Hereditary tyrosinemia type I

Introductory information
Hereditary tyrosinemia type I

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

(too much) tyrosine in the blood
Dietary management of the condition should only be done under medical supervision.

Food – Components of a normal diet

Protein consists of chains of amino acids

Natural Food

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

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

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

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

- **Protein**
  - eg. oil, margarine
Enzymes

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

Fumarylacetoacetate hydrolase (FAH) is the enzyme that participates in the metabolism of the amino acid tyrosine.

In type 1 tyrosinemia the activity of the FAH enzyme is decreased.
In normal metabolism: FAH works

Phenylalanine → Tyrosine

Phenylalanine is converted to Tyrosine by the enzyme FAH.

Fumarylacetoacetate

Fumarylacetoacetate is a metabolite of the conversion of Phenylalanine to Tyrosine.

FAH

FAH is the enzyme that catalyzes the conversion from Phenylalanine to Tyrosine.

Fumarate

Fumarate is a metabolite of the FAH enzyme.

Acetoacetate

Acetoacetate is another metabolite of the FAH enzyme.

Energy production

Energy is produced from the conversion of Phenylalanine to Tyrosine through the FAH enzyme.

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In Hereditary Tyrosinemia Type I: FAH deficiency

Phenylalanine \( \rightarrow \) Tyrosine

\[
\begin{align*}
\text{Enzyme} & \quad \text{Enzyme} & \quad \text{Enzyme} \\
\text{Maleylacetoacetate} & \quad \text{Fumarylacetoacetate} & \quad \text{Succinylacetoacetate & Succinylacetone}
\end{align*}
\]

Metabolic Block

\[
\begin{align*}
\downarrow \text{Fumarate} & \quad \downarrow \text{Acetoacetate}
\end{align*}
\]

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Diagnosis of HT-1

Dried blood spots

Metabolic/Newborn screening

Tyrosine and Succinylacetone

Increased
Normal

Urine sample
Venous blood

Confirmation of diagnosis

Succinylacetone

Increased
Normal

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Pathogenesis of HT-1

High concentrations of maleylacetoacetate, fumarylacetoacetate, succinylacetoacetate, and succinylacetone damage the liver, kidneys and the brain, and cause neurological symptoms.

The disease course is variable:
from acute liver failure in the first weeks of life to the development of symptoms in adulthood.
Pathogenesis if HT-1

Maleylacetoacetate
Fumarylacetoacetate

The liver is the organ that is most affected

Symptoms in the first weeks of life: signs of acute liver failure
- Vomiting, diarrhea, liver enlargement, bleeding tendency, jaundice, edemas

Liver diseases
- Acute liver failure
- Cirrhosis (early)
- Hepatocellular carcinoma (early)
Pathogenesis of HT-1

- Maleylacetoacetate
- Fumarylacetoacetate

- Succinylacetoacetate
- Succinylacetone

Renal (Kidney) damage
- Renal tubular dysfunction (can cause rickets = abnormal bone development)
- Renal failure

Neurological symptoms
- Acute neurological crises with painful paresthesia (sensation of pins & needles), paralyses

Learning difficulties

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Written by U. Wendel
Reviewed & revised for North America by S. van Calcar
Dietary management of the condition should only be done under medical supervision.

Metabolism in HT-1: Before management

Phenylalanine → Tyrosine

- Maleylacetoacetate
- Fumarylacetoacetate

Metabolic Block

- Fumarate
- Acetoacetate

↑ Succinylacetoacetate
↑ Succinylacetone

Enzyme
Treatment with NTBC (Nitisinone)

Regular intake of NTBC is the most important part of the treatment! Liver damage can be prevented! However, the level of tyrosine increases in the blood – so a low-tyrosine and low-phenylalanine diet is required!

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Low-tyrosine and low-phenylalanine diet

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

NTBC blocks this enzyme’s activity to reduce production of abnormal metabolites

**Phenylalanine** ➔ **Tyrosine** ➔ **Prevent or reduce Eye symptoms**

Maleylacetoacetate ➔ Fumarylacetoacetate ➔ Succinylacetoacetate ➔ Succinylacetone ➔ Acetoacetate ➔ Fumarate

**FAH**

**Metabolic Block**
Food – Components of a typical diet

Protein consists of chains of amino acids

Protein
- Tyrosine
- Phenylalanine
- Valine
- Leucine
- Threonine

Fat

Carbohydrates

Natural Food

Protein
- eg. milk, yogurt

Fat

Carbohydrates

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

Fat

Carbohydrates

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

Carbohydrates

Carbohydrates

Fat

eg. sugar, lemonade

eg. oil, margarine

Dietary management of the condition should only be done under medical supervision.
Diet Management of HT-1

A diet low in natural protein decreases the amount of tyrosine and phenylalanine intake.

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Diet Management of HF-1
Low natural protein diet + tyrosine-free and phenylalanine-free metabolic formula

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Follow-up in HT-1

Frequent follow-up is necessary with NTBC (Nitisinone) treatment and a low-tyrosine and low-phenylalanine diet. This includes the following tests:

1. Succinylacetone: as low as possible in blood and in urine
2. Plasma tyrosine: goal < 500 µmol/L
3. Plasma phenylalanine: prevent levels that are too low
3. Liver tests, coagulation tests
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 the recipe.

The fumarylacetoacetate hydrolase (FAH) 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 HT-1

Parents are carriers of HT-1 in autosomal-recessive

Mother is a carrier of HT-1

Father is a carrier of HT-1

Dietary management of the condition should only be done under medical supervision.
Inheritance of HT-1

Possible combinations

Mother is a carrier of HT I

Father is a carrier of HT I

Child will not be a carrier of HT I

Child will be a carrier of HT I

Child will have HT I
Inheritance of HT-1

Where does HT-I come from?

Mother is a carrier of HT-I

Father is a carrier of HT-I

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Summary

What is HT-I?

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<th>Defect in tyrosine metabolism</th>
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<td>↑ Fumarylacetoacetate, ↑ Succinylacetone, ↑ Tyrosine</td>
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What is HT-I?

- Laboratory tests
  - Succinylacetone
  - Liver function tests
  - Kidney function tests
  - Tyrosine and phenylalanine

- Physical development
  - Height and weight
  - Head circumference

- Imaging of the liver
  - Ultrasound, CT/MRT

- Development
  - Intelligence (IQ)
  - Neuropsychology

Optimal Management

1. Intensive care
2. NTBC (Nitisinone)
3. Low-protein diet

Result

- Quick reversal of symptoms of acute liver damage
- Significantly lower risk of liver cirrhosis, hepatocellular carcinoma, kidney disease
- No neurological crises

Insufficient Management

Result

- Chronic disease course
  - Hepatocellular carcinoma
  - Neurological crises
  - Kidney damage
  - Liver cirrhosis

Acute liver failure
Death

Follow-up

- Physical development
- Imaging of the liver
- Development

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