Polskie Towarzystwo Okulistyczne
www.pto.com.pl

KLINIKA OCZNA 2024, 126
Received: 29.12.2023 **Accepted:** 18.03.2024

REVIEW ARTICLE

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2024.141302

Mucopolysaccharidosis in children as seen through the eyes of an ophthalmologist

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ABSTRACT

Mucopolysaccharidosis is a rare, genetically determined metabolic disease. It arises from abnormalities related to the absence or deficiency of lysosomal enzymes needed to break down glycosaminoglycans. Glycosaminoglycans are involved in the metabolic processes of living organisms. Disturbances in lysosomal metabolism causes their accumulation in body tissues and organs, accompanied by pathological symptoms including characteristic general and visual changes. There is no causal (genetic) therapy for mucopolysaccharidosis. Treatment is exclusively symptomatic. Available therapeutic modalities include enzyme replacement therapy and bone marrow transplantation. Ophthalmological treatment comprises correction of refractive errors and other conservative and surgical methods aimed to improve the ocular condition.

SŁOWA KLUCZOWE: etiology of the disease, general and ocular symptoms, laboratory diagnostics, enzyme replacement therapy, bone narrow transplantation, ophthalmological management.

Mucopolysaccharidosis (MPS) is a genetically determined metabolic condition classified as a rare hereditary disease. Rare diseases, also referred to as orphan diseases, encompass conditions with various etiologies. According to European data, a disease is considered rare if it affects not more than five individuals per 10,000 (i.e. one person per 2,000) in the general population. The criterion also applies to rare diseases diagnosed in Poland.

The etiology of mucopolysaccharidosis lies in abnormalities caused by the absence or deficiency of lysosomal enzymes necessary for breaking down glycosaminoglycans (GAGs). Glycosaminoglycans constitute a group of polysaccharides consisting of repeating disaccharide units in which one of the monosaccharides is always an amino sugar and the other is either uronic acid or galactose, and hexosamines [1]. These chemical compounds undergo continuous breakdown and synthesis in the body's metabolic processes. This is possible thanks to lysosomes, cytoplasmic organelles present in eukaryotic cells, appearing morphologically as small vesicles, typically measuring around 0.5 μm (rarely 0.1 to 1 μm) in diameter, enclosed by a lipid-protein membrane, usually single or double-layered, with a thickness of approximately 7 nm. Lysosomes contain acid hydrolases that break down proteins, nucleic acids, carbohydrates and fats. Under normal conditions, they play a crucial role in transporting lipids, which are carried as lipoproteins, through the body's aqueous environments with blood and tissue fluid. Lysosomal enzymes play a role in intracellular digestion, contributing significantly to the breakdown of GAGs and the formation of the extracellular matrix. Normal gradual breakdown of glycosaminoglycans inside lysosomes is essential for maintaining the proper function of cells, tissues, and the extracellular matrix. Lysosomes contribute to both the degradation of materials absorbed by the cell from its external environment and the breakdown of the body's own structures, including those that are redundant or damaged. Most glycosaminoglycans have the ability to bind to proteins, resulting in complex structures known as proteoglycans [2]. Glycosaminoglycans and proteoglycans form structural elements of living organisms. They can also function as biologically active compounds involved in various biochemical reactions. Almost all glycosaminoglycans (GAGs) contain a sulfate group, which is used to identify different types of mucopolysaccharidosis. They include chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), keratan sulfate (KS), and hyaluronate [3]. Not being a sulfated polysaccharide, hyaluronic acid is an exception

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among GAGs. After the transformation cycle, glycosaminoglycans present in the tissues of living organisms are secreted into the bloodstream and then excreted in the urine.

