Maple Syrup Urine Disease
Introductory information
Maple syrup urine disease

MSUD

MSUD refers to the (sweet, malty, caramel-like) maple-syrup-like odor of the urine of untreated patients.
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”.

Branched Chain Keto Acid Dehydrogenase (BCKD) is the enzyme that breaks down the amino acids leucine, isoleucine and valine.

In MSUD, the activity of the BCKD enzyme is deficient.
In normal metabolism: BCKD works

Leucine, isoleucine and valine are called Branched-Chain Amino Acids = BCAA
KICA, KMVA and KIVA are called Branched-Chain Keto Acids = BCKA
In MSUD: BCKD is deficient

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

Newborn/Metabolic screening

1st blood sample

Confirmation of diagnosis

2nd blood sample

Normal concentration of BCAA in blood
- Leucine: 77-153 µmol/L (1.0 - 2.0 mg/dl)
- Isoleucine: 39-76 µmol/L (0.5 - 1.0 mg/dl)
- Valine: 135-260 µmol/L (1.6 - 3.0 mg/dl)

At confirmation of MSUD:
Leucine concentration is elevated
800 - 4000 µmol/L (10.5 - 52.0 mg/dl)

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Pathogenesis of MSUD

High concentrations of leucine and KICA damage the brain.

Of the BCAA and ketoacids, leucine and KICA appear to be the most neurotoxic. In MSUD, they are always present in approximately equimolar (equal molar) concentrations in plasma.
Acute brain dysfunction

When the leucine level increases rapidly to high concentrations in blood.

In newborns before starting management: poor feeding, drowsiness, neurologic signs, somnolence, convulsions, cerebral edema, coma

In infancy, childhood and adolescence during metabolic decompensations: apathy, ataxia, hallucinations, convulsions, cerebral edema, coma

Chronic brain damage

When the leucine concentrations are moderately but continuously increased

- Behavioral and intellectual disabilities
- Caused by dysmyelination of the white matter of the brain
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**Food – Components of a typical diet**

**Protein**
- Leucine
- Isoleucine
- Valine
- Phenylalanine
- Threonine

Protein consists of chains of amino acids

**Natural Food**

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

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

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

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

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

- **Carbohydrates**
Principles of diet management

Very low natural protein diet + leucine–valine–isoleucine free metabolic formula

+ a metabolic formula that does not contain leucine, isoleucine and valine

Natural Food

- **Protein**
  - **Fat**
  - **Carbohydrates**

  - *eg.* milk, yogurt, nuts

- **Protein**
  - **Fat**
  - **Carbohydrates**

  - *eg.* meat, poultry, fish, cheese, eggs

- **Protein**
  - **Carbohydrates**

  - *eg.* fruit, vegetables, potatoes, cereal, pasta, rice

- **Carbohydrates**

  - *eg.* sugar, lemonade

- **Fat**

  - *eg.* oil, margarine

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Dietary management of the condition should only be done under medical supervision.
Diet management during the first 4 to 6 months of life

Natural Protein

Breast milk or infant formula

Natural protein = all amino acids with leucine, valine and isoleucine included
Fat
Carbohydrates

Metabolic Formula = amino acids without leucine, valine and isoleucine
Fat
Carbohydrates

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

Foods + special low-protein products + metabolic formula

Nutritional components of a MSUD diet once the baby is weaned and solids are introduced

↓↓ Natural Protein

- Leucine
- Isoleucine
- Valine
- Tyrosine
- Phenylalanine
- Threonine

+ metabolic formula = all amino acids except leucine, valine and isoleucine

Natural protein food

- eg. vegetables, fruits, potatoes

Special low protein products

- eg. special bread, pasta and ready-made meals

Leu-ile-val-free metabolic formula

- eg. sugar, lemonade

Fat

Carbohydrates

- eg. oil, margarine
Goals of diet management

**MSUD diet**
Very low-protein natural foods
+ special low-protein products
+ leucine-isoleucine-valine-free metabolic formula
+ supplement with isoleucine and/or valine to prevent low blood levels

**Management goals (can vary by clinic)**
Long-term plasma concentrations should be

- **Leucine:** 100 – 300 µmol/L (1.3 - 3.9 mg/dl)
- **Isoleucine:** 200 - 400 µmol/L (2.6 – 5.2 mg/dl)
- **Valine:** 200 - 400 µmol/L (2.4 – 4.8 mg/dl)

**Conversions**
- Leucine: $1 \text{ mg/dl} = 76 \text{ µmol/L}$
- Isoleucine: $1 \text{ mg/dl} = 76 \text{ µmol/L}$
- Valine: $1 \text{ mg/dl} = 85 \text{ µmol/L}$
Monitoring BCAA and other labs

Remember!

The MSUD diet requires frequent monitoring of BCAA levels to prevent nutritional deficiencies.

The diet needs to be evaluated often to ensure that all nutrients (natural and metabolic formula protein, energy, vitamins and minerals) meet the recommendations for normal growth of the child.
Metabolic Emergencies

During the following conditions, a metabolic episode may occur with rapidly rising concentrations of leucine and KICA

- **Febrile illnesses**, e.g. vomiting and diarrhea, infectious diseases
- Vaccinations
- Surgeries

These conditions can cause an increase in catabolism

During catabolism, body tissue is broken down and leucine and KICA (and all other amino acids) are released from muscle protein! The accumulation of leucine and KICA can cause rapid neurologic deterioration!

**Catabolism during the first few days of life results in a neonatal metabolic episode**

- Very high amounts of protein in the diet can also increase leucine
What are the signs of a metabolic crisis?

- Apathy
- Anorexia, vomiting
- Abnormal movements (ataxia)
- Hallucinations
- Reduced response to stimuli
- Lethargy and coma

The urgent initiation of an emergency protocol is necessary in order to stop a metabolic crisis!
Emergency management during catabolism

1. Manage according to an emergency plan. Metabolic clinics may:
   - Start frequent feeding of carbohydrate-rich meals
   - Temporarily reduce natural protein in the diet
   - Continue intake of the leucine-isoleucine-valine-free metabolic formula.

2. A child may need to visit the metabolic clinic to monitor plasma amino acid levels

3. In cases of deterioration, inpatient management may be necessary

Emergency management has to start immediately after the first signs of illness!
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 BCKD 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 MSUD

Parents are carriers in autosomal-recessive inheritance

Mother is a carrier of MSUD

Father is a carrier of MSUD

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

Possible combinations

Mother is a carrier of MSUD

Father is a carrier of MSUD

Child will not be a carrier of MSUD

Child will be a carrier of MSUD

Child will have MSUD
Inheritance of MSUD

Where does MSUD come from?

Mother is a carrier of MSUD

Father is a carrier of MSUD
Summary

Enzyme defect in breakdown of leucine, valine and isoleucine

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**Optimal management**

1. Diet management to maintain blood levels of leucine, valine and isoleucine in the goal range
2. Early diagnosis and early management of illness and other catabolic conditions

**Monitoring**

**Lab**
- Regular amino acids routine lab tests

**Physical development**
- Height, weight, head circumference

**Nutrition**
- Regular adjustment of the diet

**Development**
- Neuropsychology
- Intelligence (IQ)

**Result**
Normal neurological and cognitive development

**Insufficient management**

1. Long-term elevations in blood concentrations of leucine, isoleucine and valine
2. Severe and late-treated metabolic crises

**Result**
Impairment of neurological and cognitive development

Coma, cerebral edema, death, or severe brain damage

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