LYSOSOMAL STORAGE DISEASES AND CARDIOVASCULAR SYSTEM (REVIEW ARTICLE)

ЛІЗОСОМАЛЬНІ ЗАХВОРЮВАННЯ ТА СЕРЦЕВО-СУДИННА СИСТЕМА (ОГЛЯД ЛІТЕРАТУРИ)

Сергій Пивовар (Sergiy Pyvovar), доктор медичних наук, доцент, ВПНЗ «Львівський мединий університет», Україна (Lviv medical University, Lviv, Ukraine)
Юрій Рудик (Iurii Rudyk), доктор медичних наук, професор, Національний інститут терапії імені Л.Т. Малої Національної академії медичних наук України, Україна (L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine, Ukraine)
***Corresponding author: Sergiy Pyvovar**

Abstract. The analysis of literature data reflecting the issues of the pathology of the cardiovascular system in mucopolysaccharidosis are presented. It was found out that heart and vessels damage is one of the cardinal signs of this pathology, often leading to death. Cardiac pathology is recorded in all types of mucopolysaccharidosis, but it is most significant for patients with three clinical variants of Hurler syndrome, Hunter, and Maroteaux–Lamy syndromes. Typical signs of damage to the cardiovascular system in mucopolysaccharidosis are thickening of the valves with the development of their dysfunction (while the severity of damage to the left-sided valves is more pronounced), myocardial hypertrophy, conduction disturbance, coronary artery disease, arterial hypertension. Many researchers emphasize the difficulties of clinical and functional examination of the cardiovascular system in patients with mucopolysaccharidosis, which is due to the presence of physical and intellectual limitations in patients, ands a gradual increase in symptoms. For the treatment of cardiovascular pathology at mucopolysaccharidosis, medical and surgical methods are used, including enzyme replacement therapy and stem cell transplantation.
Keywords: lysosomal storage disease, mucopolysaccharidosis, cardiovascular system, diagnostics, treatment.

Анотація. Проведено аналіз даних літератури, які відображають питання патології серцево-судинної системи при мукополісахаридозах. Встановлено, що ураження серця та судин є однією з основних ознак цієї патології, яка часто призводить до смерті. Враження серцево-судинної системи реєструється при всіх видах мукополісахаридозах, але найбільш значущою вона є у хворих із трьома клінічними варіантами синдромів Герлера, Хантера та Маро-Лемі. Характерними ознаками ураження серцево-судинної системи при мукополісахаридозах є потовщення клапанів з розвитком їх дисфункції (вираженість ураження мітрального та аортального клапанів є більшою), гіпертрофія міокарда, порушення провідності, ІХС, артеріальна гіпертензія. Багато дослідників наголошують на труднощах клініко-функціонального дослідження серцево-судинної системи у хворих мукополісахаридозами, що зумовлено наявністю фізичних та інтелектуальних обмежень у них, поступовим наростанням симптомів. Для лікування серцево-судинної патології при мукополісахаридозах використовуються медикаментозні та хірургічні методи, включаючи замісну ферментну терапію та трансплантацію стовбурових клітин.
Ключові слова: лізосомальна хвороба накопичення, мукополісахаридози, серцево-судинна система, діагностика, лікування.

Introduction. Chronic heart failure (CHF) is an urgent problem of modern medicine due to the widespread, progressive course and adverse outcome [1]. The most common causes of CHF in the European population are ischemic heart disease, arterial hypertension, myocarditis, arrhythmias, dilated and hypertrophic cardiomyopathy [1]. Meanwhile, there is a large group of hereditary metabolic disorders, in which the clinical manifestation of heart disease occurs at the age of 30-40. Hereditary metabolic disorders are the most complex and large group of diseases,

errors in the diagnosis of which are often take place in pediatric practice, and especially in adult patients. Hereditary metabolic disorders include about 800 diseases [2]. Their incidence, according to mass screening, is estimated as 1:500 - 1:1000 births [2]. These inherited conditions are also referred to as storage diseases [2].