Defects in lysosomal enzymes cause extensive intracellular and extracellular accumulation of these compounds. Disruptions in the expression of lysosomal enzymes impair metabolic processes, leading to a build-up of excess undegraded glycosaminoglycans in the lysosomes of cells across various body tissues and organs. The accumulation of these compounds damages lysosomes, adversely affecting the structure and physiology of tissues and organs, and culminating in the development of MPS [1]. The incidence of MPS is estimated to be 1.9–4.5/100,000 live births [4]. In Poland, studies by Jurecka *et al.* show that the incidence of MPS is 1.81 per 100,000 live births [5]. The most common diagnosis is MPS III (Sanfilippo syndrome), followed by MPS II (Hunter syndrome). Cases of MPS I, IV, and VI have also been reported [3]. All types of MPS are inherited in an autosomal recessive manner, except for MPS II (Hunter syndrome), which is transmitted in an X-linked recessive pattern (women are carriers of the disease, while men are affected).

Mucopolysaccharidosis is characterized by progressive skeletal, visceral, and neural abnormalities. Unmetabolized complexes of glycosaminoglycans with dermatan sulfate are primarily responsible for transformations involving connective tissue, while keratan sulfate is associated with biochemical processes occurring in bone and joint tissues. When these compounds accumulate excessively, they lead to somatic dysfunctions, alterations in bone structure, impaired ossification, and changes in the structure and function of joints, resulting in their stiffness or, sometimes, flaccidity. Children with MPS typically have a distinctive appearance with short stature and low body weight, hydrocephalus (in MPS types I, VI, and VII), short neck, coarse facial features with gargoyle-like characteristics, low hairline on the forehead, dry hair, and claw-shaped hands. In infants, umbilical hernia occurs as a result of laxity of skin and connective tissue in that body region. Older children are more prone to developing inguinal hernia. Mucopolysaccharidosis is also associated with mucosal polyps. Children are prone to frequent infections. Patients with MPS often experience enlargement of the spleen and liver; changes in the heart and circulatory, respiratory, and nervous systems; and involvement of sensory organs manifested as hearing issues (otitis media and hearing loss) and problems with the organ of vision. Impairment of the immune system is also observed. Intellectual development is abnormal, with differing degrees of intellectual disability. However, in milder forms of the disease, the child's intellectual level remains unaffected.

The clinical presentation and progression vary based on the type of MPS and severity of the disease. MPS can manifest at birth, but it typically appears within the first 2-3 years of life or, less commonly, at a later age. The condition affects life expectancy, and can result in death within the first few months of life. Seven types of MPS are classified based on the absence or defect of one of 11 specific lysosomal enzymes and designated as MPS I through MPS IX (excluding MPS V and VIII, which are no longer identified as independent disease entities) [4, 6–7]. Giugliani *et al*. distinguish 11 distinct subclasses of MPS disorders, each associated with a specific lysosomal hydrolase: MPS I (Hurler syndrome, Hurler-Scheie syndrome, Scheie syndrome), MPS II (Hunter syndrome), MPS III (Sanfilippo syndrome with MPS IIIA, IIIB, IIIC, and IIID subtypes), MPS IV (Morquio syndrome with IVA and IVB subtypes), MPS VI (Maroteaux-Lamy syndrome), MPS VII (Sly syndrome), and MPS IX [8].

Mucopolysaccharidosis I (Hurler syndrome, Hurler-Scheie syndrome, Scheie syndrome) is caused by a deficiency in the enzyme α-L-iduronidase. It leads to the accumulation of heparan sulfate and dermatan sulfate in lysosomes. MPS I causes significant physical deformities with prominent gargoyle-like features; it primarily impacts the nervous system, resulting in intellectual impairment. The disease often results in death around the age of 10.

Mucopolysaccharidosis II (Hunter syndrome) results from an enzymatic disorder involving iduronate sulfatase. These abnormalities give rise to pathologies affecting primarily the nervous system.

