethargy, vomiting, seizures or coma. Since MCADD is an autosomal recessive genetic disorder, there is a 25% chance that sibs of the identified infant may also have MCADD. A family history of SIDS or other children in the family becoming seriously ill is very significant.

**Examination**

The infant will most likely appear entirely healthy and well. Neonatal symptoms, while rare, do occur. The sick infant will be lethargic and have hepatomegaly. Laboratory findings during neonatal illness will probably include hypoglycemia, metabolic acidosis, hyperammonemia and abnormal liver function test results, particularly of coagulation factors (PT, PTT). ANY signs of illness must be treated as a medical emergency and treated immediately. **Go to Acute illness protocol, MCADD.**

**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 C8****

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 C8**

## Contact metabolic physician for markedly elevated C8

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

The metabolic physician's role

- Provides you with information on MCADD
- Discuss, in further detail, the meaning of the test result with the family
- Start appropriate [treatment](#)
- Provide supportive counseling for the family
- Undertake [definitive investigations](#)
- Provide genetic / prenatal counseling
- Hospitalize, 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 C8](#)

## Discussion with parents for markedly elevated C8

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

A highly elevated C8 acylcarnitine (octanoylcarnitine) level of  $> 2 \mu\text{mol/L}$  (with or without concomitant elevations in C6 and/or C10:1) usually means that the infant has MCADD. Very rarely is it indicative of another condition.

MCADD is a disease in which fat cannot be properly utilized for energy. It is TREATABLE and if managed appropriately should not affect the child's well being. However, if not treated preventatively, children can become ill very rapidly if their blood sugar drops too low and sudden death can occur. As the mainstay of treatment is prevention, it is essential that they 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

- Their child is healthy and, if treated, will remain so.

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- But note that failure to treat a baby with MCADD may result in life threatening illness that could produce mental retardation or sudden death.

Treatment for MCADD 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. 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 C8**

#### Commonly asked questions

##### **1. What is MCADD?**

MCADD, also known as Medium Chain Acyl-CoA Dehydrogenase Deficiency, is the most common 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 and when exercising vigorously.

##### **2. How and when will we know if my baby has MCADD?**

If your baby's newborn screening result showed a C8 level  $> 2 \mu\text{mol/L}$ , he or she probably has MCADD. If the result was  $1-2 \mu\text{mol/L}$  your baby either could still have MCADD 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 MCADD 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?**

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

##### **4. What does it mean for my child?**

If your baby has MCADD, he or she will have to be fed regularly on a relatively low fat diet and can not 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. With this treatment, your child will be quite normal and indistinguishable from other children.

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

MCADD is primarily treated by a high carbohydrate and low fat diet that is given at regular defined intervals around the clock. As the diet is essentially normal it should not be an added 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 MCADD 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 MCADD. Your other children can appear healthy and still have MCADD. If they have MCADD, 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 MCADD it is important to let your obstetrician and pediatrician know that you have a child with MCADD 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, medium-chain dicarboxylic acids are elevated with a characteristic pattern while ketones are inappropriately low. Nevertheless, standard urine organic acid profiles may be uninformative when those with MCADD are stable and are not fasting.

**2. Plasma acylcarnitines**

The profile of patients with MCADD is characterized by accumulation of C6 to C10 species, with C8 (octanoylcarnitine) as the most prominent abnormality. A potential pitfall of acylcarnitine analysis in the diagnosis of MCADD is the possibility that patients with secondary carnitine deficiency may not show a significant elevation of acylcarnitines.

**3. Urinary acylglycines**

Quantitative determination of urinary n-hexanoylglycine, 3-phenylpropionylglycine and suberylglycine requires only a random urine sample from asymptomatic subjects and can be informative immediately after birth on the basis of increases in one or more of these acylglycines. However, in asymptomatic infants who are not fasting, the urinary excretion of these acylglycines may be < 5 µmol/mol creatinine, levels not detectable by this analysis.

**4. Acute illness labs**

As can be seen from above, many of the lab tests can be uninformative 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

and acylglycines. However, treatment should **NEVER** be delayed to obtain these labs and acute management labs should take priority (see [Acute illness protocol, MCADD.](#) )

### **5. Enzyme assay**

MCAD enzymatic activity can be measured in leukocytes and cultured fibroblasts as well as skin, liver, heart, skeletal muscle, and amniocytes using the ETF reduction assay. A frequently employed assay involves acylcarnitine analysis of the medium in cultured fibroblasts. The accumulation of C6-C10 acylcarnitines usually confirms the diagnosis. Patients with MCADD usually exhibit less than 10% of normal MCAD activity.

### **6. Molecular testing**

Mutation testing of the gene can help to confirm the diagnosis and for prenatal testing for future pregnancies. However, mutation testing limited to the common A985G mutation will not identify all cases, so a completely normal mutation analysis for this one mutation does NOT rule out a diagnosis of MCADD and a more comprehensive analysis for MCAD mutations may be indicated. [Go to genetests](#)

## **Treatment**

### **Diet,**

The mainstay in the treatment of MCADD is avoidance of fasting. Infants require frequent feedings, initially every 4 hours. A relatively high carbohydrate, low-fat diet (*e.g.*, <30% of total energy from fat) could be beneficial.

### **Carnitine,**

Oral supplementation with 100 mg/kg/day of carnitine is used in some cases to correct secondary carnitine deficiency though efficacy has not been proven as yet.

### **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 MCADD. 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.](#)