Mucopolysaccharidoses

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

We recognize 10 enzyme defects in the MPS group. Inheritance is **autosomal recessive** except for MPS II, where inheritance is **gonosomal recessive** . Historical classification is based on phenotype. The most common are types III (includes 4 enzyme deficiencies), 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 length. Gradually, craniofacial dysmorphia (coarse facial features, gargoylism), retardation, arrest and regression of psychomotor development, hepatosplenomegaly, cardiomyopathy often with valvular involvement, bone and joint changes with growth disorder, corneal opacity (with the exception of type II and III), hearing impairment appear . Umbilical and inguinal hernias and repeated respiratory infections are common. Clinical symptoms in MPS III are distinguished by severe CNS involvement, while other somatic symptoms are rarely expressed. Aggressive behavior and hyperactivity are typical.

During the **morphological examination**, lysosomal storage is manifested by vacuolation of the cytoplasm of cells in commonly available biopsy samples (fibroblasts, sweat glands, lymphocytes).

Laboratory diagnostics

Laboratory diagnosis of MPS is based on evidence of increased GAG excretion in the urine. Qualitative analysis (electrophoresis of GAGs isolated from urine) reveals the spectrum of GAGs, on the basis of which it is possible to partially direct subsequent enzymological diagnostics. Definitive diagnosis of MPS is based on evidence of enzyme deficiency in peripheral blood leukocytes, or cultured skin fibroblasts.

For some types of MPS (II, I), molecular-genetic diagnostics are gradually being introduced, which is very important especially for identifying carriers in a family diagnosed with MPS II, as their identification by enzymatic analysis is problematic. However, this information is essential for the proper guidance 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), accumulation of dermatan sulfate occurs
- **Clinical manifestations**: skull enlargement, thick hair, gargoyle expression (low forehead, wide nose, enlarged lips), blindness, deafness, mental retardation, short neck, chest deformities, hepatosplenomegaly, gibbus
  - the spectrum of the severity of the clinical manifestation is very wide, from *severe* (**m. Hurler**) to *a mild form* (**m. Scheie**) with preservation of intellect
    - Clinical symptoms **of Hurler's disease** develop after an asymptomatic period of various lengths, usually starting between 6 and 24. month of age. **Gradually, craniofacial dysmorphia** (coarse facial features, gargoyles), retardation, arrest and regression of psychomotor development, hepatosplenomegaly, cardiomyopathy often with valvular involvement, bone and joint changes with growth disorder, corneal opacities, hearing impairment appear . Umbilical and inguinal hernias and repeated respiratory infections are common.
      - the disease is inauspicious, patients usually die before the age of 10 from cardiorespiratory failure
    - **Schei's disease** is a clinically milder form of MPS I. Onset is around age 5, and growth and intelligence are normal. Stiffness of the joints, cloudiness of the cornea, involvement of the heart valves and nerve compression are noticeable.
    - **The Hurler-Scheie** clinical phenotype begins around age 3, growth is delayed, but intelligence is normal. Corneal opacity and deafness are typical.
- **Treatment:** bone marrow transplantation is possible in some cases before the significant development of clinical symptoms (if a suitable donor is found), and in milder forms, delivery of the missing enzyme is also tested; untreated disease ends in the death of a child under the age of 10 (most often due to heart failure)
- **Diagnosis:** MPS I is confirmed by determining the deficiency of αL-iduronidase activity in leukocytes isolated from peripheral blood or in cultured skin fibroblasts. An additional examination in cases with a confirmed

diagnosis is a DNA analysis. There is an accumulation of glycosaminoglycans in lysosomes, and in the urine there is an increased excretion of DS in two fractions and a variable amount of HS. The total amount of GAGs excreted in the urine decreases with the age of the patient.

- **Prenatal diagnosis**: in families with 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 sulfatase** deficiency , accumulation **of heparan sulfate**
- **Clinical manifestations**: manifestations are similar to **MPS I** − patients do not have corneal opacities and retinal degeneration is milder
  - the spectrum of severity of the clinical manifestation is very wide, from severe to a mild form with preservation of intellect
  - *mild form*
    - the first manifestations begin at a younger school age (disabled people can live to be 50 years old)
    - the main manifestations include: slow growth, flexion of the fingers of the hand (disturbing when writing), retinitis pigmentosa, hearing loss, they have a normal intellect
  - *harder form*
    - the first manifestations begin around 1.−3. year, faster progression of the disease (disabled people die before the age of 15 − often from heart failure)
    - the main manifestations include: macrocephaly, prominent forehead, broad nose, malformed teeth, macroglossia, short neck, hepatosplenomegaly, hearing impairment, dementia, cardiomegaly, narrowing of coronary vessels, hypertrophic gums
- **Treatment**: not yet available
- **Diagnosis**: There is an accumulation of glycosaminoglycans in lysosomes and there is an increased excretion of DS in two fractions and a variable amount of HS 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. An additional examination in cases with a confirmed diagnosis is a DNA analysis, but it is necessary to confirm the heterozygous state. The total amount of GAGs excreted in the urine decreases with the age of the patient.
- **Prenatal diagnosis**: in families with enzymatically proven diagnosis, analysis of chorionic villi, amniotic fluid and 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 syndrome)

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

Mucopolysaccharidosis IV. type (Morquio syndrome)

- **AR** disease
- **Defect**: deficiency of **galactose-6-sulfatase** activity , accumulation **of keratan sulfate** and **chondroitin sulfate**
- **Clinical manifestations**: skeletal deformities (dwarfism, genua valga) that progress with age (short trunk and neck, kyphosis, hyperlordosis, scoliosis, vertebral deformities, valgus position of the knee joints) and delayed growth, the limbs are noticeably long compared to the short spine (the patient is rests hands on thighs); the joints are noticeably loose, the hyperflexibility of the wrist impairs the function of the hand; neurological problems in childhood are not present; later, corneal opacities, liver enlargement, abnormal tooth development, and hearing impairment occur; intellect is normal
- **Treatment**: not available
- **Diagnosis**: MPS IVA is confirmed by determining the deficiency of galactose-6-sulfatase activity in leukocytes isolated from peripheral blood or cultured skin fibroblasts
- **Prenatal diagnosis**: in families with 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 electrophoresis of GAGs isolated from amniotic fluid

Mucopolysaccharidosis type V (formerly Scheie's syndrome)

- Today it is a subtype of **mucopolysaccharidosis type I** with mild manifestations (no 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**: deficiency of **N-acetylgalactosamine-4-sulfatase (arylsulfatase B)** activity , accumulation **of dermatan sulfate**
- **Clinical manifestations**: are similar to Hurler's disease; early skeletal abnormalities, corneal opacities, joint stiffness; in severe forms there may be cardiomyopathy; intelligence is normal
- **Treatment**: 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 diagnosis:** in families with 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 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**: deficiency of **β-glucuronidase activity,** accumulation **of dermatan sulfate**
- **Clinical manifestations**: the spectrum of clinical manifestations is similar to that of **mucopolysaccharidosis I** , ranging from a mild form with late onset of symptoms to a severe neonatal form manifesting as hydrops fetalis and dysostosis multiplex
- **Treatment**: 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 diagnosis**: in families with 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 electrophoresis of GAGs isolated from amniotic fluid
- OMIM 253220 (https://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253220)

Mucopolysaccharidosis IX. of type

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

Links

Related Articles

- Lysosomes
- Lysosomal disease
- Hereditary disorders of sugar metabolism
- Achondroplasia ■ Thanatophoric 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>

References

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