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Lysosomal storage diseases as a complex pathophysiological and clinical problem - part one

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Abstract

Lysosomal storage diseases (LSDs) are a group of rare genetic diseases that are characterized by the accumulation of undecomposed molecules in lysosomes due to deficits in specific enzymes. One of the most common subtypes of LSDs is mucopolysaccharidoses (MPS), in which there is an accumulation of glycosaminoglycans (GAGs) in cells. These molecules have important functions in mammalian organisms, including being the building

blocks of connective tissue and participating in numerous cellular processes. Their accumulation causes numerous clinical manifestations, particularly evident in the nervous, skeletal or cardiovascular systems. The following article discusses the pathophysiology and clinical picture of MPS. Emphasis is placed on the heterogeneity of clinical manifestations, which can vary depending on the subtype of the disease, significantly complicating the diagnostic process. In turn, early diagnosis is crucial for the implementation of treatment, which can significantly improve the quality and length of life of patients.

Keywords: lysosomal storage diseases, mucopolysaccharidoses, glycosaminoglycans, pathophysiology, symptoms

1. Introduction

Lysosomal storage diseases (LSDs), are a group of diseases with a genetic basis, whose common feature is the accumulation of undegraded molecules in lysosomes as a result of impaired function of particular enzymes [1]. These molecules can be either undegraded glycosaminoglycans (GAGs) in mucopolysaccharidoses (MPS), glycoproteins in oligosaccharidoses, sphingolipids in sphingolipidoses or glycogen in Pompe disease [1]. Since it is impossible to describe all of these entities in a single article, this paper will focus mainly on the former group of diseases.

MPS are a group of genetically determined storage diseases whose main pathomechanism is the accumulation of GAGs within cells [2, 3, 4]. GAGs are linear, negatively-charged sulfate-rich polysaccharides composed of repeating disaccharides such as heparan sulfate (HS), dermatan sulfate (DS), chondroitin sulfate (CS), keratan sulfate (KS) and hyaluronan sulfate (HA) [2, 4]. They are one of the main building blocks of connective tissue that perform a variety of functions in mammalian bodies [2]. They are included in bones, cartilage, tendons, skin, valves of the heart, eyes, brain, etc. [4]. Enzymes such as lysosomal hydrolases, exoglycosidases, sulfatases are responsible for their breakdown [2]. The aforementioned enzymes function in a specific order, which means that the absence or impaired function of

one of them blocks further decomposition of GAGs [2]. This leads to an accumulation of undegraded molecules [2]. Depending on which enzyme function is impaired, there is a specific disease subtype and clinical manifestations [5]. There are many types classified as MPS: MPS I (there are three subtypes: Hurler syndrome, Hurler-Scheie syndrome and Scheie syndrome), MPS II (Hunter syndrome), MPS IIIA, IIIB, IIIC, IIID (Sanfilippo syndrome IIIA, IIIB, IIIC, IIID), MPS IVA, IVB (Morquio syndrome IVA, IVB), MPS VI (Maroteaux-Lamy syndrome), MPS VII (Sly syndrome), MPS IX (Natowicz syndrome) and MPS X [4]. In addition, there is MPS-plus syndrome - this nomenclature is due to the presence of symptoms that do not appear in classic MPS - e.g.: renal and hematopoietic impairment, congenital heart defects, etc. [4]. Impaired function of a particular enzyme is genetically determined and can be caused by a range of different mutations, most commonly of the missense type [5]. MPS are inherited autosomal recessively, with the exception of MPS II, which is inherited in conjunction with the X chromosome [5].

Individuals with MPS present with a wide range of symptoms, which brings them to specialists in various fields before obtaining a proper diagnosis. In this article, we will focus on the pathophysiology of the disease and list symptoms that should arouse the vigilance of physicians and put the diagnosis on the right track.

