Glutaric aciduria type I

Introductory information

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Glutaric aciduria type I



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Glutaric aciduria type I

Glutaric acid in urine

GA

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Food – Components of a normal diet



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.

Glutaryl-CoA dehydrogenase (GCDH) is an enzyme that is necessary for the metabolism of the following protein components – the amino acids **lysine** and **tryptophan**.

In GA I the activity of GCDH enzyme is decreased.

In a person without GA1: GCDH works



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In a patient with GA I: GCDH is deficient



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Diagnosis of GA1



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Organic acids are toxic to the brain. High concentrations of glutaric acid and of 3-hydroxyglutaric acid can damage the brain.



3-Hydroxyglutaric acid

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Pathogenesis of GA1

Glutarylcarnitine

reduces the amount of carnitine in the body

The synthesis of **glutarylcarnitine** and its removal in urine reduces the amount of **carnitine** in the body. **Carnitine** is important to assure a sufficient supply of energy to many organs to maintain their functions.

Low amounts of carnitine can reduce the production of energy.

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Metabolic crises

During metabolic crises, the production of organic acids and the deficit of carnitine intensifies. The following situations can lead to a metabolic crisis in GA1:

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

In these situations catabolism develops

The term "catabolism" refers to the metabolic reactions leading to the breakdown of body tissues. Glutaryl-CoA, glutaric acid and 3-hydroxyglutaric acid are produced from protein, especially the breakdown of muscle!

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What are the symptoms of a metabolic crisis?

- Unusual tiredness or a progressive alteration of consciousness
- Loss of appetite
- Motor difficulties (the child cannot sit or stand anymore, becomes "floppy", reduced movements) followed by spasms in the arms and legs

• 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.

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Principles of Diet Management

Dietary management decreases intake of lysine and tryptophan



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Food – Components of a normal diet



Management:

1. Diet low in natural protein + a formula that does not contain lysine and limits tryptophan





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Management:

2. Carnitine supplementation



Glutarylcarnitine leaves the cells and the kidneys eliminate it in the urine. As a result the body loses carnitine. **This loss is replaced by giving a medication containing carnitine.**

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Three management components

- 1. Diet low in natural protein + GA1 formula without lysine and little tryptophan
- 2. Carnitine supplementation
- 3. Emergency management (especially in the first six years of life): Follow an emergency plan including prompt initiation of management in cases of acute illness:
 - a) Frequent feeding with carbohydrate-rich products
 - b) Continuation of carnitine
 - c) Continuation of GA1 formula
 - d) In cases of fever >101 ^{0}F use antipyretic drugs
 - e) If the patient's condition deteriorates, contact the metabolic clinic immediately for hospital admission to start treatment with infusions and i.v. drugs

Important: All patients with GA1 need an emergency protocol and plans for emergency management at the nearest children's hospital.

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** glutaryl-CoA dehydrogenase (GCDH) is produced constantly in the body following a specific recipe (**gene**). If the gene carries abnormal **mutations**, the **enzyme** cannot be properly produced.

Inheritance of GA1

Both parents are carriers in autosomal-recessive inheritance



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Inheritance

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



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Inheritance

How **GAI** is inherited in families



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Summary

GA I?	▲GlutaryI-CoA, ▲Glutaric acid, ▲3-Hyroxyglutaric acid, ▲GlutaryIcarnitine
What is	Disorder of lysine and tryptophan metabolism

Optimal Management

- 1. Diet low in natural protein + GA1 formula without lysine and limited tryptophan
- 2. Carnitine supplementation
- 3. Early diagnosis and effective early management in "catabolic situations"

Result

- Normal intellectual development
- Mild neurological abnormalities

Follow-up

Laboratory tests Special tests: amino acids, carnitine, acylcarnitines, organic acids Routine tests Physical development Body height and weight, head circumference Psychomotor development Neuropsychological tests, Intelligence (IQ), motor patterns

Brain imaging

Ultrasound, MRI

Insufficient Management

- If early management in "catabolic situations" is not sufficient
- \rightarrow development of severe metabolic crises

Result

Severe (late-treated) metabolic crises leads to severe movement abnormalities with dystonia (involuntary muscle contractions that cause slow repetitive movements or abnormal postures) and severe developmental delays.

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