Mucopolysaccharidosis (MPS) is one of the most common nosological forms of storage disease. In this pathology, as a result of a deficiency of lysosomal enzymes, the catabolism of the main substance of the connective tissue - glycosoaminoglycans is disrupted, they accumulate in lysosomes, which leads to gross cellular changes and the formation of a characteristic clinical picture.

The purpose of the study was to analyze the literature data on damage to the cardiovascular system in patients with mucopolysaccharidosis.

Materials and methods. The narrative review represents an assessment of the most pertinent literary sources published in English language from 1994 to 2024, which dealt with the issues of lysosomal storage diseases and damage cardiovascular system.

The research of the article is a fragment of research works: Lviv Medical Institute on the topic of "Improving the system of circulation of drugs during pharmacotherapy on the basis of evidentiary and forensic pharmacy, organization, technology, biopharmacy and pharmaceutical law" (state registration number 0120U105348, implementation period 2021-2026) and Department of clinical pharmacology and pharmacogenetics non infective diseases of The state institute “National Institute of Therapy n.a. L. Malaya of NAMS of Ukraine” on the topic of "Develop pharmacogenetic methods for prevention of decompensation of heart failure in patients with ischemic heart disease who have survived COVID-19" (state registration number 0122U000391, implementation period 2022-2024).

Results and discussion. According to the literature, the most common clinical types of mucopolysaccharidoses are Hurler and Hunter syndromes (MPS I and II). Hunter syndrome is characterized by recessive inheritance linked to the X chromosome; other types of mucopolysaccharidosis are inherited in an autosomal recessive manner. MPS I include three clinical variants: Hurler, Hurler-Scheie, and Scheie syndromes.

Hurler syndrome is characterized by the highest incidence, early manifestation (in the first months of life), the most severe clinical manifestations, and a shorter life span of the patient [3**Error! Reference source not found.**].

Hurler-Scheie syndrome (MPS IH / S) is characterized by later (on 1-2 years of life) symptoms manifestation, less severe, longer life expectancy and normal or slightly reduced intelligence. Patients are usually adequately socially adapted, successfully study in general education schools, often have hobbies and receive secondary special or higher education (more often humanitarian) [3**Error! Reference source not found.**].

Sheye syndrome (MPS IS) is characterized by an even milder course of the disease, mild manifestations of craniofacial dysmorphism (dysostosis), and normal intelligence. Patients, as a rule, are perfectly integrated into society, can have academic degrees, hold leadership positions, as well as marry and have healthy

offspring [4**Error! Reference source not found.**].

Hunter syndrome is divided into two forms by severity of clinical symptoms: mild and severe. Patients with a severe form of the disease have severe mental retardation and a shorter life expectancy (usually not exceeding 15-16 years). Children with a mild form of the disease are distinguished by normal intelligence, longer life expectancy (up to 50 years or more), can study in a general education program, successfully graduate from higher educational institutions, and work no less successful in their specialty, as well as marry and have healthy offspring [4].

All 4 types of Sanfilippo syndrome are some of the most severe forms of pathology. In the Slavic population, Sanfilippo A syndrome is more common, while cases of MPS IIID were not recorded in all. The disease is distinguished by a gross decrease in intelligence, as a rule, normal indicators of physical development, and less pronounced damage to other vital organs and systems of the body. According to researchers [5], clinically all 4 types of Sanfilippo syndrome are indistinguishable.

Morquio A and B syndromes are characterized by disproportionate dwarfism, rickets-like skeletal changes, and normal intelligence, which contributes to their normal integration into society [5].

Maroteaux–Lamy syndrome is distinguished by dwarf growth with pronounced changes in the musculoskeletal system, pathology of the cardiovascular system, parenchymal organs, eyes, and hearing, as well as normal intelligence. There are two forms of the disease - mild and severe [6].

