Very-long-chain acyl-CoA dehydrogenase deficiency

Introductory information
Very-long-chain acyl-CoA dehydrogenase deficiency

VLCAD
Food – Components of a typical diet

Natural Food

- **Fat**
  - **Carbohydrates**
  - **Protein**
  - **eg. milk, yogurt, nuts**

- **Fat**
  - **Carbohydrates**
  - **Protein**
  - **eg. meat, poultry, fish, eggs, cheese**

- **Fat**
  - **Carbohydrates**
  - **Protein**
  - **eg. oil, butter, margarine**

- **Carbohydrates**
  - **Protein**
  - **eg. fruit, vegetables, potatoes, cereals, pasta, rice**

- **Carbohydrates**
  - **Protein**
  - **eg. sugar, lemonade**

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

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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.

Fat has a backbone of glycerol with 3 fatty acids.

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

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How the body uses these nutrients

- **Food intake**
  - 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** (Muscle, other tissues)
In VLCAD deficiency, there is a problem using some fatty acids.
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 that break down fatty acids. The **VLCAD enzyme** breaks down long-chain fatty acids.

In **VLCAD deficiency** the activity of the **VLCAD 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 VLCAD starts, the enzyme MCAD continues, the enzyme SCAD finishes
In VLCAD deficiency, long-chain fatty acids cannot be broken down in cells

Break down of the chain of carbon molecules cannot start
In VLCAD deficiency, long-chain fatty acids build-up and form long-chain acylcarnitines.

Long-chain fatty acids accumulate; they can damage muscles, the heart, and the liver.

+ Carnitine = Long-chain acylcarnitines
Diagnosis of VLCAD deficiency

Newborn/Metabolic screening

Dried blood spots

Confirmation of diagnosis

Urine sample Blood sample

Long-chain acylcarnitines in blood

Increased Normal

Abnormal compounds from long-chain fatty acids + long-chain acylcarnitines in urine and in blood

Increased Normal
Pathogenesis of VLCAD deficiency

- Greatly reduced production of energy without the ability to break down long-chain fatty acids
  - Long-chain acylcarnitines accumulate

- Hypoglycemia (very low glucose in blood)

Damage:
- Skeletal muscles
- Heart muscle
- Liver
- Brain

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The principles of dietary management for VLCAD deficiency

Avoid the need to use long-chain fatty acids as “fuel” for energy production.

by means of

1. Avoid fasting too long
   Fasting is the time when your child isn’t drinking or eating anything
2. Limit fat from the diet (fat in the diet is all long chain fat)
3. Replace long-chain fatty acids in the food with medium-chain fatty acids (MCT-supplements)
4. Consume sources of glucose before, during and after exercise

Energy production from long-chain fatty acids is defective.
Energy production from medium-chain fatty acids is intact.
What happens during Fasting?

Fatty tissue

- Break down to make fatty acids

Long chain fatty acids

- Used as an energy source (two-carbon units)

Glycogen (Liver)

- (Glucose-storing compound)
  - Break down to make glucose

Glucose (Blood sugar)

- Used as the main source of energy
  - Reduces need for glucose

Body protein
Management: Avoid Fasting Too Long

LIMIT FASTING!

↓ LCFA-fat + MCT-fat
(+ essential fatty acids)

Digestion

↑ Carbohydrates

MCFA

MCAD

Use as an energy source
(2-carbon units)

MCAD

Use as an energy source
(2-carbon units)

LCFA from fatty tissue

No hypoglycemia

Glucose (blood sugar)

MCFA

Use as an energy source
(2-carbon units)

MCAD

Use as an energy source
(2-carbon units)

Carbohydrates

Glucose (blood sugar)

No hypoglycemia

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Written by V. Prietsch & P. Burgard
Reviewed & revised for North America by S. van Calcar
VLCAD deficiency: Problems can develop if your child fasts too long

- **Fatty tissue**
  - Release
  - Long chain fatty acids
  - Utilization as an energy source (two-carbon units)

