Mucopolysaccharidosis

Mucopolysaccharides are disorders of mucopolysaccharide metabolism. These are inherited disorders of lysosomal enzymes (partial breakdown of cellular metabolites that accumulate intracellularly + toxic to organ systems: CNS, eye, skeleton, visceral organs) from the group of glycosidases, sulfatases and one transferase, which gradually degrade glycosaminoglycans in a healthy organism (GAG, mucopolysaccharides). GAGs are covalently bound to protein (proteoglycans) and in this complex form an integral part of cell membranes, the extracellular matrix and some intracellular structures. The following GAGs are characteristic of proteoglycans: **chondroitin sulfate** (CS), **dermatan sulfate** (DS), **heparan sulfate** (HS) and **keratan sulfate** (KS).

In the MPS group, we recognize 10 enzyme defects. Inheritance is **autosomal recessive** except MPS II, where inheritance is **gonosomally recessive**. The historical classification is based on the phenotype. The most common are types III (includes 4 enzyme deficits), II and I.

Clinical signs

For each type of **MPS**, there is a spectrum of clinical symptoms from *severe* to *mild*. **Clinical symptoms** develop after an asymptomatic period of varying lengths. Craniofacial dysmorphia (rough facial features, gargoylism), slowing, arrest and regression of psychomotor development, hepatosplenomegaly, cardiomyopathy often with valve involvement, bone and joint changes with growth failure, corneal opacity (except type II and III), hearing impairment . Umbilical hernias and recurrent respiratory infections are common. Clinical signs in MPS III vary with severe CNS involvement, while other somatic signs are poor. Aggressive behavior and hyperactivity are typical.

On **morphological examination**, lysosomal storage is a manifestation of vacuolation of the cytoplasm of cells in commonly available biopsy specimens (fibroblasts, sweat glands, lymphocytes).

Laboratory diagnostics

Laboratory diagnosis of MPS is based on the demonstration of increased urinary GAG excretion. Qualitative analysis (electrophoresis of GAGs isolated from urine) determines the spectrum of GAGs, on the basis of which it is possible to partially direct the subsequent enzymatic diagnostics. The definitive diagnosis of MPS is based on the detection of enzyme deficiency in peripheral blood leukocytes, event. cultured skin fibroblasts.

Molecular genetic diagnostics is gradually being introduced for some types of MPS (II, I), which is very important especially for the detection of carriers in a family diagnosed with MPS II, as their identification by enzymatic analysis is problematic. However, this information is essential for the proper management of genetic counseling and prenatal diagnosis in a family with MPS.

Mucopolysaccharidosis type I (Hurler's syndrome)

- **AR** disease
- *synonyms:* dysostosis multiplex
- **Defect: α-L-iduronidase** deficiency (defect in the gene encoding the enzyme protein), **dermatan sulfate** accumulates
- **Clinical manifestations:** skull enlargement, strong hair, gargoyle expression (low forehead, wide nose, enlarged lips), blindness, deafness, mental retardation, short neck, chest deformities, hepatosplenomegaly, gibbus
  - spektrum závažnosti klinického projevu je velmi široké, od těžkého (**m. Hurler**) až po mírnou formu (**m. Scheie**) se zachováním intelektu
    - The clinical symptoms of **Hurler's disease** develop after an asymptomatic period of various lengths, usually starting between 6 and 24. month old. Gradually there is **craniofacial dysmorphia** (rough facial features, gargoylism), slowing down, arrest and regression of psychomotor development, hepatosplenomegaly, cardiomyopathy often with valve failure, bone and joint changes with growth failure, corneal opacity, hearing impairment. Umbilical hernias and recurrent respiratory infections are common.
      - the disease is unfavorable, patients usually die before the age of 10 from cardiorespiratory failure
    - **Schei's disease** is a clinically milder form of MPS I. The disease begins around 5 years and growth and intelligence are normal. Joint stiffness, corneal opacity, heart valve involvement and nerve compression are noticeable.
    - The **Hurler-Schieie** clinical phenotype begins around year 3, growth is delayed but intelligence is normal. Corneal opacity and deafness are typical.
- **Therapy:** in some cases, bone marrow transplantation is possible before the clinical symptoms develop significantly (if a suitable donor is found), and in milder forms, the supply of the missing enzyme is also tested; untreated disease ends in the death of a child under 10 years of age (most often due to heart failure).
- **Diagnosis:** MPS I is confirmed by determining the deficiency of α-L-iduronidase activity in leukocytes isolated from peripheral blood or in cultured skin fibroblasts. DNA analysis is an additional examination in cases with a confirmed diagnosis. Glycosaminoglycans accumulate in lysosomes and DS excretion in two fractions and a variable amount of HS are increased in the urine. The total amount of GAGs excreted in the urine decreases