2. Methods

A literature analysis was performed using the PubMed database. Only publications from the last 10 years were included. The keywords used were lysosomal storage diseases or mucopolysaccharidoses searched alone or in combination with pathophysiology. Articles classified as review, systemic review, randomized controlled trial and meta-analysis were analyzed. Only publications in English were used.

3. Pathophysiology of MPS

In the past, it was thought that the symptoms of MPS diseases were only due to GAG deposition in cell lysosomes [6]. It has now been proven that this is a much more complex process [6]. The change in approach to MPS is also due to discoveries about lysosomes themselves [6]. It has been repeatedly demonstrated that their function is not limited to the breakdown of macromolecules such as mucopolysaccharides, oligosaccharides, lipids, glycolipids, sphingolipids [6, 7]. They are also involved in many processes essential for cell survival such as transport of vesicles, cell membrane fragments, control of autophagy, cell cycle, and regulation of metabolic processes by affecting signaling pathways [6, 8, 9]. They enable the maintenance of homeostasis [10]. Similarly, the role of GAGs is not limited to their

structural function [8]. As a major component of the extracellular matrix, they are involved in such processes as cell adhesion, signal transduction, intracellular transport, activation of inflammatory pathways and organization of collagen and elastin fibers [8, 10, 11].

Inflammatory processes are one of the mechanisms induced by GAG accumulation [12]. The presence of partially undecomposed GAGs causes immune cells to migrate and induces an innate immune response [11, 13]. There is an increase in cytokine levels, some of which vary depending on the type of MPS [12]. Impaired mitochondrial function during the course of the disease also contributes to increased inflammatory processes [13]. In nucleated organisms, mitochondria are the most important producer of energy; in addition, they are involved in such processes as apoptosis, calcium homeostasis, viral response, and generation of oxygen free radicals [14]. Levels of the latter are increased in the serum of MPS patients [14]. In contrast, levels of antioxidant substances, such as glutathione, are noticeably lower [14].

Inflammation is particularly prominent in the nervous system and joints [13]. Intracellular deposition of eg: HS in the brain leads to massive activation of microglia and astrocytes, which in turn induces cytokine production and an oxidative stress cascade [9, 12, 13]. In addition, as a result of impaired lysosome function, there is a secondary accumulation of substances such as sphingomyelins, ceramide, gangliosides, cholesterol, α-synuclein, amyloid beta, hyperphosphorylated tau [9, 13]. The role of the latter in the development of neurodegenerative processes is well known [9]. Another process that increases the concentration of amyloid-β, tau protein and α-synuclein is the impairment of autophagy in MPS [9, 10]. By not breaking down GAGs, they accumulate not only in lysosomes, but also in the Golgi apparatus, endoplasmic reticulum and other organelles - this can induce autophagy processes, which further stresses the cell and may result in subsequent apoptosis [10]. In addition, accumulation of toxins resulting from the disruption of synthesis of other compounds caused by GAG accumulation can lead to cell death [15].

Chronic inflammation in MPS is assumed to be similar to that in rheumatoid arthritis (RA) [16]. This is due to the structural similarity of GAG to lipopolysaccharide (LPS), which stimulates Toll-like receptor 4 (TLR4), resulting in the release of tumor necrosis factor (TNFα), interleukin 1β, metalloproteinases and pro-apoptotic factors [11, 16]. This phenomenon is considered the main mechanism of bone damage in MPS [16]. It also occurs within other systems involved in the course of the disease such as the nervous and circulatory systems [11]. Due to the accumulation of macromolecules, endoplasmic reticulum is also stressed, resulting in impaired chondrocyte differentiation [15]. In turn, impaired function of

lysosomes and damage to their membrane, together with oxidative stress, lead to activation of inflamasomes and release of cysteine proteases, which intensifies inflammatory processes [11, 13]. In addition, GAGs stimulate the proliferation of monoclonal B cells, T cells and macrophages [16].

