Hereditary disorders of sugar metabolism

Hereditary disorders of carbohydrate metabolism include:

- galactose metabolism disorders :
  - classic form of galactosemia (incidence 1: 50,000) - AR hereditary, galactose-1-phosphate-uridyltransferase (GALT) disorder → galactitol-toxic accumulates → liver cirrhosis, cataract, mental retardation;
  - uridine diphosphate galactose-4-epimerase deficiency; galactokinase deficiency;
- disorders of fructose metabolism :
  - congenital fructose intolerance (incidence 1: 20,000) - AR hereditary deficiency of fructose-1-phosphate-aldolase → accumulates fructose-1-phosphate - toxic, inhibits glycogenolysis and gluconeogenesis → hypoglycemia, liver and kidney damage;
  - essential fructosuria;
- glycogenosis (incidence 1:25 000) - mostly AR hereditary, disorders of glycogen synthesis or degradation;
- mucopolysaccharidoses (incidence 1: 20,000) - mostly AR hereditary (MPS II is X-linked) disorders of lysosomal enzymes involved in the degradation of glycosaminoglycans (GAGs, mucopolysaccharides) → intralysosomal storage of GAGs;
- congenital glycosylation disorders (CDGs);
- glucose transport disorders - congenital disorders of glucose transport across the cell membranes of organs;
  - congenital malabsorption of glucose and galactose, glucose transporter deficiency syndrome (GLUT 1 deficiency), Fanconi-Bickel syndrome (GLUT 2 deficiency);
- congenital hyperinsulinism;
- diabetes mellitus

Congenital disorders of galactose metabolism

Galactosemia is caused by a defect in the enzyme galactose-1-phosphate-uridyltransferase Galactosemia does not break down the monosaccharide galactose

Galactosemia (increase in serum galactose) may be caused by defects in the following enzymes: galactose-1-phosphate uridyltransferase (classical galactosemia), uridyl diphosphate galactose-4-epimerase, galactokinase;

Classical galactosemia

- severe AR inherited disease (gene on short arm of chromosome 9);
- incidence in the Caucasian population about 1:50,000;
- cause : Gal-1-P-uridyltransferase (GALT) activity disorder that metabolizes Gal-1-P
- pathogenesis : Gal-1-P accumulates in the body → in the liver it is metabolized in an alternative way to galacticol - tissue toxin, especially for hepatocytes, neurons, renal tubules and the lens of the eye;
- clinical picture : symptoms begin soon after the start of dairy nutrition,
  - malpractice, vomiting, diarrhea,
  - clinical signs of sepsis, jaundice, hepatomegaly, hepatopathy, coagulopathy,
  - cataract,
  - acute liver , kidney , brain edema ,
  - later manifestations - chronic liver dysfunction,
  - even with early treatment: speech disorders ,
  - in adolescent girls: hypergonadotropic hypogonadism;
- diagnosis :
  - in some countries (not in the Czech Republic) neonatal laboratory screening ,
  - Demonstration of elevated urinary galactitol and gal-1-P levels in erythrocytes
  - however, confirmation at the enzymatic and molecular level is always necessary (there are a large number of mutations) → genetic counseling, prenatal diagnostics;
- therapy : when a suspicion is expressed, we immediately discontinue the dairy diet,
  - when confirming the diagnosis, a lifelong non-dairy (low-galactose) diet is indicated - the main source of galactose in the diet is lactose from milk and dairy products; calcium supplementation;
  - speech therapy care;
  - hormonal treatment of girls with hypergonadotrophic hypogonadism;
- prognosis : may not be favorable even with early diagnosis, because the child was already exposed to galactose by intrauterine transplacental transfer of galactose from the mother. Galactose metabolism

For more information, see Galactose Metabolism Disorders , Galactose Metabolism .

