Isovaleric acidemia

Introductory information
Isovaleric acidemia

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

Isovaleric acid in blood

IVA
Food – Components of a normal diet

Protein consists of chains of amino acids

Protein
- Leucine
- Tyrosine
- Valine
- Phenylalanine
- Threonine

Fat

Carbohydrates

Natural Food

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

- Protein
  - Fat
  - Carbohydrates
  - eg. meat, poultry, fish, cheese, egg

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

- Carbohydrates
  - eg. sugar, juice

- Fat
  - eg. oil, margarine, butter

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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 substances in the body. This is called metabolism.

**Isovaleryl-CoA-dehydrogenase (IVD)** is an enzyme that is necessary for the metabolism of the amino acid leucine.

In IVA, the activity of the IVD enzyme is decreased.
In a person without IVA: IVD works

**Leucine** = Amino acid

- Enzyme
- Enzyme

**Isovaleryl-CoA** = activated organic acid

- **IVD**

**3 Methylcrotonyl-CoA** = activated organic acid

- Enzyme
- Enzyme
- Enzyme
- Other activated organic acids

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Metabolism in a patient with IVA: IVD deficiency

Metabolic products of isovaleryl-CoA

Urine and blood

- Isovaleric acid
- 3-hydroxy-IVA
- Isovalerylglucose
- Isovalerylcarnitine

Leucine

↑ Isovaleryl-CoA

↓ 3-Methylcrotonyl-CoA

Other activated organic acids

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Reviewed & revised for North America by: S. van Calcar
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Diagnostic investigations

- Newborn Screening
  - Dried blood spots
  - Isovalerylcarnitine in blood
    - Normal
    - Increased

- Confirmation of diagnosis
  - Urine sample
  - Isovaleric acid and metabolic products in urine
    - Normal
    - Increased
Pathogenesis of IVA

Organic acids are toxic to the brain. High concentrations of isovaleryl-CoA and isovaleric acid can damage the brain.
Pathogenesis: Metabolic crises

Isovaleryl-CoA and isovaleric acid can be especially high during metabolic crises. The following situations can lead to a metabolic crisis in IVA:

- Febrile illnesses
  - e.g. diarrhea, infectious disease, fever, etc.
- Vaccinations
- Surgeries
- Malnutrition

In these situations **catabolism develops**

The term “catabolism” refers to the metabolic reactions leading to the breakdown of body tissues.

Isovaleryl-CoA and isovaleric acid are produced from body proteins, especially the breakdown of muscle!

Catabolism can lead to a metabolic crisis in the first days of life.

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What are the symptoms of a metabolic crisis?

- Unusual tiredness, unresponsiveness
- Loss of appetite, vomiting
- Movement disorders (the child cannot sit or stand anymore, becomes “floppy”, develops abnormal movements)
- Quick and deep breathing
- Sweaty feet odor
- The child is very difficult to wake up or you cannot get him to wake up at all (coma)

It is critical that management be started immediately to prevent the patient’s condition from deteriorating. Metabolic crises can be fatal.
Principles of Management
Diet management decreases intake of leucine

- Leucine
- Isovaleryl-CoA
- 3-Methylcrotonyl-CoA
- Isovaleric acid
- 3-Hydroxy-IVA
- Isovalerylglycine
- Isovaleryl carnitine

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**Fat**

**Carbohydrates**

Natural Food

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

- Carbohydrates
  - *eg.* sugar, juice

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

Dietary management of the condition should only be done under medical supervision.
Management:
1. Diet low in natural protein

Natural Food

- **Protein**
  - Fat
  - Carbohydrates
  - *e.g.* milk, yogurt, nuts

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

- **Protein**
  - Fat
  - Carbohydrates
  - *e.g.* fruit, vegetables, potatoes, cereals, pasta, rice

- **Carbohydrates**
  - *e.g.* sugar, juice

- **Fat**
  - *e.g.* oil, margarine, butter

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Management:

2. Diet low in natural protein + a formula that does not contain leucine

Natural Food

- **Protein**: eg. milk, yogurt, nuts
- **Protein**: eg. meat, poultry, fish, cheese, eggs
- **Protein**: eg. fruit, vegetables, potatoes, cereals, pasta, rice
- **Carbohydrates**: eg. sugar, juice
- **Fat**: eg. oil, margarine, butter

+ IVA formula that contains all amino acids except leucine
Carnitine and glycine bind to isovaleryl-CoA in the cells producing isovalerylcaritnine and isovalerlylglycine.

Isovalerylcaritnine and isovalerlylglycine leave the cells and the kidneys eliminate them in the urine. As a result, the body loses carnitine. **This loss is replaced by supplementing with both carnitine and glycine** every day. (Of these, carnitine is most important).
Management:
Emergency management during illness

1. Frequent feedings of low in natural protein and high-carbohydrate foods and beverages.
2. If the child’s condition deteriorates, contact the metabolic clinic for directions. A hospital admission may be necessary to provide adequate management.

Emergency management should always be started promptly during any acute intercurrent illness!

Important:
All patients with IVA need an emergency protocol and plans for emergency management at the nearest children’s hospital.
Follow-up in IVA

Management with a diet low in natural protein, IVA formula, and carnitine and glycine supplementation requires regular laboratory tests!

These include:
1. Measuring the concentrations of amino acids and acylcarnitines in blood
2. Basic laboratory blood tests
3. Analysis of organic acids in the urine
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 isovaleryl-CoA-dehydrogenase (IVD) is produced constantly in the body following a specific recipe (gene). If the gene carries abnormal mutations, the enzyme cannot function properly or be properly produced.
Inheritance of IVA

Both parents are carriers in autosomal-recessive inheritance

Mother is a carrier of IVA

Father is a carrier of IVA
Inheritance

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

- **Mother is a carrier of IVA**
- **Father is a carrier of IVA**

Child **will not be** a carrier of IVA

Child **will be** a carrier of IVA

Child **will have** IVA

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Inheritance

How IVA is inherited in families

Mother is a carrier of IVA

Father is a carrier of IVA
Summary

What is IVA?

Disorder of leucine metabolism

↑ Isovaleryl-CoA, ↑ Isovaleric acid, ↑ 3-Hydroxy-IVA

Optimal management

1. Diet low in natural protein & IVA formula without leucine
2. Early and effective management of metabolic crises during illness
3. Pharmacological treatment with the use of carnitine, and glycine

Follow-up

Laboratory tests

Special tests
• Amino acids, acylcarnitines, organic acids

Routine tests

Physical development
• Body height and weight, head circumference

Psychomotor development
• Neuropsychological tests
• Intelligence (IQ)

Management results in case of insufficient therapy

• Developmental delay
• Neurological symptoms, movement disorders
• Psychological and intellectual deficits
• Severe and late-managed metabolic crises can result in brain damage!

Management results

• Normal intellectual and neurologic development

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