Damage to the cardiovascular system is one of the cardinal signs of mucopolysaccharidosis. These changes are of a varied nature and are observed in almost all types of the disease. The first cardiological studies in patients with mucopolysaccharidosis were performed about 50 years ago [6, 7]. It was found that the first place in incidence, timing of manifestation and severity of the pathological process of the cardiovascular system is occupied by MPS I, II and VI, while in patients with Sanfilippo and Morquio syndromes, these changes are much less common [8, 9, 10**Error! Reference source not found.**]. Too low prevalence of MPS VII did not allow to determine the frequency of heart damage in Sly syndrome.

Analysis of the causes of death in patients with various types of mucopolysaccharidosis who did not receive pathogenetic therapy showed that death most often occurred as a result of respiratory failure or heart disease [11]. Among the latter, the most significant are heart failure, sudden death from arrhythmia (including complete atrioventricular block) [12] and coronary artery occlusion [12].

Heart damage in mucopolysaccharidosis for a long time is not accompanied by characteristic clinical symptoms and therefore remains undiagnosed. This fact entails a significant decrease in the true percentage of the incidence of heart disease in mucopolysaccharidosis. So, only 6 of 26 patients with MPS and echocardiographic signs of heart damage had clinical manifestations from the cardiovascular system [13]. This gave the researchers reason to emphasize the importance and need for patients to conduct a complete examination of the heart after mucopolysaccharidosis diagnosed [14].

The frequency and severity of heart disease. Very high prevalence and severity of cardiovascular disorders (ranging from 60 to 100%) was revealed in

individuals with various types of mucopolysaccharidosis (mainly MPS I, II, and VI) [3, 8]. The relationship between the damage of heart valves and the disorder of dermatan sulfate catabolism was revealed. This primarily applies to three clinical variants of mucopolysaccharidosis I, as well as Hunter and Maroteaux–Lamy syndromes (MPS II and VI), but does not apply to MPS III and IV at all, since Sanfilippo and Morquio syndromes are characterized by the accumulation of heparan- and keratan sulfates, respectively [9**Error! Reference source not found.**].

In individuals with MPS I clinical variant (Hurler syndrome), heart disease usually develops at an early age and progresses rapidly [14**Error! Reference source not found.**], while in Hurler-Sheye and Sheye syndromes, heart damage manifests itself much later and is characterized by a milder and slower course [16, 17**Error! Reference source not found.**]. Nevertheless, researchers pay attention to the progression of all types of mucopolysaccharidosis and emphasize that this primarily concerns heart damage, the frequency and severity of which increases with the patient's age [8**Error! Reference source not found.**].

Most researchers consider the most characteristic heart pathology in mucopolysaccharidosis to be progressive damage to its valves, which is recorded in 60-90% of patients [8**Error! Reference source not found.**]. Valve thickening with the development of dysfunction is observed in all patients with severe MPS VI [16, 18**Error! Reference source not found.**], in more than 80% of individuals with three clinical variants of MPS I [19**Error! Reference source not found.**] and 57 % of patients with Hunter syndrome (MPS II) [20**Error! Reference source not found.**]. Most studies report that valve regurgitation is more common than stenosis. In this case, the damage of the mitral valve is more common than the aortic one. Left-sided valves (mitral and aortic) are damaged more significantly comparing to right-sided (tricuspid and pulmonary) [19**Error! Reference source not found.**]