GAG accumulation in cells also interferes with processes necessary for normal cell function, including impairing the function of cathepsins [17]. This is a group of proteolytic enzymes involved in processes such as protein production, coagulation, digestion, immune mechanisms, etc [17]. Under normal conditions, interaction with GAGs allows cathepsins to autoactivate [17]. They are produced as inactive proenzymes, and contact with GAGs induces changes in their conformation, which increases their affinity for the substrate and also protects them from degradation in an alkaline environment, as these proteins need a mildly acidic environment to function [17]. In MPS, this interaction is impaired [17]. In addition, it has been proven that in the course of MPS III there is an abnormal structure of cell membranes, resulting in impaired trans-membrane transport, neurotransmitter release and recycling of synaptic vesicles [9]. Cellular signaling pathways are also disrupted in the course of MPS [2]. This may be due, among other things, to the hindrance of the interaction of normal GAGs with receptors by unspliced molecules [2]. Their non-physiological activation translates into clinical symptoms such as pain, skeletal, nervous system and cardiac damage [2]. It is also noteworthy that the accumulation of undecomposed GAG molecules results in a deficit of normal molecules, thus interfering with all the previously mentioned functions performed by GAGs [11].

4. Clinical features of MPS

MPS often present a heterogeneous picture [18, 19]. They can lead to lesions in multiple systems at different ages, which significantly complicates diagnosis [18, 20]. Symptoms can present varying degrees of severity, from mild to moderate to severe [19]. Patients usually present no symptoms at birth, which develop gradually over the first few years of life [21]. Patients are generally diagnosed by specialists in various fields for diseases that give similar symptoms and are more common than MPS.

Symptoms already apparent at the first contact with the patient are dysmorphic facial features, abnormal body structure and skin lesions, most of which are nonspecific [19]. The following may be present: coarse facial features, protruding or depressed frontal bone, broad saddle nose, flat nasal bridge, wide nasal alae, enlarged mouth, angled and hypoplastic mandible, among others [19, 22]. Hair abnormalities - hypertrichosis, hirsutism, lanugo hair,

thinning of the eyebrows and eyebrow fusion - are also common [19]. Specific to Hurler's syndrome (MPS subtype I) are reticularly arranged ivory-colored nodules and papules usually located in the interlobular region, but may also occur in the neck, chest, upper and lower extremities [19]. In addition, extensive dermal melanocitosis and thickening of the skin of the palms may be present in Hunter syndrome (MPS II) and less commonly in Hurler syndrome. In contrast, telangiectasias are characteristic of Morquio syndrome (MPS IV) [19].

Nasal, ear and pharyngeal involvement occur in up to 90% of patients with MPS [22]. Characteristic symptoms include hypertrophy of the tongue, tonsils, gums, and tooth deformity [22]. In addition, patients with MPS often have obstruction of the upper and lower airways, which includes factors such as an irregular nasal septum, high epiglottal detachment, mandibular hypoplasia, ankylosis of the temporomandibular joint, abnormal cervical and thoracic spine, narrow and tortuous trachea, and ubiquitous mucopolysaccharide infiltration [22]. The clinical manifestation of the above-mentioned abnormalities can be dyspnea, cough, cyanosis, sleep apnea, difficulty taking food, frequent upper and lower respiratory tract infections [22]. Moreover, due to the small volume of the thorax and organomegaly, diaphragm function is impaired [22]. In turn, ear involvement results in more frequent ear infections and deterioration or loss of hearing [22].

The frequently involved organ in most types of MPS is the eye [20]. Refractive defects such as hypermetropia and astigmatism, corneal opacity, dry eye syndrome, both open- and closed-angle glaucoma, and retinopathy may be present [20]. The most common and significant ocular complaints in patients with individual MPS are: MPS I - corneal clouding, MPS II - hypertelorism and exophthalmos, MPS III - retinopathy, MPS IV - corneal clouding and refractive errors, MPS VI - corneal opacity with corneal thickening, optic nerve abnormalities, MPS VII - corneal opacification [20].