with age.

- **Prenatal diagnostics:** in families with an enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible; additional examinations are analysis of the ultrastructure of chorionic villi and two-dimensional electrophoresis of GAGs isolated from amniotic fluid

Mucopolysaccharidosis II. type (Hunter syndrome)

- **GR** disease – the second most common type of MPS
- **Defect: L-iduronosulfate sulfate** defatase, **heparan sulfate** accumulation
- **Clinical manifestations:** manifestations are similar to **MPS I** - in patients, however, there is no corneal opacity and retinal degeneration is milder
  - the spectrum of severity of clinical manifestation is very broad, from severe to moderate with intellect
  - *milder form:*
    - the first manifestations begin at a younger school age (people with disabilities can live to be 50 years old)
    - the main manifestations include: slow growth, flexive holding of fingers (bothers when writing), retinitis pigmentosa, hearing loss, have a normal intellect
  - *heavier form*
    - the first speeches begin around 1. − 3. year, faster disease progression (disabilities die by the age of 15 - often due to heart failure)
    - the main manifestations include: macrocephaly, prominent forehead, wide nose, malformed teeth, macroglossia, short neck, hepatosplenomegaly, hearing impairment, dementia, cardiomegaly, coronary artery stenosis, hypertrophic gums
- **Therapy:** not yet available
- **Diagnosis:** Glycosaminoglycans accumulate in lysosomes and DS excretion in two fractions and a variable amount of HS are increased in the urine. The diagnosis of MPS II is confirmed by determining the deficiency of iduronate-2-sulfatase activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts. DNA analysis is an additional examination in cases with a confirmed diagnosis, but it is necessary to confirm the heterozygous condition. The total amount of GAGs excreted in the urine decreases with age.
- **Prenatal diagnostics:** in families with an enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible; additional examinations are analysis of the ultrastructure of chorionic villi and two-dimensional electrophoresis of GAGs isolated from amniotic fluid.

Mucopolysaccharidosis III. type (Sanfilip's syndrome)

- **AR** disease – the most common type of MPS
- **Defect:** heparan sulfamidase activity deficit, heparan sulfate accumulation
- **Clinical manifestations:** mental retardation, hyperactivity, aggression, restlessness, sleep disorders, increased hair, no corneal opacity
- **Therapy**: not available
- **Diagnosis:** MPS III is confirmed by determining heparan sulfamidase activity deficiency in leukocytes isolated from peripheral blood or cultured skin fibroblasts
- **Prenatal diagnostics:** in families with an enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible; additional examinations are analysis of the ultrastructure of chorionic villi and two-dimensional electrophoresis of GAGs isolated from amniotic fluid.

Mucopolysaccharidosis IV. type (Morqui syndrome)

- **AR** disease
- **Defect: galactose-6-sulfatase** activity deficit, **keratan sulfate** and **chondroitin sulfate** accumulation
- **Clinical manifestations:** deformity skeletu,(trpaslictví, genua valga) které progredují s věkem (krátký trup a krk, kyfóza, hyperlordóza, skolióza, deformity obratlů, valgózní postavení kolenních kloubů) a opožděný růst, končetiny jsou nápadně dlouhé oproti krátké páteři (nemocný si opírá ruce o stehna); klouby jsou nápadně volné, hyperflexibilita zápěstí zhoršuje funkci ruky; neurologické problémy v dětství nejsou přítomny; později dochází k zákalům rohovky, zvětšení jater, vývoji abnormálních zubů a poruchám sluchu; intelekt je normální
- **Therapy:** not available
- **Diagnosis:** MPS IV is confirmed by determining a deficiency of galactose-6-sulfatase activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts
- **Prenatal diagnostics:** in families with an enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible; additional examinations are analysis of the ultrastructure of chorionic villi and two-dimensional electrophoresis of GAGs isolated from amniotic fluid.

