Medium-chain acyl-CoA dehydrogenase deficiency

Introductory information
Medium-chain acyl-CoA dehydrogenase deficiency

MCAD
Food – Components of a typical diet

**Natural Food**

- **Fat**
  - Milk, yogurt, nuts
- **Carbohydrates**
  - Meat, poultry, fish, eggs, cheese
- **Protein**
  - Oil, butter, margarine
- **Carbohydrates**
  - Fruit, vegetables, potatoes, cereals, pasta, rice
- **Protein**
  - Sugar, lemonade

Dietary management of the condition should only be done under medical supervision.

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Written by V. Prietsch & P. Burgard
Reviewed & revised for North America by S. van Calcar
Fat vs Fatty Acids

Fatty acids are made from chains of carbon atoms. There are different lengths of fatty acids; short-chain, medium-chain, and long-chain.

- **Short-chain fatty acids**: < 6 carbon atoms
- **Medium-chain fatty acids**: 6-12 carbon atoms
- **Long-chain fatty acids**: > 12 carbon atoms

Fat has a backbone of glycerol with 3 fatty acids.
How the body uses these nutrients

- **Eating and Drinking**
  - **Fat**
  - **Carbohydrates**
  - **Protein**

- **Digestion**
  - **Fatty Acids**
  - **Glucose (Blood Sugar)**
  - **Amino Acids**

- **Immediate use as an energy source**

- **The excess is stored as**
  - **Fatty tissue**
  - **Glycogen (Glucose-storing compound in liver and muscles)**

**Body Protein (Muscles, other tissues)**

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In MCAD deficiency, there is a problem using some fatty acids.

Eating and Drinking

Fat → Digestion → Fatty Acids

Carbohydrates → Digestion → Glucose (Blood Sugar) → Immediate use as an energy source

Protein → Digestion → Amino Acids

Body Protein (Muscles, other tissues)

The excess is stored as

Fatty tissue

Glycogen (Glucose-storing compound in liver and muscles)

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Enzymes

**Enzymes** are proteins that facilitate various chemical reactions in the body. They are involved in the biosynthesis (anabolism) and the degradation (catabolism) of all the substances in the body. This is called **metabolism**.

**Acyl-CoA Dehydrogenases** are enzymes required to break down fatty acids. The **MCAD enzyme** breaks down “medium chain” fatty acids.

In MCAD deficiency the activity of the **MCAD enzyme** is greatly reduced.
Fatty Acids

Fatty acids are made from chains of carbon (=C) atoms

Example: a fatty acid containing 18 carbon atoms

- Long-chain fatty acids: > 12 carbon atoms
- Medium-chain fatty acids: 6-12 carbon atoms
- Short-chain fatty acids: < 6 carbon atoms
How enzymes break down a fatty acid

3 enzymes are needed for this process:
The enzyme \text{VLCAD} starts, the enzyme \text{MCAD} continues and the enzyme \text{SCAD} finishes.

\begin{itemize}
\item \text{C}_{18} \rightarrow \text{C}_{17} \rightarrow \text{C}_{16} \rightarrow \text{C}_{15} \rightarrow \text{C}_{14} \rightarrow \text{C}_{13} \rightarrow \text{C}_{12} \rightarrow \text{C}_{11}
\item \text{VLCAD}
\item \text{1st CUT}
\item \text{2nd CUT}
\item \text{3rd CUT}
\item \text{SCAD}
\item \text{4th CUT}
\item \text{C}_{10} \rightarrow \text{C}_{9} \rightarrow \text{C}_{8} \rightarrow \text{C}_{7} \rightarrow \text{C}_{6} \rightarrow \text{C}_{5} \rightarrow \text{C}_{4} \rightarrow \text{C}_{3} \rightarrow \text{C}_{2} \rightarrow \text{C}_{1}
\item \text{8th CUT}
\item \text{7th CUT}
\item \text{6th CUT}
\item \text{5th CUT}
\end{itemize}
In **MCAD deficiency**, medium-chain fatty acids can not be broken down

Only the first three steps are possible

![Diagram showing MCAD deficiency](image)
In MCAD deficiency: Medium-chain fatty acids build-up and form medium-chain acylcarnitines