Another system whose involvement has a significant impact on patients' life expectancy is the cardiovascular system [23]. GAGs are deposited in the valves, myocardium and coronary vessels, impairing their function [23, 24]. The most severe cardiac manifestations occur in patients with MPS I, II and VI [23, 24]. In this group of patients, aortic and mitral valve regurgitation is common [24]. In addition, patients present with increased aortic stiffness, which is particularly seen in patients with Scheie syndrome (a subtype of MPS I) [24]. The cardiac conduction system is also involved, which can cause arrhythmias [24].

The central nervous system is mainly involved in patients with MPS I, II, III and VII [25]. Typically, patients initially develop normal or delayed development, followed by stunted growth and a plateau phase, until eventually regression of previously acquired skills occurs

[25]. The timing of the plateau phase varies depending on the type of MPS and the individual patient's disease course [25]. In MPS I, it usually occurs around age 2-4, in MPS II - 4-4.5 years of age, MPS III - 3 years of age [25]. In addition, patients with MPS II often present with deterioration of motor function, sensorineural deafness, epilepsy and sleep disturbances [25]. Behavioral disorders are characteristic of MPS II and III [25]. MPS VII is characterized by a wide variety of neurological symptoms, which may include intellectual disability, speech delay, deafness, hydrocephalus, and spinal cord compression [25].

One of the most commonly affected systems is the musculoskeletal system, which is why patients often end up first seeing a rheumatologist or orthopedist [8, 18]. In the course of MPS, GAGs are deposited in the joints impairing their function. Joint dysplasia, pain and stiffness occur [21, 26]. The exception is MPS IV, in which there is excessive limpness instead of stiffness [26]. The joints are usually involved symmetrically, which may suggest a diagnosis of juvenile idiopathic arthritis [8]. Unlike inflammatory joint diseases, however, local and systemic signs of inflammation, such as increased warmth, swelling, elevated ESR and CRP, are not present in MPS [8]. In MPD, there is also thickening of the skeleton near the joints which may mimic swelling and suggest arthritis [8]. Contractures in the small joints of the hands are also a characteristic feature, which can cause claw-like hand positioning [8]. The ankle joints and Achilles tendon may also be involved - the result is walking on tiptoe [8]. Other symptoms caused by GAG deposition in tendon sheaths include carpal tunnel syndrome and trigger digits [8, 27]. These disorders are rare in the pediatric population, so they should always prompt further diagnosis [27]. The disease can also involve major joints - knee valgus and hip dysplasia are common in the patient population [8, 27]. Among spinal abnormalities, the most common is excessive thoracic kyphosis caused by wedge-shaped deformation of the vertebrae in this segment and odontoid hypoplasia, which can lead to spinal instability, resulting in spinal cord compression and quadriplegia [8, 27]. A disorder that can accompany excessive kyphosis is scoliosis [27].

Table. 1. Classification of MPS [5, 14, 28, 29]

Type	Eponym	Gene involved	Enzyme deficiency	Accumulated GAG	Main clinical symptoms
MPS I	Hurler (severe phenotype)	IDUA (4p16.3)	α-l-iduronidase	DS and HS	Multiple dysostosis, organomegaly, CNS impairment [14], cardiac valve regurgitation and stenosis [24], ivory to white papules and nodules, extensive dermal melanocitosis, skin thickering over the hands [19], corneal clouding, glaucoma, retinopathy, optic neuropathy [20], Fetal hydrops [29]
	Scheie (mild phenotype)	IDUA (4p16.3)		DS and HS	Joint stiffness, normal CNS [14], cardiac valve regurgitation and stenosis, aortic stiffness [24], corneal clouding, glaucoma, retinopathy, optic neuropathy [20]
	Hurler-Scheie (intermediate phenotype)	IDUA (4p16.3)		DS and HS	Cardiac valve regurgitation and stenosis [24], corneal clouding, glaucoma, retinopathy, optic neuropathy [20]
MPS II	Hunter	IDS (Xq28)	Iduronate-2-sulfatase	DS and HS	Multiple dysostoses, organomegaly [14], cardiac valve regurgitation and stenosis [24], extensive dermal melanocitosis, skin thickering over the hands [19], behavioral issues, sleep disturbances [25], hypertelorism, exophthalmos, glaucoma, retinopathy, optic neuropathy [20]
MPS IIIA	Sanfilippo A	SGSH (17q25.3)	Heparan N-sulfatase (sulfamida	HS	Retinopathy [20], behavioral issues, sleep disturbances [25], hyperactivity, mild somatic manifestations [2]