Mucopolysaccharidosis V. type (formerly Scheie's syndrome)

- today it is a **subtype of mucopolysaccharidosis type I** with mild manifestations (without neurological impairment, normal intellect, mild skeletal manifestations)[1]
- OMIM 607016 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=607016)

Mucopolysaccharidosis VI. type (Marotaux-Lamy syndrome)

- **AR** inheritance
- **Defect:** deficit of **N-acetylgalactosamine-4-sulfatase activity (arylsulfatase B)**, accumulation of **dermatan sulfate**
- **Clinical manifestations:** are similar to Hurler's disease; skeletal abnormalities, corneal opacity, joint stiffness soon appear; in severe forms there may be cardiomyopathy; intelligence is normal
- **Therapy:** not available
- **Diagnosis:** MPS VI is confirmed by determining the deficiency of N-acetylgalactosamine-4-sulfatase activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts
- **Prenatal diagnostics:** in families with an enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible; additional examinations are analysis of the ultrastructure of chorionic villi and two-dimensional electrophoresis of GAGs isolated from amniotic fluid.
- OMIM 253200 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253200)

Mucopolysaccharidosis VII. type (Sly's syndrome)

- **AR**
- **Defect: β-glucuronidase** activity deficit, **dermatan sulfate** accumulation
- **Clinical manifestations:** the spectrum of clinical manifestations is similar to that of **mucopolysaccharidosis I**, from a mild form with late onset of symptoms to a severe neonatal form manifesting as hydrops fetalis and dysostosis multiplex
- **Therapy:** not available
- **Diagnosis:** accumulation of glycosaminoglycans in lysosomes and increased urinary excretion of dermatan sulfate, heparan sulfate and chondroitin sulfate; The diagnosis of MPS VII is confirmed by determining the deficiency of b-glucuronidase activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts
- **Prenatal diagnostics:** in families with an enzymatically proven diagnosis, analysis of native and cultured chorionic villi or cultured amniocytes is possible; additional examinations are analysis of the ultrastructure of chorionic villi and two-dimensional electrophoresis of GAGs isolated from amniotic fluid.
- OMIM 253220 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253220)

Mucopolysaccharidosis IX. type

- **AR** inheritance
- **Defect:** hyaluronidase activity deficiency (lysosomal endoglycosidase cleaving hyaluronan)
- **Clinical manifestations:** the syndrome was described in a 14-year-old girl of small stature, with mildly dysmorphic features, flat root of the nose, cleft uvula and multiple periarticular masses of soft tissue around the ankles, fingers and patella, the soft tissue was swollen and painful
- **Diagnosis:** accumulation of glycosaminoglycans in lysosomes and increased urinary excretion

Links

Related articles

- Lysosomes
- Lysosomal diseases
- Hereditary disorders of sugar metabolism
- Achondroplasia ■ Tanatophoric dwarfism ■ Diastrophic dysplasia ■ Larsen syndrome

External links

- Handbook of Genetic Counseling/Mucopolysacharidosis (https://en.wikibooks.org/wiki/Handbook_of_Genetic_Counseling/Mucopolysacharidosis_%28MPS%29)
- National MPS Society (https://mpssociety.org/)

Source

- <http://www.sekk.cz/ELM_ukonceni.pdfencyklopedie/A/AJEJG.htm>

Reference

1. DUNGL, P.. *Ortopedie.* 1. edition. Praha : Grada Publishing, 2005. ISBN 80-247-0550-8.