TEMPLE
Tools Enabling Metabolic Parents LEarning

Homocystinuria (HCU) caused by CBS deficiency

Page 1: Title page

Page 2: Topic = Definitions, some facts about the disease

We invited you to the clinic today because a metabolic disease was detected in your child. The disease is called homocystinuria, abbreviation HCU.

The disease name means: homocystine (an elevated amount) is excreted in the urine. Sometimes the name hyperhomocysteinemia is also used. This means: an increased amount of homocysteine in blood.

The difference between homocysteine and homocystine is that homocystine is composed of two units (molecules) of homocysteine. Homocysteine is measured in blood, whereas homocystine is measured in urine.

Homocysteine is present in the blood of every person, however its concentration is relatively low. In patients with homocystinuria, the blood concentration of homocysteine is 30 to 50 times higher than normal. The reason for this metabolic disease is an inherited abnormality of protein metabolism.

Page 3: Topic = Food components

To explain the problem of homocystinuria it is necessary to discuss the role of protein first. The best method is to consider food components.

Food consists of nutrients, which are classified as protein, fat and carbohydrates. In homocystinuria protein is crucial. Protein is composed of chains of amino acids. Among other amino acids (altogether protein contains 20 different amino acids), you can see one, which is called methionine. We are emphasizing the presence of this amino acid as it can be metabolized into homocysteine.

What does the metabolism of the amino acid methionine mean?

The term metabolism refers to the processing and use of nutrients. With regard to the amino acid methionine it means:

1) The release of the amino acid from protein during digestion in the bowels

2) The absorption of the amino acid into blood and it's transport to various organs

3) The degradation, modification and utilization of the amino acid resulting from chemical reactions in these organs.

Every human, including people with homocystinuria, needs methionine. However, the amount of this amino acid in natural food is higher than necessary.

To minimize the production of homocysteine and homocystine in patients with homocystinuria, low-protein food should be introduced.

In the lower part of the picture you can see some data on the composition of different types of food and on their protein content. As you can see, natural food contains different combinations of protein, fat and carbohydrates. In some types of food all of these three nutritive components are present. In others, there are only two components. Finally, some food types contain only carbohydrates or fat. One can distinguish between high-protein, low-protein, and no-protein food. We are going to discuss this further with regards to the treatment of homocystinuria.

Page 4: Topic = Enzymes and enzyme deficiency

A metabolic error results from a deficiency of an enzyme. In homocystinuria, the function of the enzyme cystathionine beta-synthase (CBS) is affected. From now on we will use the abbreviation "CBS" to describe the enzyme.

Comment: This page is self-explanatory and the text should be read aloud.

Page 5: Topic = Enzymes

Another enzyme, which is important for the metabolism of methionine and homocysteine is called betaine-homocysteine-methyltransferase (BHMT). BHMT functions properly in a person with homocystinuria. It plays an important role in the treatment of homocystinuria.

Page 6: Topic = The enzyme and the cofactor – vitamin B6

Some enzymes require cofactors (vitamins). CBS is such an enzyme. It requires vitamin B6 (Vit B6) as a cofactor. The inactive enzyme (without Vit B6) is depicted on the left and the active enzyme (with Vit B6) on the right.

Page 7: Topic = Normal metabolism of methionine

It has already been mentioned that in homocystinuria an error of protein metabolism exists and specifically this is an error of metabolism of the amino acid methionine. You can see on this page that this amino acid is transformed over several steps into homocysteine, this transformation is facilitated by various enzymes. The subsequent metabolic step results in the production of cystathionine and the following one in the production of cysteine. Cystathionine is not important for the body, but cysteine (also an amino acid) is very important for the growth and function of various organs. Transformation of homocysteine into cystathionine and cysteine can only take place if the necessary enzyme CBS works properly.

This picture shows that around 50% of the produced homocysteine is transformed back into methionine, this transformation is facilitated by the enzyme BHMT. For this reverse-direction metabolic step three substances are required. These are: betaine, vitamin B12 and folic acid. All of them are usually present in the body in sufficient amounts. They are present in food and can be produced by the body.

Page 8: Topic = Abnormal metabolism in homocystinuria

In a person with homocystinuria, the effectiveness of all metabolic steps except for the one described above is normal. The CBS enzyme does not function properly. This means that a

metabolic block occurs at this step. Subsequently, homocysteine accumulates and the

production of cystathionine and cysteine is practically absent. This situation is not harmful with regards to cystathionine. On the contrary, a cysteine deficit can be harmful.

Methionine can also accumulate. High concentrations of homocysteine are harmful to various organs whereas the accumulation of methionine seems to be harmless.

Page 9: Topic = Diagnostic investigations in homocystinuria

This page shows the diagnostic process of homocystinuria. The concentration of homocysteine in the blood is largely elevated. The measurement of homocysteine concentration requires a special method, which is only available in some laboratories. The previously mentioned accumulation of methionine in blood can be variable.

In the past, the detection of high concentrations of homocystine in the urine was used in the diagnostic process of homocystinuria. This method has become secondary now and such a measurement is no longer necessary. The measurement of the blood concentration of homocysteine is significantly more sensitive.

Page 10: Topic = Pathogenesis

A permanent presence of very large amounts of homocysteine in the body results in the development of HCU disease symptoms after some years. The symptoms are listed on this page.