- **Glycogen** (Liver)
  - (Glucose-storing compound)
  - Release
  - Glucose (Blood sugar)
  - Utilization as the only source of energy
  - Glucose stores are used up
  - Hypoglycemia = low blood sugar

- **Body protein**

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Dietary Management: very-low-fat diet + MCT-supplements

Food

↓ Fat (long-chain fatty acids)

+ MCT-supplements
  + essential fatty acids

Natural Food

Choose low- or no-fat versions of foods in the red & yellow boxes

Fat
  Carbohydrates
  Protein
  eg. milk, yogurt, nuts

Fat
  Carbohydrates
  Protein
  eg. oil, butter, margarine

Fat
  Carbohydrates
  Protein
  eg. meat, poultry, fish, eggs, cheese

Carbohydrates
  eg. fruit, vegetables, cereals, bread, pasta, rice

Carbohydrates
  eg. sugar, lemonade
Dietary Management: very low-fat diet + MCT-supplements

Abbreviations:
- LCFA-fat = Fat from long-chain fatty acids (LCFA)
- MCT-fat = Fat from medium-chain fatty acids (MCFA)
- MCAD = enzyme that breaks down medium chain fatty acids

Food intake

↓LCFA-fat + supplement MCT-fat (+ essential fatty acids)

Digestion

MCFA

MCAD

Use as an energy source (two-carbon units)
Illness and other stresses can cause problems for patients with VLCAD deficiency

• **What causes problems?**
  Decreased energy production from long chain fatty acids
  Toxicity of long chain acylcarnitines and other metabolites
  Hypoglycemia (low blood sugar)

• **When can problems occur?**
  Illness, especially with vomiting and poor food intake
  Infections
  Prolonged fasting
  Excessive exercise (when older)
  Surgery and anesthesia

• **What can happen?**
  Heart problems – enlarged heart (cardiomyopathy), abnormal beats (arrhythmia)
  Liver problems
  Muscle breakdown – muscle pain, blood in urine
  Problems with consciousness – coma is possible

The severity of the disease varies between individuals with VLCAD deficiency
Illness and other stressors can cause problems for patients with VLCAD deficiency

• Symptoms to watch out for
  Vomiting
  Increased sleepiness (lethargy)
  Child is more difficult to wake up
  Complains that muscles ache

• 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!

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

A chromosome is like a cookbook.

A gene is like a recipe in the cookbook.

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

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

Both parents are carriers in autosomal-recessive inheritance

Mother is a carrier of VLCAD deficiency

Father is a carrier of VLCAD deficiency
Inheritance of VLCAD deficiency

There are 4 possible combinations for any child born to parents who are carriers.

- **Mother is a carrier of VLCAD deficiency**
  - Child will not be a carrier of VLCAD deficiency
  - Child will be a carrier of VLCAD deficiency

- **Father is a carrier of VLCAD deficiency**
  - Child will have VLCAD deficiency

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Inheritance of VLCAD deficiency

How VLCAD deficiency is inherited in families

Mother is a carrier of VLCAD deficiency

Father is a carrier of VLCAD deficiency
Prognosis of VLCAD deficiency

Optimal management
1. Reduction of long-chain fatty acids in diet and supplement MCT-fat
2. Plus essential fatty acids
3. Avoid fasting too long
4. Caution with illness, especially if child refuses to eat or is vomiting

Follow-up

Laboratory tests
• Special tests
  - Acylcarnitines
  - Carnitine
  - Essential fatty acids

• Routine tests
  - Muscle enzymes
  - Liver tests

Physical development
- Height and weight, head circumference

Cardiology consultations

Monitoring motor and developmental skills

Result
• Normal development
• No cardiomyopathy
• Muscle weakness and muscle pain associated with excessive exercise can still occur

Insufficient management
1. Insufficient reduction in dietary fat and MCT supplementation
2. Fasting too long
3. Insufficient preventive measures during illness or other stresses.

Result
• Life-threatening hypoglycemic episodes with unconsciousness, brain edema, coma, permanent brain damage
• Sudden death
• Cardiomyopathy
• Skeletal muscle weakness

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