Mucopolysaccharidosis III (Sanfilippo syndrome) arises due to deficiencies in one of four lysosomal enzymes: heparan-N-sulfatase (MPS IIIA), alpha-N-acetylglucosaminidase (MPS IIIB), acetyl-CoA:alpha-glucosaminide N-acetyltransferase (MPS IIIC), or N-acetylglucosamine-6-sulfatase (MPS IIID). Patients with the condition experience excessive accumulation of heparan sulfate in lysosomes. MPS III affects multiple systems, presenting with a variety of clinical symptoms. It significantly damages the central nervous system, impairs intellectual development, and has a detrimental impact on the immune system.

Mucopolysaccharidosis IV (Morquio syndrome) is marked by disrupted activity of the enzymes N-acetylgalactosamine sulfate sulfatase, which impairs the metabolism of keratan sulfate (in subtype A), and beta-galactosidase, which leads to abnormalities in dermatan sulfate metabolism (in subtype B of the disease) Mucopolysaccharidosis IVA is the most common type; the symptoms of the disease are distinct and severe. In subtype B, the changes are less pronounced, and the disease follows a milder course. Clinical symptoms resulting from the malfunction of these enzymes lead to disorders in the skeletal and joint systems. The joints become flaccid, and conditions such as thoracic deformity, lumbar hump, and dwarfism develop. Patients exhibit gargoyle-like features, short stature, heart valve defects, impaired intellectual development, and changes in the organ of vision. Bone and muscle changes in the chest can potentially cause airway obstruction, while complications affecting the spinal cord elevate mortality during the second and third decades of life [9].

Mucopolysaccharidosis VII (Sly syndrome) is caused by a deficiency of beta-glucuronidase. It leads to a buildup of chondroitin sulfate, dermatan sulfate, and heparan sulfate in body tissues. Occurring in 1 : 1,000,000 live births, Sly syndrome is classified as an ultra-rare disease. The condition has

a wide range of multi-organ clinical manifestations, including skeletal abnormalities, short stature, coarse facial features, heart defects, and hernias. Newborns with severe disease may exhibit abnormalities due to the accumulation of bodily fluids in different tissues, resulting in hydrops fetalis. Neurological changes are also present, including those affecting the sensory organs. Moderate intellectual disability does not progress as the child grows [1, 8].

Mucopolysaccharidosis IX (Natowicz syndrome) is a condition caused by a deficiency in the enzyme hyaluronidase, which is needed to break down hyaluronate (hyaluronic acid). Presumed causative mutations have been identified in the *HYAL1* gene, which encodes one of the three hyaluronidases. Mucopolysaccharidosis IX is an extremely rare type of MPS. Since the first diagnosis in 1966, only a handful of cases have been documented. Symptoms may include short stature, soft tissue hyperplasia, cysts, cleft palate, and recurrent middle ear infections [1]. There are no reports of ophthalmic lesions in the available literature.

Changes in the organ of vision have been noted across all types of mucopolysaccharidosis (excluding MPS IX), though with varying degrees of severity. Ocular disorders stem from the buildup of unmetabolized glycosaminoglycans in different components of the visual system, from the protective apparatus of the eye to the retina and optic nerve, leading to damage. Typically, abnormalities manifest very early, thus facilitating the diagnosis of the disease [7, 9-20]. More than 80% of the information received from the outside world is processed by the visual pathway, significantly influencing various aspects of child development. Damage to the organ of vision caused by lysosomal disorders adversely affects the child's psychophysical state, emotions, cognition of the environment, and social interactions [8]. Parents and guardians of children with MPS, who are in daily contact with their child, might notice impaired vision, changes in the position of the eyes, and "heavy" drooping eyelids slightly earlier than doctors. Such observations are likely based on knowledge of the family history of the disease [13].