			se)		
MPS IIIB	Sanfilippo B	NAGLU (17q21)	α-N-acetylglucosaminidase	HS	
MPS IIIC	Sanfilippo C	HGSNAT (8p11.1)	Acetyl CoA: α-glucosamine N-acetyl transferase	HS	
MPS IIID	Sanfilippo D	GNS (12p14)	N-acetylglucosamine-sulfate-6-sulfatase	HS	
MPS IVA	Morquio A	GALNS (16q24.3)	N-acetylgalactosamine-6-sulfate sulfatase	KS and CS	Short stature, skeletal dysplasia [14], joint laxity [29], teleangiectasias [19], corneal clouding, astigmatism, myopia, hyperopia, pseudoexophthalmos [20], Fetal hydrops [29]
MPS IVB	Morquio B	GLBI (3p21.33)	β-galactosidase	KS	Short stature, skeletal dysplasia [14], corneal clouding, astigmatism, myopia, hyperopia, pseudoexophthalmos [20]
MPS VI	Maroteaux-Lamy	ARSB (5q11-q13)	N-acetylgalactosamine-4-sulfatase (arylsulfatase B)	DS	Multiple dysostoses [14], cardiac valve regurgitation and stenosis [24], corneal opacity with corneal thickening, optic nerve abnormalities, papilledema, strabismus and amblyopia [20]
MPS VII	Sly	GUSB (7q21.11)	β-glucuronidase	HS, DS, and CS	Multiple dysostoses, hepatosplenomegaly [14], developmental delay, speech delay, intellectual disability [25] corneal

					opacification [20], fetal hydrops [29]
MPS IX	Natowicz	HYALI (3p21.3-p21.2)	Hyaluronidase	HA	Short stature, soft-tissue masses [14], joint stiffness [29]
MPS X	-	VPS33A	Arylsulfatase K	DS	Short stature, coarse facial features, dysostosis multiplex, cardiac and ophthalmological abnormalities [14], proteinuria, cytopenia [29]

DS - Dermatan sulfate; HS - Heparan sulfate; KS - Keratan sulfate; CS - Chondroitin sulfate; HA - Hyaluronic acid, CNS – Central Nervous System

5. Summary

Lysosomal storage diseases encompass a wide range of diseases that cannot be discussed in a single article. One of the more well-known subgroups is MPS. The primary pathophysiological process in MPS involves blocking the action of enzymes specific to particular subtypes of the disease as a result of genetic mutations. This translates into an accumulation of GAGs and secondary processes such as increased inflammation, oxidative stress, disruption of signaling pathways and the functioning of cellular organelles e.g.: mitochondria and cell membranes. The result is damage observed in many organs and systems, such as the nervous system, musculoskeletal system, heart, eyes, etc. As a group of diseases with a heterogeneous clinical picture, MPS requires special attention and the cooperation of specialists in various fields. Due to its genetic basis, it is not possible to cure it. Nonetheless, a prompt correct diagnosis is extremely important, as there are a number of modern therapies that prolong the lives of patients. For this to be possible, however, it is important to educate physicians of all specialties in order to increase their attentiveness to unusual symptoms occurring in patients.

Author's Contribution

Conceptualization, methodology, software, check, formal analysis, investigation, resources, data curation, writing - rough preparation, writing - review and editing, visualization, supervision, project administration: Karolina Mikołajczak.

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