Valvular stenosis or insufficiency leads to volume overload of the left atrium and/or ventricle, dilatation, and hypertrophy of the latter, and ultimately to systolic and diastolic dysfunction. Retrospective observation of patients with various types of mucopolysaccharidosis states that left ventricular hypertrophy and diastolic dysfunction are manifested in the early stages of the underlying disease, while ventricular dilatation and systolic dysfunction are characteristic of the later stages of the disease. The results of a pathomorphological examination of the mitral valve leaflets in patients with mucopolysaccharidosis indicate their noticeable diffuse thickening and significant compaction (cartilage-like consistency). Chordae tendineae are shortened, papillary muscles are thickened, which leads to restriction of leaflet mobility [21**Error! Reference source not found.**]. Calcium deposits are usually found in the mitral annulus [22, 23**Error! Reference source not found.**]. A similar picture is observed at the aortic valve: its progressive thickening and dysfunction occurs. These pathological changes cause insufficiency and / or stenosis, which are easily identified by two-dimensional echocardiography and Doppler scanning [24**Error! Reference source not found.**]. Such violations are recorded, as a rule, at a late stage of the disease.

Damage to the coronary arteries. Narrowing of the coronary arteries and / or occlusion have been described in patients with all types of mucopolysaccharidosis

[25**Error! Reference source not found.**], but most often this pathology occurs in the Hurler and Hunter syndromes (MPS I and II).

Diffuse proliferation of the intima of large epicardial coronary arteries, leading to a narrowing of the vessel lumen, is due to glycosaminoglycans accumulation. These changes are most early manifested in patients with the first clinical variant of Hurler syndrome [16**Error! Reference source not found.**]. Coronary arteries occlusion almost always occurs in the central zone. Apical left ventricular aneurysms and occlusions of coronary arterioles are also characteristic of MPS II and VI (Hunter and Maroteaux-Lamy syndromes) [25**Error! Reference source not found.**]**Error! Reference source not found.**.

Other vascular abnormalities. In patients with mucopolysaccharidosis, an increase in the wall thickness of large vessels with a narrowing or expansion of their diameter is found [16**Error! Reference source not found.**]. Diffuse narrowing of the thoracic and abdominal aorta occurs in 30% of individuals with mucopolysaccharidosis I and II. Narrowing of the aortic isthmus may require surgical intervention [26**Error! Reference source not found.**]. Arterial hypertension due to vasoconstriction is common among people with MPS I and II [27**Error! Reference source not found.**] and less common in other types, primarily in Maroteaux-Lamy syndrome [28**Error! Reference source not found.**]. The expansion of the ascending aorta is accompanied by a significant decrease in the elasticity of the vessel with MPS I [29**Error! Reference source not found.**]. This may be due to the effect of glycosaminoglycans on tropoelastin, resulting in a decrease in elastin content [30**Error! Reference source not found.**].

Studies carried out on experimental animals with MPS I and VII have shown that dilatation of the aorta occurs due to elastin degradation under the influence of matrix metalloproteinase-12 and / or cathepsin S [31, 32**Error! Reference source not found.**].

Heart rhythms and conduction abnormality. Conduction abnormalities are most often (44%) recorded in patients with MPS VI and much less frequently (7%) in patients with MPS I [4**Error! Reference source not found.**]. In a number of cases, in probands with MPS II, III and VI, the development of complete atrioventricular block was documented, followed by the need for implantation of a pacemaker [33**Error! Reference source not found.**]. Fibrosis of conduction system of the heart with infiltration with glycosaminoglycans was identified in one patient with MPS VI, who died suddenly [33**Error! Reference source not found.**].

The role of glycosaminoglycans in the genesis of cardiovascular disorders. Most authors believe that glycosaminoglycans accumulation with their increasing infiltration of the tissue of the heart and blood vessels is responsible for the anatomical and functional changes in the valves, coronary arteries, blood vessels, the conduction system and the myocardium [33**Error! Reference source not found.**].

A large number of studies on the analysis of histological and morphological parameters in patients with mucopolysaccharidosis is devoted to MPS I, especially with its first clinical variant – Hurler syndrome. It was found that the characteristic of the disease is an increased content of glycosaminoglycans in the heart and blood vessels, as well as the penetration of "light" and granular cells into the valves of the

heart (leaflets, annulus and chordae tendineae), endocardium, myocardium, coronary arteries, aorta and conduction system [35**Error! Reference source not found.**]. Examination of heart tissue using light microscopy revealed vacuolated cells with increased cytoplasm, which are morphological consequences of the accumulation of glycosaminoglycans [16**Error! Reference source not found.**].