Conducting an ophthalmological examination on children with MPS can be challenging due to the difficulty in establishing contact and lack of patient cooperation. Medical professionals need to possess a great deal of empathy, attention, and patience. In the majority of children, visual impairment that is evident to those around them is caused by refractive errors. Refractive abnormalities arise from the shortening of the anterior-posterior axis of the eye due to the deposition of glycosaminoglycans in the ocular layers or as a result of abnormalities associated with increased stiffness of the cornea and sclera arising from the same causes, flattening of the cornea and changes in the radius of its curvature [10, 13, 14, 20]. In a study by Lin *et al.*, reduced visual acuity was observed in the majority of the 50 patients studied (100 eyes) [4]. In 34% of the group of 44 individuals who could have their visual acuity tested, it was less than 0.5 in the better seeing eye. The issue affected 71% of patients with MPS VI, 38% with MPS IV, 29% with MPS I, and 14% with MPS II. The predominant refractive error among MPS patients was hyperopia, detected in 69% of the subjects studied, while myopia was observed in 11% of patients. The refraction threshold for the diagnosis of hyperopia or myopia was equal to or greater than 0.5 diopters. Astigmatism affected 69% of the subjects and was diagnosed when the difference in refraction between the assessed perpendicular meridians equaled or exceeded 1.5 diopters. Amblyopia was noted in 22% of patients, including 71% of cases with MPS VI, 28% with MPS I, 15% with MPS IV, and 6% with MPS II. Villas-Bôas *et al.*, in their study involving 29 patients with MPS, found comparable deficiencies in visual acuity [13]. Refractive error was diagnosed in 26 patients, including hyperopia in 79.3%, astigmatism in 51.7%, and myopia in 10.3% of the study's participants. The data suggest that refractive errors play a significant role in inducing disturbances in visual acuity, particularly in patients with mucopolysaccharidosis I and IV. Both Lin *et al.* and Villas-Bôas *et al.* observed that hyperopia, including hidden hyperopia, in children with MPS does not decrease as the eye grows with age, as typically seen in healthy children, but instead remains elevated [4, 13]. In MPS children aged 3.5 years, the mean refraction was +6.07 D, and from the age of 6 years, it continued to show higher than expected averages. Best-corrected visual acuity was achieved in 60% of affected children, with a mean value of 0.45 logMAR. In cases of MPS, shallowing of the orbits has been observed, attributed to excessive accumulation of glycosaminoglycans in the connective tissue of the orbits, leading to forward protrusion of the eyes. Villas-Bôas *et al.* propose to refer to these changes as exorbitism because, as they state, the ocular protrusion is essentially due to the shallow conformation of the orbits rather than an increase in volume in the intraconal space [13]. Corneal protrusion in forward-positioned eyes impedes proper moisturization, promotes dry eye symptoms, and can lead to epithelial defects or corneal ulceration. Misalignment of the eyes, with a deviation from the straight-ahead axis, arises from the accumulation of unmetabolized glycosaminoglycans in the oculomotor muscles. Among the 29 patients with MPS, 17.2% exhibited strabismus. In the group of strabismic children, 60% had exotropia, while 40% had esotropia [13]. Extraocular accumulation of glycosaminoglycans can reduce ocular motility, lead to strabismus, and be implicated in amblyopia [6]. Esotropia may occasionally occur due to increased intracranial pressure associated with hydrocephalus in MPS [20]. The same etiological factor induces pseudoptosis due to a mechanical increase in the weight of the eyelids caused by the accumulation of undegraded metabolic products in the eyelid connective tissue. The condition is usually bilateral, with varying degrees of severity, and may adversely affect the development of vision in children with MPS by narrowing the palpebral fissure. One of the early inherent symptoms of MPS I, MPS IVA, MPS VI, and MPS VII is corneal opacity. It may occur from an early age in MPS I and VI [10, 12, 19]. However, these changes are absent in patients with MPS IIIA and B. The deposition of glycosaminoglycans (primarily dermatan sulfate and keratin sulfate) in various layers of the cornea, substantia propria,