Congenital disorders of fructose metabolism

The enzyme fructose-6-β-aldolase

Hereditary fructose intolerance

- severe AR hereditary disease (gene on chromosome 9);
- incidence 1:20 000;
- cause : fructose-1-phosphate aldolase deficiency
- pathogenesis : fructose-1-phosphate accumulates,
  - toxic → damage to the liver, kidneys and intestines,
  - competitive phosphorylase inhibitor → inhibits glycogenolysis (and gluconeogenesis) → hypoglycemia;
- clinical signs : appear shortly after the inclusion of fructose (sugar) in the diet (breast milk and infant formula do not contain fructose);
  - vomiting, diarrhea, postprandial hypoglycaemia , lethargy, convulsions,
  - jaundice, hepatomegaly → severe hepatic impairment with coagulopathy;
  - older children directly reject foods containing fructose and sucrose (fruits and sweets), they typically do not have tooth decay;
- diagnosis : demonstration of enzymatic activity in liver tissue or enterocytes, molecular genetic examination;
  - postprandial hypoglycemia;
  - kidney damage → chronic metabolic acidosis;
  - liver damage → elevation of aminotransferases, hyperbilirubinemia, coagulopathy;
  - decreased serum phosphate levels;
  - urine: hyperaminoaciduria, elevated levels of reducing agents in negative glycosuria;
  - fructose tolerance test is contraindicated - risk of severe hypoglycaemia;
- treatment : complete elimination of fructose from nutrition; vitamin substitutions (multivitamin preparations);
- prognosis : very good with early diagnosis, late complications do not occur.

Note: hypoglycaemia, jaundice and hepatomegaly accompany type I tyrosinemia, classic galactosemia and congenital fructose intolerance.

Benign fructosuria (essential fructosuria)

- AR hereditary, benign fructokinase deficiency, frequency 1: 50,000;
- fructose is not phosphorylated and is excreted in the urine → hyperfructosemia, fructosuria;
- intestinal-absorbed fructose cannot be used metabolically in the body and is excreted in the urine without clinical symptoms
- there are no clinical signs, no treatment is necessary.

See Fructose Metabolism Disorders for more information .

Congenital disorders of glycogen metabolism - *glycogenosis*

- mostly AR hereditary, glycogen synthesis or degradation disorders ;
- occurrence 1:25 000;

Overview of type IV glycogenoses

type of glycogenosis	damaged enzyme	place of storage	manifestations in infants / toddlers	manifestations in adulthood	therapy
Von Gierkeho	glucose-6-phosphatase	liver, kidneys, intestine	fasting hypoglycemic spasms , slow growth, delayed puberty	hyperlipidemia (xanthomas), osteoporosis, renal insufficiency, hypertension, hyperuricemia, liver adenomas	frequent diet
II - Pompe	lysosomal α-1,4-glucosidase	muscles, liver	severe muscle hypotension , heart failure	muscle weakness (plait) → chronic respiratory insufficiency	enzyme replacement therapy
III - Corriho / Forbesova	amylo-1,6-glucosidase glycogen branching enzyme	liver, muscles	liver form : fasting hypoglycemia, hepatomegaly, hepatopathy muscle form : myopathic syndrome, cardiomegaly	progressive muscle weakness	frequent diet
IV - Andersen	glycogen branching enzyme	liver, muscles	liver cirrhosis , portal hypertension, hepatosplenomegaly		liver transplantation
V - McArdle	(glycogen) phosphorylase	muscles	-	muscle cramps during exercise, muscle weakness	exercise reduction, frequent diet

See the Glycogenosis page for more information .

Type 0 glycogenosis

- aglycogenosis , lack of glycogen synthetase enzyme in liver (not muscle, leukocytes and enterocytes)
- liver glycogen is reduced below 2% of normal
- clinical picture : conditions of severe hypoglycemia with convulsions - lead to brain damage and mental retardation
  - they occur mainly in the morning, after a night of fasting, they are accompanied by ketonemia

    - after glucose application we observe prolonged hyperglycemia and an increase in serum lactate (the liver does not form glycogen, it forms lactate)
- urgent diagnosis is essential for a child's survival
- episodes of hypoglycaemia can be prevented by frequent administration of protein-rich foods

Glycogenosis type Ia

- von Gierk's disease , hepatorenal glycogenosis
- impaired glucose-6-phosphatase activity (converts glc6P to glc)
- AR hereditary disease, the gene is on chromosome 17
- clinical picture : begins in infancy with progressive hepatomegaly and fasting hypoglycemic convulsions
    - hypoglycaemia is more common during fever and is accompanied by lactic acidosis with Kussmaul respiration
    - characteristic facies: "doll face"
    - the organism adapts to hypoglycemia - insulin secretion decreases , it activates lipase in adipose tissue → hyperlipoproteinemia occurs → their increased breakdown produces ketone bodies , which together with lactate participate in acidosis
    - Glucagon administration does not increase glucose but lactate
    - growth slows and puberty is delayed
    - in adulthood, xanthomas , renal disorders with hypertension and gout , adenomas in the liver may occur
- laboratory : fasting hypoglycaemia (common in infants and toddlers only)
    - hyperlipidemia and hyperlactacidemia, which blocks the excretion of uric acid and conditions hyperuricemia
- sono : hepatomegaly and nephromegaly, there may be adenomas in the liver
- liver biopsy : steatosis and glycogen withdrawal
- Therapy : The goal is to prevent severe hypoglycemia and MAc
    - diet therapy - frequent administration of nutrition with reduction of animal fats, lactose , sucrose and fructose
    - we pay for caloric needs mainly maltodextrins and starches
    - from toddler age we serve cornstarch after each meal
    - at night, continuous feeding with a nasogastric tube is suitable so that we give 30% of the daily intake at night
    - in acute metabolic breakdown with lactic acidosis during infections, glucose must also be administered
- prognosis : good in childhood, there is a risk of developing liver, renal and cardiovascular complications in adulthood