Page 11: Topic = Treatment's goal

The goal of any homocystinuria treatment is to decrease the homocysteine concentration in the blood until it reaches a safe level at which homocysteine is no longer harmful.

Page 12: Topic = Treatment elements

At first it should be emphasized that there is no possibility to restore the full activity of the CBS enzyme as it is in a person without homocystinuria. However, there are three elements of treatment which can be very effective in some patients with homocystinuria. These elements are marked on the present page with numbers 1, 2 and 3. In a newly diagnosed patient with homocystinuria the treatment sequence 1 to 3 is usually implemented. If the desired treatment effect (decrease of blood homocysteine concentration) is missing, the next treatment element is gradually added.

1. Treatment is always started with vitamin B6. Relatively large amounts of vitamin B6 used daily in the form of pills can increase the activity of the inactive CBS enzyme. In some patients this form of treatment results in the lowering of the blood homocysteine level. In some cases the homocysteine level can even return to normal. In such situations vitamin B6 is used continuously and no other treatment elements are necessary.

2. In cases of unsatisfactory results of the treatment with vitamin B6 the next treatment element is added – the use of betaine. The aim is to transform a certain amount of homocysteine into methionine with the result of lowering the homocysteine level. In

addition vitamin B12 and folic acid are prescribed to avoid a deficiency of these substances.

3. If the treatment results are still unsatisfactory, the most difficult method must be initiated, namely the reduction of the amount of amino acid methionine in food. In addition the amount of cysteine in the food has to be increased to secure a sufficiently high cysteine level. Therefore, this treatment requires the use of a low-methionine and cysteine-rich diet. From the practical point of view this uses low-protein food supplemented with "synthetic protein" (= mixture of amino acids) designed for patients with homocystinuria.

Page 13: Topic = Composition (quantitative) of food

The next pages present the low-protein diet supplemented with "synthetic protein" (= mixture of amino acids) designed for patients with homocystinuria.

Page 13 shows the composition of food as on page 3. However, the difference is, that the food types in the lower part of this page are marked with red, yellow or green.

The food types containing very high amounts of protein and, consequently, also high amounts of methionine are red. The food containing less protein and simultaneously less methionine is yellow, and green food contains no protein and therefore no methionine.

Page 14: Topic = Treatment with low-protein diet and amino acid mixture

Patients with homocystinuria are treated with a low-protein and, subsequently, low-methionine diet. This means that meals are composed mainly of food from the yellow and green groups. Many products from the red group have to be excluded from meals. In exchange patients receive methionine-free "synthetic" protein in the form of a methionine-free amino acid mixture. This mixture also contains cysteine.

An experienced clinical dietitian will explain the details of this special diet during a separate meeting. We will continuously advise and guide you regarding feeding issues, as your child gets older.

Page 15: Topic = Follow-up

Systematic follow-up is necessary during treatment. As part of it blood concentrations of homocysteine and of methionine have to be measured. If the homocysteine concentration in blood cannot be reduced to below 50 µmol/L other treatment options have to be initiated to lower the risk of the development of thromboembolism.

Page 16: Topic = Chromosomes, genes, mutations, enzyme defect

What is the reason for the enzyme defect in your child? Probably, you have already heard about chromosomes, genes and mutations.

The text should be read aloud.

Page 17: Topic = Inheritance

How does your child inherit the mutation?

You can see here the principle of (autosomal recessive) inheritance in homocystinuria. At first you can see the father and the mother depicted as green-red icons. Both, the mother and the father inherited and carry a green gene without a mutation and a red gene containing a mutation. As a result, the mother can generally produce egg cells without a mutation (in the picture marked as green) and egg cells containing a mutation (in the picture marked as red). Similarly, the father produces sperm with a mutation and without a mutation (in the picture red or green, respectively). The father and the mother are defined as carriers. This means that both of them have one gene with a mutation and one gene without a mutation, and consequently no homocystinuria.

Page 18: Topic = Inheritance

Now, for the conception of a child there are three theoretical possibilities:

1. If at the conception the child receives two mutations (one from each parent) the activity of the cystathionine beta-synthase (CBS) is reduced with resulting homocystinuria.

2. If at the conception the child receives only one mutation from one parent – from the father or from the mother – the child becomes a carrier.

3. If at the conception the child receives no mutations from either of the parents, of course the child will not become a carrier.

These possibilities are the same for each new pregnancy. The distribution is not influenced by the fact that the older child in the family is ill or is not.

Page 19: Topic = Inheritance

This picture should make it clear why the father and the mother are carriers. As you can see, the father and the mother received their mutations from their parents and grandparents and so on.

There are three conclusions we can make from the depicted situation:

1. There may be many generations of undetected carriers in a family, who show no metabolic abnormality and, subsequently, no disease symptoms.

2. Both families equally contribute to the fact that your child has homocystinuria.

3. The fact that your child has homocystinuria results from inheritance and definitely not from any fault neither in your life nor during pregnancy.

Page 20: Topic = Prognosis

Comparison of treatment results:

Treatment initiation in a symptom-free newborn and later when symptoms are already present. In every case the most important thing is avoiding thromboembolism (which often develops following eye surgery).

The effective decrease of homocysteine level can significantly lower the risk of thromboembolism.