keratocytes, and epithelium, leads to damage to collagen fibers and the appearance of vacuoles in keratocytes. As a result, the cornea thickens and loses its transparency and optical properties [16]. Children with MPS exhibit differences in corneal structure including altered distances between collagen fibers and their abnormal packing, as well as larger fiber diameters, compared to a reference group of healthy children [6]. Corneal opacity varies both in degree and extent. When located in the limbal area of the cornea, in the region of the anterior chamber angle, it may impede the outflow of ventricular fluid from the eye, increase intraocular pressure, and promote the development of glaucoma. A rare abnormality of the iris observed in patients with MPS VII is coloboma, i.e. defects in iris tissue [20]. Loss of lens transparency is not common. Lenticular opacity is diffuse, affecting both the cortex and the periphery of the lens. It has been diagnosed primarily in MPS IV and MPS III [9, 14]. Glaucoma develops due to structural and functional irregularities in the trabecular meshwork, cornea, sclera, and ciliary body, attributed to abnormal accumulation of GAGs in cell lysosomes [18]. Open-angle glaucoma may arise due to the buildup of GAG deposits in the trabecular meshwork, leading to a blockage in the outflow of the ventricular fluid from the eye. Closed-angle glaucoma can develop due to similar morphological changes in the anterior segment of the eye. The formation of intracellular cysts in different regions of the ciliary body and iris plays a role in the development of closed-angle glaucoma. Glaucoma has been documented in individuals with MPS I, IV, and VI, with approximately 10% of MPS I patients affected. However, it has not been observed in individuals with MPS VII and IX, and its occurrence in children with MPS III is infrequent. Accumulation of GAGs in the optic nerve and retina leads to optic disc edema and secondary optic nerve atrophy. These changes may also stem from elevated intracranial pressure, develop as a result of nerve compression by sclera and dura mater engorged with unmetabolized GAGs, or emerge due to intracellular deposition of GAGs in the ganglion cells of the optic nerve [10]. The buildup of GAGs in the retinal pigment epithelial cells and in the photoreceptor matrix leads to a progressive loss of photoreceptors [20]. Retinitis pigmentosa may develop, and individual pigment clusters may form due to the accumulation of unmetabolized glycosaminoglycans. In rare cases, retinal folds occur, typically on the periphery of the retina. Clinically, retinal degeneration manifests as photophobia or nyctalopia. The asymptomatic onset of retinal changes is attributed to a reduction or loss of corneal transparency caused by GAG deposits, which leads to difficulties in evaluating the posterior segment of the eye [20]. Damage to the optic nerve and retinopathy have detrimental effects on the development of vision in children with MPS.

Alongside history taking, the diagnostic examination should focus on the child's clinical condition, including symptoms involving the organ of vision. The diagnosis of MPS is complicated by the similarity of symptoms to other childhood diseases. According to Wiśniewska *et al*. [3], MPS requires differential diagnosis from other diseases including idiopathic juvenile arthritis, Perthes' disease, muscular dystrophy, rickets, autism spectrum disorders, motor hyperactivity, and intellectual disability. Laboratory diagnostic tests are of primary importance in diagnosing MPS. The initial step in the laboratory diagnostic work-up is urinalysis; elevated levels of GAGs are indicative of MPS. Another important diagnostic test involves measuring enzyme activity in both the blood and skin. Enzyme levels are significantly lower in affected children, with test results indicating which enzyme is responsible for the lysosomal disease. The gold standard in MPS diagnosis is the measurement of enzymatic activity in leukocytes and fibroblast culture. Where indicated, genetic testing is performed to check the carrier status, and prenatal tests are done at weeks 14 to 16 of fetal development.