It is known that sulfated glycosaminoglycans: heparan-, dermatan-, chondroitin- and keratan sulfates are normal components of heart valves and major vessels [36**Error! Reference source not found.**, 37**Error! Reference source not found.**]. Studies have showed the effect of impaired catabolism of proteoglycans on the genesis of mitral valve myxomatosis [38**Error! Reference source not found.**], aortic aneurysms [38**Error! Reference source not found.**] and vascular atherosclerosis [38**Error! Reference source not found.**]. It was previously noted that dermatan sulfate is an important component of normal valve tissue [37**Error! Reference source not found.**]. This explains the strong association of MPS I, II and VI with the pathology of the heart valves, characterized by the predominant accumulation of dermatan sulfate [13**Error! Reference source not found.**]. In the heart valves of patients with all types of mucopolysaccharidosis, there are glycosaminoglycan cells, the so-called "clear" cells, "Gargoyle", or "Hurler" cells. These cells have also been identified in mucopolysaccharidosis type I [40, 41**Error! Reference source not found.**].

The mechanisms by which the accumulation of heparan sulfated proteoglycans and the presence of vascular interstitial cells affect the major vessels and coronary arteries in mucopolysaccharidosis types I, II, and III remain unknown. According to one hypothesis, glycosaminoglycans induce inflammation by activating the Toll-like receptor 4, which leads to the degradation of proteases [42**Error! Reference source not found.**].

Diagnosis of mucopolysaccharoidosis is based on the clinical picture, genetic testing and determination of the levels of metabolites in the urine: dermatan sulfate, heparan sulfate, chondroitin 4-sulfate, chondroitin 6-sulfate, keratin sulfate [5**Error! Reference source not found.**].

Diagnosis of the pathology of the cardiovascular system with mucopolysaccharidosis. A complete examination of the patient should include measuring blood pressure in the upper and lower limbs (to exclude coarctation of the aorta), measurement of the pulse rate, palpation of the pulse in all limbs, and careful auscultation of the heart and lungs. Other aspects of cardiac examination, such as evaluation of the jugular veins or hepatosplenomegaly, may not be feasible due to the short neck and enlargement of the patient's internal organs. Multiple dysostosis and joint contractures complicate the measurement of blood pressure. Auscultation of heart sounds is often difficult due to the patient's noisy breathing.

The absence of heart murmurs does not exclude the presence of valvular disease. It is known that valvular stenosis / or regurgitation of mild and moderate degree is often not accompanied by changes in the auscultatory signs [13**Error! Reference source not found.**].

Transthoracic echocardiography provides a reliable measurement of the dimensions of the ventricular chambers (both systolic and diastolic), the thickness of

the interventricular septum and posterior wall, and myocardial mass, which are calculated taking into account the relative surface area of the body.

With the help of echocardiography, the precise parameters of the contractility function of the left ventricle (fractional shortening and ejection fractions) can be determined. Doppler flows of heart valves allow to differentiate stenosis and regurgitation of valves, as well as to assess the state of the right ventricle and pressure in the pulmonary artery [13**Error! Reference source not found.**].

However, despite its advantages, echocardiography provides only limited information about the condition of the coronary arteries. So, in some cases, transthoracic echocardiography is difficult to perform, due to the presence of scoliosis or pulmonary emphysema in the patient. In this situation, **transesophageal echocardiography** is more informative.

Magnetic resonance imaging and computed tomography are highly informative methods for studying the cardiovascular system in adult patients with mucopolysaccharidosis [43**Error! Reference source not found.**]. It should be noted that the picture of coronary arteriopathy in patients with mucopolysaccharidosis is very different from that in ischemic heart disease [44**Error! Reference source not found.**].