Glycogenosis type Ib

- glc-6-P transport defect
- clinically indistinguishable from Ia, but neutropenia and, as a result, aphthous stomatitis and intestinal ulceration are common

Glycogenosis type II

- Pompe disease , generalized glycogenosis
- has two forms:
    - IIa affects infants (enzymopathy)
    - IIb affects older children and adults (enzymopenia)
- it is a disorder of the lysosomes of the liver, muscles and heart - glycogen accumulates in them
- glycogen also accumulates in the cytoplasm of muscle (including myocardium)
- prenatal diagnosis is possible - finding abnormal lysosomes in amniocytes
- *the classic form* is always a deadly disease - even after birth, the size of the heart is borderline
- clinical picture :
    - within weeks and months, the baby becomes completely hypotonic - sucking weakly, breathing shallowly
    - marked cardiomegaly , ECG high P, shortened PQ and transmission disorders
    - liver slightly enlarged
    - consciousness is not violated, nor is the intellect
    - common aspiration pneumonia with atelectasis , death around 2 years due to respiratory failure
- effective therapy is not available
- *adult forms* - muscle weakness arises later
    - sometimes it does not have to shorten the life expectancy, it allows sedentary employment
    - others die around the 30s and 40s
    - cardiomegaly is smaller, ECG normal, often arrhythmias
- diagnosis : skin biopsy - detection of abnormal lysosomes under an electron microscope

Glycogenosis type III

- Cori's disease , Forbes' disease
- rare AR hereditary disease
- disorder of glycogen branching enzymes
- similar to GSD I, milder

Glycogenosis type IV

- Andersen's disease
- rare AR hereditary disease, so far described about 10 cases
- branching enzyme disorder
- in hepatocytes there is long-chain glycogen without branching (amylopectin)

Congenital disorders of mucopolysaccharide metabolism - *mucopolysaccharidoses*

See the Mucopolysaccharidosis page for more information .

- these disorders can be classified as lysosomal disorders
- The following mucopolysaccharides (MPS) play an important role : heparan sulphate , keratan sulphate and dermatan sulphate
- because mucoploys saccharides are part of binders, bone changes are characteristic (dysostosis multiplex), the CNS (mental retardation) is affected, as well as KVS, liver , spleen , skin , joints and tendons
- are AR inherited - except for Hunter's sy (MPS II) he is XR bound
- The diagnosis of MPS is based on the child's phenotype, evidence of urinary GAG excretion, X-ray dysostosis, enzymatic examination
- the prognosis is generally unfavorable, many die in preschool or school age, patients with milder forms may live to adulthood
- therapy : except MPS I is symptomatic

Hurler Syndrome (MPS I)

- the most serious MPS
- accumulation of dermatan sulphate and keratan sulphate in tissues and their excretion in the urine
- during the first year of life we usually find only a delay in psychomotor development, we can detect hepatosplenomegaly, accentuation of kyphosis, wheezing
- after the 1st year the symptoms develop: a typical face develops - gargoloid (resembles gargoyles), macrocephaly , dolichocephaly with a prominent forehead, nose is wide and flat with a deep root, macroglossia
- corneal cataracts appear, psychomotor skills accelerate only after the 2nd year, the patient ceases to be mobile
- valve involvement, cardiomyopathy, insuff.
- death usually by puberty
- therapy : bone marrow transplantation and / or ERT (enzyme replacement therapy)

Links

- ws:Dědičné poruchy metabolismu cukrů

Related articles

- Dědičné poruchy metabolizmu tuků
- Hereditary disorders of amino acid metabolism
- Disorders of glucose metabolism

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