Ophthalmic diagnostic work-up evaluates several aspects including visual acuity, refractive status, ocular position and motility, presence of strabismus, examination of the anterior and posterior segments of the eye, measurement of intraocular pressure, and, if feasible, assessment of the visual field. Most diagnostic tests are typically conducted under general anesthesia, overseen by an anesthesiologist, because of the child's poor psychophysical condition and lack of cooperation. Additional examinations including diagnostic imaging, electrophysiological evaluations, pachymetry and electroretinography are also employed to complement the ophthalmic diagnostic work-up. A-scan ultrasonography, ultrasonic biomicroscopy (UBM), and optical coherence tomography (OCT) are among other potential diagnostic modalities. OCT examination allows assessment of the thickness of the corneal layers and central retina, as well as the photoreceptor layers and optic nerve. Measuring intraocular pressure and diagnosing glaucoma in children with MPS can be challenging and ambiguous, and often necessitates multiple measurements for clarity. In children with MPS presenting corneal lesions it is very helpful to assess the central corneal thickness, which allows for appropriate correction of intraocular pressure. Ashworth et al. assessed glaucoma test results in 14 patients (27 eyes) of a total of 294 patients diagnosed with MPS [19]. The mean age of the children at diagnosis was 8 years. Central retinal thickness was assessed in 26% of the subjects, and the iridocorneal angle in 15%. Optic disc images were obtained in 67% of children with glaucoma, and the visual field was determined in 19%. Diagnostic difficulties were largely due to an increased thickness of the opacified cornea. Pachymetric examination results are essential for accurately determining intraocular pressure values, contributing to the diagnosis of glaucoma in patients with MPS.

Ocular changes caused by the deposition of unmetabolized glycosaminoglycans have a devastating effect not only on this sensory organ but also on the overall well-being of the child. Hence, ophthalmological assessment stands as a crucial component of the diagnostic process, essential for systematic monitoring of the child with MPS and ensuring specialized medical oversight of their condition.

There is no causal (genetic) treatment for MPS. The therapeutic approaches used are focused on alleviating the symptoms of the disease, enhancing the quality of life for children with MPS, and extending their life span. Essentially, the treat-

ment is systematic. In certain types of mucopolysaccharidosis, bone marrow transplantation (BMT) is considered as a treatment option. However, in addition to being a high-risk procedure, BMT is not successful in MPS III and IV. Another therapeutic approach is enzyme replacement therapy (ERT), which involves direct intravenous administration of a purified enzyme breaking down mucopolysaccharides accumulating in the body. Administration of enzymes is necessary in MPS patients throughout their lives, with the dosage adjusted according to the child's weight. According to Prusek *et al.*, substances used in medical practice for enzyme replacement therapy include laronidase for treating MPS I to substitute the enzyme α-L-iduronidase; galsulfase for MPS VI to address the deficiency of arylsulfatase B; and idursulfase for MPS II to compensate for the missing enzyme L-iduronate sulfatase [21]. It is important to note that the treatment comes with a significant financial burden.

Considering the genetic nature of the disease, ophthalmological interventions may not always meet the expectations of affected children and their parents, let alone the doctors involved. Nevertheless, an ophthalmologist may be the first healthcare provider suspecting a metabolic disease and contributing to the accurate diagnosis of mucopolysaccharidosis. Ophthalmic assistance encompasses both conservative and surgical approaches, depending on the specific ocular changes. Corrective and photochromic spectacles are advised to manage refractive errors and alleviate symptoms of photophobia, respectively. Patients with corneal opacity may undergo corneal transplantation. Before determining eligibility for surgery, it is essential to consider individual contraindications related to the type of MPS and the risk of graft opacification in the future [22, 23]. The treatment of glaucoma involves both conservative modalities and surgical interventions. Photographic documentation is beneficial, serving two key purposes: evaluation of the present condition of the organ of vision and assessment of the dynamic evolution of ocular changes over time.

In conclusion, both the diagnosis and specialized care of a child with MPS, with particular emphasis on the role of an ophthalmologist, as well as treatment modalities should consider the chronic nature of the disease and the current absence of opportunities for underlying causal treatment, i.e. gene therapy.

DISCLOSURES

The authors declare no conflict of interest.
This research received no external funding.
Approval of the Bioethics Committee was not required.

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