Congenital defects of metabolism with acute symptomatology

Congenital defects of metabolism are a very extensive and heterogeneous group of diseases. They are **caused by faulty function of one or more enzymes** or **changes in the composition or quantity of structural or transport proteins**. They are usually inherited autosomal recessive or gonosomal recessive; mitochondrial diseases have a maternal type of inheritance. Some of them manifest themselves already in the newborn period. Some of these disorders are targeted by newborn laboratory screening.[1]

The clinical manifestation of congenital metabolic defects can involve virtually any system. The most common are neurological and gastrointestinal symptoms. Manifestations can be acute or chronic. Acute symptoms include: vomiting with dehydration to shock, lethargy and coma, rhabdomyolysis, hypoglycemia during illness, stress or prolonged starvation. The **chronic symptoms** include: signs of metabolic disease with growth failure/delay, hepatomegaly, cardiomyopathy, spastic diplegia, delay in psychomotor development or regression in development.[2]

The first symptoms of congenital metabolic defects can appear **at any age** from the prenatal period to the elderly, and they can manifest differently at different ages. The onset and severity of difficulties are affected by a number of factors, such as a change in diet, starvation, dehydration, ongoing illness, medication, exertion, childbirth, trauma, surgery.[2]

For some defects, the **typical age of manifestation'** is:

- non-ketotic hyperglycinemia, urea cycle disorders, organic acidemia (of branched chains) present as a life-threatening illness (lethargy, anorexia, vomiting, shock) between the 12th and 72nd hours of life,
- maple syrup disease usually appears later in the first week of life.[2]
- neonatal hemochromatosis is manifested by acute hepatic failure in the first week of life,
- galactosemia is manifested by acute liver failure in the first or second week of life,
- tyrosinemia manifests as acute liver failure anytime after the first week of life,
- alpha1-antitrypsin deficiency, Niemann-Pick disease, defects in bile acid synthesis are manifested by acute liver failure after the third week of life,
- mitochondrial disease can occur at any time.[2]

Common laboratory findings include:

- metabolic acidosis/alkalosis, hyperlactic acidemia, hyperammonemia, elevation of liver enzymes, hypoglycemia, ketosis.

Therapy before diagnosis:

- treatment of cardiopulmonary failure, total parenteral nutrition with protein restriction (0.5-0.8 g/kg/day) and without lipids, the energy source is glucose (except for pyruvate dehydrogenase complex defects).

Therapy after diagnosis:

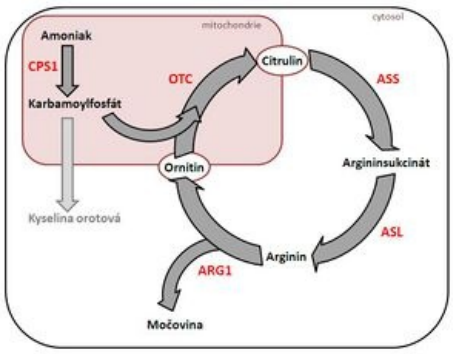
- pharmacotherapy to induce an alternative metabolic pathway, in case of accumulation of toxic metabolites due to enzyme block, eliminative treatment (hemodialysis or hemodiafiltration), dietary measures.[1]

Congenital defects of newborns' metabolism

Congenital disorders of metabolism with manifestation in newborn and infant age[3]	
Disorders of sugar metabolism	Galactosemia • Fructose metabolism disorders • Glycogenosis
Disorders of amino acid metabolism	Leucinosis • Nonketotic hyperglycinemia • Tyrosinemia • Disorders of sulfur amino acid metabolism
Organic aciduria	Methylmalonic acidemia • Propionic acidemia • Isovaleric aciduria • Glutaric aciduria
Disorders of pyruvate metabolism and the electron transport chain	Pyruvate carboxylase deficiency • Pyruvate dehydrogenase deficiency
Urea cycle disorders	Hyperammonemia I, II • Citrullinemia • Arginine succinaturia • Argininemia
Lysosomal disease	Gaucher disease • Niemann-Pick disease • Mucopolysaccharidosis VII. type • Glycoproteinoses
Peroxisomal disease	Zellweger syndrome • Neonatal adrenoleukodystrophy • Infantile Refsum disease • Rhizomelic chondrodysplasia punctata
Different	Congenital adrenal hyperplasia • Disorders of bilirubin metabolism (Crigler-Najjar syndrome and others) • Pyridoxine-dependent convulsions • Antitrypsin deficiency • Disorders of beta oxidation of fatty acids • Smith-Lemli-Opitz syndrome • Neonatal hemochromatosis

Urea cycle disorders

- the consequence of defects is **hyperammonemia** → serious neurological consequences and multi-organ failure;
- the most severe forms begin in the first days (refusal of food, apathy, hypotonia, convulsions → vomiting, progression of impaired consciousness, hypothermia, bleeding manifestations, circulatory failure) and have a lethal course;
- laboratory findings: hyperammonemia;
- autosomal recessive or gonosomal recessive inheritance;



The urea cycle. CPS1: carbamoyl phosphate synthetase, OTC: ornithine transcarbamylase, ASS: arginine succinate synthetase, ASL: arginine succinate lyase, ARG1: arginase.