Medium-chain fatty acids accumulate

+ Carnitine = Medium-chain acylcarnitines

Blood, Urine

8th CUT

7th CUT

6th CUT

5th CUT

1st CUT

2nd CUT

3rd CUT

4th CUT
Diagnosis of MCAD deficiency

Newborn/Metabolic screening

Medium-chain acylcarnitines in blood

Increased
Normal

Abnormal compounds from medium-chain fatty acids in urine and blood

Increased
Normal

Dried blood spots

Blood sample

Urine sample

Confirmation of diagnosis

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What happens during Fasting?
(Fasting is the time between meals when your child isn’t drinking or eating anything)

- **Fatty tissue**
  - Break down to make fatty acids

- **Glycogen** *(Glucose-storing Compound in liver and muscles)*
  - Break down to make glucose

- **Body Protein**
  - Used as the main energy source

Used as an energy source (two-carbon molecules)

Reduces need for Glucose
MCAD deficiency: Problems can develop if your child fasts too long

**Fatty tissue**
- Break down to make Fatty acids
  - Used as an energy source (Increase in medium chain fatty acids)
  - **X**

**Glycogen** (Glucose-storing Compound in liver and muscles)
- Break down to make glucose
- **Glucose** (Blood sugar)
  - Used as (nearly) the only energy source
  - Glucose stores are used up
  - **Hypoglycemia** = Low blood sugar

**Body Protein**

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Preventative measures for patients with MCAD deficiency

Dietary management of the condition should only be done under medical supervision.

<table>
<thead>
<tr>
<th>Carnitine</th>
<th>LIMIT FASTING!</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>Carbohydrates</td>
</tr>
<tr>
<td>Digestion</td>
<td>Digestion</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Glucose</td>
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<tr>
<td>Removal of Medium-chain fatty acids</td>
<td>No hypoglycemia</td>
</tr>
</tbody>
</table>

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Problems caused by increased medium-chain fatty acids and hypoglycemia in patients with MCAD deficiency

- There is an increased risk for problems in the following situations:
  Febrile illness, especially with feeding problems (the child refused to eat or drink) or with vomiting.
  General anesthesia and surgery.

- Necessary measures:
  Reduce fasting time.
  Offer a maltodextrin solution, juice or other food or beverage that will provide glucose.
  An emergency room visit to start an intravenous glucose infusion may be necessary.
  During fasting periods before anesthesia/surgery - always initiate an intravenous glucose infusion.

  -> Intravenous fat emulsions should NEVER be used!

- Symptoms to watch out for:
  Vomiting
  Increased sleepiness (lethargy)
  Child is more difficult to wake up

Ask your clinic for an Emergency Protocol!
Chromosomes, Genes, Mutations

A chromosome is like a cookbook.

A gene is like a recipe in a cookbook.

A mutation is like an error in the recipe or even a complete lack of a recipe.

The enzyme MCAD is produced constantly in the body following a specific recipe (gene). If the gene contains abnormal mutations, the enzyme cannot function correctly or be properly produced.
Inheritance of MCAD deficiency

Both parents are carriers in autosomal-recessive inheritance

Mother is carrier of MCAD deficiency

Father is a carrier of MCAD deficiency
Inheritance of MCAD deficiency
There are 4 possible combinations for any child born to parents who are carriers

Mother is a carrier of MCAD deficiency

Father is a carrier of MCAD deficiency

Child will not be a carrier of MCAD deficiency
Child will be a carrier of MCAD deficiency
Child will have MCAD deficiency
Inheritance of MCAD deficiency

How MCAD deficiency is inherited in families

Mother is a carrier of MCAD deficiency

Father is a carrier of MCAD deficiency
Prognosis of MCADD deficiency

**Optimal management**

Hypoglycemia is avoided during:

1. Unusually long periods of fasting
2. Illnesses, especially with feeding problems and vomiting

**Result**

- Completely normal development
- Prevention of any kind of brain damage that can cause neurological symptoms, seizures

**Insufficient management**

Presence of hypoglycemia during:

1. Unusually long periods of fasting
2. Illnesses, especially with feeding problems and vomiting

**Result**

- Acute: life-threatening hypoglycemia with unconsciousness, brain edema and coma
- Sudden death
- Chronic: severe brain damage, severe neurological symptoms, seizures