Hereditary metabolic disorders / Treatment of diseases caused by disorders of amino acid and carbohydrate metabolism

Treatment of DMP caused by disorders of AMK and carbohydrate metabolism

About 850 metabolic diseases are currently known, of which about 70 are treatable or diet - modifiable (according to the lecture, 1/3 of all DMPs are treatable). Mostly AR, less GR, rarely AD inheritance.

Treatments:

1. Reduction of accumulated substrate = diet or inhibition of the metabolic pathway at the level of an enzyme;
2. replacement of the missing product - especially in disorders of beta oxidation of fatty acids;
3. reduction of toxic effects of metabolites;
4. stimulation of residual activity enzyme;
5. replacement of missing enzyme.

Where treatment is not possible, an effort is made to at least alleviate the symptoms and associated complications. The main effort is diagnostics at gene level, with predictability and genetic counseling in the family. The treatment is very expensive, ranging from hundreds of thousands to millions of crowns (for example PKU CZK 250,000 / patient / year, tyrosinemia CZK 1,000,000 / patient / year).

1. **Reducing the amount of accumulated substrate.**
    1. **The D**
    2. **diet** is based on the & nbsp; limited intake of indigestible AMK and dietary supplements such as mixtures of amino acids, vitamins, Minerals. The diet can only be used if AMK is not synthesized in the body.
    3. ***Inhibition of the metabolic pathway*** at the level of an enzyme:
        - Type I tyrosinemia- fumarylacetoacetase deficiency;
            - Nitisone treatment - blocks the conversion of hydroxyphenylpyruvate to homogentisate.
2. **Replacement of the missing product** - especially in disorders of beta oxidation of MK.
    - The product may favorably affect the clinical course, eg carbohydrate administration in glycogenosis (GSD), arginine or citrulline in urea cycle disorders or tyrosine in PKU.
3. **Toxicity reduction** - org. aciduria, maple syrup syndrome.
    - Hemodialysis, hemofiltration;
    - exchange transfusion in newborns - through the umbilical cord to take part of the blood and replenish the volume with donor;
    - peritoneal dialysis;
    - removal of a toxic substance by another metabolic route.
        - Eg Isovaleryl aciduria - binding to glycine and leaving the body as isovalerylglycine.
4. **Stimulation of residual enzyme activity** - pharmacological chaperones.
    - Clinical testing phase- how to prevent the degradation of poorly packaged enzymes, even though they have residual activity (even this can favorably affect the course of the disease).
5. **Deficient enzyme replacement**;
    1. **organ transplantation** - liver - glycogenosis, org. aciduria × high mortality;
    2. **administration of enzymes** using endocytosis;
        - Gaucher's disease - delivery of glucocerebrosidase (binding via M6PR on microphases) × high cost, does not cross the blood-brain barrier, ie does not affect CNS disorders;
    3. gene therapy - research phase.

Amino acid metabolism disorders

Phenylketonuria

- 1: 6,000;
- phenylalanine hydroxylase deficiency;
- accumulation of phenylalanine in the body leads to CNS disorders (mental retardation, dementia…);
- **treatment: low-protein diet** - a combination of gluten-free, lactose-free and low-protein diets;
    - avoid eating meat, milk, cereals (ie flour meals), cereals, nuts, legumes, most fruits and vegetables and the artificial sweetener aspartame;
    - patients can eat food from specialty stores, honey, vegetable and animal fats (butter, lard) and precisely weighed portions of fruit and vegetables;
    - Strict adherence to diet can **avert mental retardation** and ensure a normal life for the individual - the diet is lifelong (although it is believed that high levels of phenylalanine do not harm the brain at an older age).

Homocystinuria

- 1:83 000, according to some authors up to 1: 15 000.

- Disorder of cystathione beta-synthase (either impaired activity or deficient).
- Disorder of methionine to cysteine conversion, **accumulation of cysteine** and **homocysteine** in the organism.
- A special form is the so-called remethylation form, where homocysteine is not converted back to methionine. This form is rarer, but also more serious.
- Homocysteine **toxic** acts on the CNS, skeleton, eyes and vascular endothelium.
- The aim of the therapy is to reduce the concentration of homocysteine and optimize the level of methionine.
- Two ways:
  1. Some patients respond well to a combination of high doses of vitamin B_6 (up to several hundred milligrams per day) and folic acid (5-10 mg / day), but the response to treatment may manifest itself in a few weeks;
  2. The second method of therapy is a low-protein diet with reduced methionine content and synthetic supplements of essential AMK.
     - **Prohibited Foods** [1]**:**
       - all kinds of meat (chicken, poultry, pork, beef, game, fish...), offal, cold cuts, sausages, ham, sausages, tripe, canned meat and any other meat and fish products;
       - hard cheeses, processed cheeses, low-fat cottage cheese and other low-fat dairy products;
       - eggs as a separate dish;
       - legumes - all kinds (beans, lentils, peas, soybeans);
       - nuts, almonds.
  - If the results of the diet are unsatisfactory, betaine can be given, which also reduces the concentration of homocysteine in the body (adults 6-9 g / day) - it helps its demethylation to methionine.
  - The success of treatment depends primarily on early diagnosis of the disease and the introduction of diet - this will reduce the rate of mental retardation, later onset of lens dislocation, reduction in the number and extent of convulsions and the risk of thromboembolism.