Leucinosis (maple syrup disease)

- impaired activity of dehydrogenases for branched-chain 2-oxoacids, which are formed from the branched-chain amino acids valine, leucine and isoleucine → neurotoxic acids (2-oxoacids and 2-OH-acids) accumulate → disorders of food intake and vomiting, disorders muscle tone, impaired consciousness → brain edema, circulatory and respiratory failure;
- laboratory findings: ketoacidosis;
- autosomal recessive inheritance;

Nonketotic hyperglycinemia

- dysfunction of the mitochondrial enzyme complex that splits glycine (neurotransmitter – excitatory in the cerebral cortex and inhibitory in the medulla oblongata and spinal cord; importance in the metabolism of hemoglobin, purines and creatinine) → accumulation of glycine, especially in the CNS → **convulsions (pharmacologically difficult to influence);**
- laboratory finding: elevation of glycine in cerebrospinal fluid (compared to plasma);
- autosomal recessive inheritance;
- unfavorable prognosis, only symptomatic treatment;

Organic aciduria

- lead to the accumulation of carboxylic acids without a free amino group, which are excreted in the urine;
- laboratory findings: hyperlactic acidemia, ketoacidosis, hyperammonemia; pancytopenia; hemocoagulation disorders;

Disorders of carbohydrate metabolism

Galactosemia

- galactose-1-phosphaturidyl transferase disorder → accumulation of galactose-1-phosphate → '*nephrotoxic, hepatotoxic and neurotoxic* galacticol;
- manifestations after starting milk nutrition → loss of appetite, vomiting, weight loss, hepatomegaly, lethargy → liver and kidney failure, edema, ascites, brain edema;
- laboratory findings: elevation of aminotransferases, unconjugated hyperbilirubinemia, hypoglycemia, hemocoagulation disorder, anemia, etc.
- diagnostics: galactitol in urine and increased values of galactose and galactose-1-phosphate in erythrocytes → enzymatic and/or molecular diagnostics;
- autosomal recessive inheritance;

Persistent hyperinsulinemic hypoglycemia

- insulin hypersecretion → severe hypoglycemia already in the first days of life;
- treatment: glucose, glucagon, diazoxide, octreotide, possibly subtotal pancreatectomy;[1]

Disorders of mitochondrial energy metabolism

- mitochondrial diseases are hereditary metabolic diseases caused by mutations either in the nucleus in the genes for mitochondrial enzymes or in mitochondrial DNA (non-Mendelian maternal inheritance), which have different clinical manifestations;
- the citrate cycle, oxidative phosphorylation, β-oxidation of fatty acids, part of the urea cycle take place in the mitochondria;
- disorders of energy metabolism:
  - clinical picture: psychomotor retardation and developmental regression, myoclonic epilepsy, central hypotonic syndrome or spastic quadriparesis;
  - laboratory finding: "increased lactate and alanine level" in blood, urine and cerebrospinal fluid; in myopathic manifestations, the level of creatine kinase is increased; aminotransferase elevation in hepatopathy.[1]

Disorders of beta-oxidation of fatty acids

- typical finding: **hypoketotic hypoglycemia** during starvation.

Odkazy

Related Articles

- Inherited metabolic disorders
- Newborn Screening

External links

References

1. JANOTA, Jan – STRAŇÁK, Zbyněk. *Neonatologie.* 1. edition. Praha : Mladá fronta, 2013. pp. 259-269. ISBN 978-80-204-2994-0.
2. SUTTON, V R. *www.uptodate.com* [online]. UpToDate, ©2020. [cit. 2023-02-15]. <https://www.uptodate.com/contents/inborn-errors-of-metabolism-epidemiology-pathogenesis-and-clinical-features>.
3. GOMELLA, TL – A KOLEKTIV,. *Neonatology : Management, Procedures, On-Call Problems, Diseases, and Drugs.* 7. edition. Lange, 2013. pp. 686-709. ISBN 978-0-07-176801-6.