Tyrosinemia type I

Not only *tyrosine* accumulates in the body (increased levels in the blood can be found), but also metabolites of its metabolism (mainly succinylacetone - increased levels in the urine). It is toxic mainly to the liver and renal tubule cells. Types II and III are rarer and their symptoms milder.

- 1: 100,000.
- Fumarylacetoacetate hydrolase (FAH) activity disorder.

Subtypes by manifestation:

- acute - up to 6 months of age;
- subacute - between 6th month and 1st year;
- chronic - after 1 year;

Therapy

- Based on a low-protein diet and essential amino acid supplements without phenylalanine and tyrosine.
- The aim is to keep the tyrosine levels in children's blood at 250-500 mol / l, according to which the amount of permitted proteins in the diet and the amount of the preparation is determined.
- It is also important to monitor and, if necessary, supply carnitine and calcium levels.
- Administration of nitisone (Orfadin) - increased survival from two years to five years (later development of hepatocellular carcinoma).
- Prevents tyrosine degradation (is a 4-hydroxyphenylpyruvate dioxygenase inhibitor).
- Liver transplant is successful.

Organic aciduria

These are usually disorders of one of the enzymes in the catabolism of branched-chain amino acids (leucine, isoleucine, valine), which leads to increased urinary carboxylic acid excretion. Common symptoms are toxic brain damage, ketone positivity, acidosis and hypoglycemia. These diseases are autosomal recessively inherited.

- Leucinosis (maple syrup syndrome); (1:20 000 - 50 000) - The smell and color of the urine are reminiscent of maple syrup.
- Isovaleric aciduria; (1:50,000) - urine smells like a mouse.
- Methylmalonic aciduria; (1:50 000).
- Propionic aciduria; (1: 100,000).
- Glutaric aciduria type I; (1: 100,000). In particular, the metabolism of lysine and tryptophan is impaired.

Therapy

- Acute treatment: an attempt to compensate for the acute condition - glucose infusion.
- Dialysis and blood exchange transfusion to remove excess ketone bodies and the like.
- Lifelong protein-reduced diet and essential amino acid supplements.
- L-carnitine supplementation and isovaleric aciduria and L-glycine.
- Some patients respond positively to OH-cobalamin and metronidazole is also recommended (it reduces the growth of intestinal bacteria and thus prevents the production of propionic acid, from which methylmalonic acid is formed by metabolic conversion).
- The prognosis also differs from type to type and depends on early diagnosis.

- Despite early treatment, 10-30% of patients do not have good prospects.
- For example, patients with leucinosis usually live a normal life with occasional states of metabolic decompensation, but they usually observe lower intelligence than peers.
- In patients with methylmalonic aciduria, the prognosis is poor.

Urea cycle disorders

The most common disorder in the urea cycle is X-linked OTC (ornithintrascarbamoylase) deficiency, which is involved in the conversion of carbamoyl phosphate to citrulline (see urea cycle).

- Associated with the occurrence of ***hyperammonemia*** and in the beginning with respiratory alkalosis.
- Development possible at any age, the greatest risk is in newborns and infants.
- Symptoms: vomiting, lethargy, severe neurological impairment due to toxic plasma ammonia levels (> 400 µmol / L).
- Ammonia increases the transport of some substances across the blood-brain barrier (eg tryptophan).

Therapy

- Low protein diet;
- food mixtures of essential amino acids;
- efforts to remove excess nitrogen by other metabolic routes - administration of sodium benzoate (conjugates with glycine to hippurate, which is rapidly excreted), phenylacetate or phenylbutyrate (phenylacetate conjugates glutamine to phenylglutamine, which is again excreted in the urine; 1 mole of phenylacetate (2 moles of nitrogen);
- an effort to keep ammonia levels normal while ensuring sufficient protein for normal development.

Prognosis

- Despite aggressive treatment, it is very poor, inversely proportional to the age at which the disease develops.

Carbohydrate metabolism disorders and their treatment

Galactosemia

- 1:40 000-60 000.
- Disorder of galactose-1-P-uridyltransferase (GALT) activity.
- **Galactose-1-P** accumulates in the body **-**is metabolized by an alternative route to **galactitol** , which is detected in the urine.
- Both of these substances are toxic to the liver, brain, kidneys and eye lens.
- **Treatment:** lactose-free and low-galactose diet (non-dairy diet is not enough).
- The presence of galactose is in the following foods:
  - fruits and some cereals, vegetables (cabbage, cauliflower, beets, brussels sprouts, cabbage, tomatoes) and legumes (peas, soybeans, beans, lentils); it is also necessary to exclude from the diet cocoa, chocolate, ice cream, almonds, nuts, cinnamon.
- However, galactose cannot be completely ruled out by diet.
- You also need to control some medications and vitamin supplements, because galactose is a part of them.
- However, the long-term prognosis may not be entirely favorable, the body may self-synthesize galactose from glucose ("self-intoxication"), intrauterine transmission through the placental blood.
- Despite following the diet, we monitor speech disorders, mental retardation, disorders of orientation in space and, in adolescent girls, peripheral ovarian failure (a type of hypogonadism).

Disorders of fructose metabolism

- Hereditary fructose intolerance.
- It is a deficiency of aldolase B (fructose-1,6-bisphosphate aldolase) - it breaks down fructose-1-phosphate.
- Patients lead a normal life, only ingestion of fructose (sucrose or sorbitol) causes acute hypoglycemia and gastrointestinal problems, nausea, vomiting, restlessness, sweating, tremor, lethargy and finally apathy, coma, twitching and convulsions.
- If it is not recognized (ie with constant administration of fructose), it does not thrive, liver damage, hepatomegaly, jaundice, increased bleeding, swelling, ascites and manifestations of proximal renal tubular dysfunction.

Therapy

- acute intoxication - intensive care and supportive care (eg administration of frozen plasma);
- exclusion of fructose from the diet - replacement with glucose, maltose and starch (to prevent an increase in the proportion of fat in the diet);
- vitamin substitution (to prevent hypovitaminosis caused by the exclusion of fruits and vegetables from the diet).
- **Cave**: some medicines may contain fructose (syrups, immunoglobulin solutions).
- Danger at every hospitalization - life-threatening infusions of fructose.
- The prognosis is excellent.

Glycogenosis (GSD)

- Hereditary metabolic disorders caused by disorders of glycogen degradation, glycolysis and, paradoxically, disorders of glycogen synthesis.
  1. Liver
     - often hypoglycemia, marked hepatomegaly and delayed growth, sometimes cardiomyopathy;
     - manifestations of liver cirrhosis to liver failure.
  2. Muscle
     - exercise intolerance with myalgia and muscle cramps, which are often followed by rhabdomyolysis and myoglobinuria;
     - All symptoms are reversible at rest.
  3. Generalized

Therapy

- primarily dietary - an effort to prevent hypoglycemia and suppress secondary metabolic decompensation;
- frequent feeding during the day and in GSD I and in some patients with GSD III continuous night feeding with a nasogastric tube.

Mucopolysaccharidosis

They are mostly caused by an enzyme disorder in the mucopolysaccharide degradation pathway, transport disorders, lysosomal transport disorders, galactosialidosis.

- AR inherited, MPS II (Hunter's sy) is AD.
- Clinical signs and abnormalities of the body are not completely known.
- These include CNS disorders, facial dysmorphia, bone dysplasia and upper airway obstruction.
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Therapy

- incurable;
- limited to palliative care;
- for MPS I, hematopoietic cell transplantation or substitution of the missing enzyme is performed, in others, the procedures are just being put into practice.

Links

Related Articles

- Disorders of fructose metabolism
- Disorders of galactose metabolism

Reference

1. Informační brožurka pro pacienty. *Homocysteinurie z deficitu CBS*. 2004. Available from <https://www.nspku.cz/assets/other/hcu-brozura-f5fc97a9010c2b7fa25616e7bf3c5c78a3a8ea5add218578d6eb60d0d9544c6b.pdf>.

Used literature

- Lectures in pathobiochemistry for the 3rd year at the 1st Faculty of Medicine, Charles University - ac. year 2009/2010
- http://www.medicabaze.cz

Recommended literature

Source

- ws:Dědičné metabolické poruchy/Léčba onemocnění způsobených poruchami metabolismu aminokyselin a sacharidů