Treatment of lesions of the cardiovascular system with mucopolysaccharidosis. Patient treatment depends on the type of mucopolysaccharidosis and includes symptomatic medication and surgery, enzyme replacement therapy, or hematopoietic stem cell transplantation [24**Error! Reference source not found.**]. If symptomatic medical care is focused on drug therapy (including the treatment of heart failure) and cardiac surgery, pathogenetic therapy (hematopoietic stem cell transplantation and enzyme replacement therapy) is aimed at restoring the function of the enzyme, which gradually stops the progression of the disease.

Pathogenetic therapy prolongs life expectancy and improves medical condition. Currently, enzyme replacement therapy drugs have been obtained for the treatment of MPS I (laronidase), MPS II (idursulfase) and MPS VI (galsulfase) [5**Error! Reference source not found.**]. A genetically engineered enzyme replacement drug is undergoing clinical trials for the treatment of patients with MSP-IVA - Morquio A syndrome [5**Error! Reference source not found.**]. The principle of enzyme replacement therapy is based on restoring the level of enzymatic activity sufficient for hydrolysis of accumulated substrates and to prevent their further accumulation. The drugs are administered parenterally [5**Error! Reference source not found.**]. Long-term use of enzyme replacement therapy can improve the systolic function of the ventricles and lead to the disappearance of cardiac hypertrophy in both adults and children with mucopolysaccharidosis types I and II. However, enzyme replacement therapy does not prevent the progression of valve stenosis and regurgitation in MPS I, II and VI [5**Error! Reference source not found.**] According to the publications [24, 44**Error! Reference source not found.Error! Reference source not found.**] it will be more effective to use other stem cells, for example, mesenchymal or neuronal, as well as a combination of hematopoietic stem cell transplantation with other methods of therapy, primarily with enzyme replacement.

Conclusions. The early diagnosis and timely pathogenetic treatment of mucopolysaccharidosis will help prevent disability of patients and their adequate integration into society. Effective medical and genetic counseling of families will significantly reduce the occurrence of new cases of these severe hereditary diseases. Gene therapy is considered one of the priority directions in the treatment of mucopolysaccharidoses. The most significant advances in gene therapy using viral vectors have been obtained in experimental models of mice with mucopolysaccharidosis type VII. The basis for the prevention of mucopolysaccharidosis is medical and genetic counseling of families, followed by prenatal diagnosis using molecular genetic methods (DNA diagnostics).

Conflict of interest disclosure: The authors declare no conflict of interest.

Funding. The authors state, that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability statement. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

References.

1. McDonagh T.A., Metra M., Adamo M. et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2021. Vol. 42. No. 36. P. 3599-3726. DOI: https://doi.org/10.1093/eurheartj/ehab368
2. Williams K.B., Brigatti K.W., Puffenberger E.G. et al. Homozygosity for a mutation affecting the catalytic domain of tyrosyl-tRNA synthetase (YARS) causes multisystem disease. Human Molecular Genetic. 2019. Vol. 28. No. 4. P. 525-538. DOI: https://doi.org/10.1093/hmg/ddy344
3. Viskochil D., Clarke L., Bay L., et al. Growth patterns for untreated individuals with MPS I: Report from the international MPS I registry AJMG. 2019. Vol. 179. No. 12. P. 2425-2432. DOI: https://doi.org/10.1002/ajmg.a.61378
4. Tomanin R., Karageorgos L., Zanetti A. et al. Mucopolysaccharidosis type VI (MPS VI) and molecular analysis: Review and classification of published variants in the ARSB gene. Human Mutation. 2018. Vol. 39. No. 12. P. 1788-1802. DOI: https://doi.org/10.1002/humu.23613
5. Parini R., Deodato F., Rocco M.D., et al. Open issues in Mucopolysaccharidosis type I-Hurler Orphanet Journal Rare Diseases. 2017. Vol. 15. No. 12(1). P. 112-117. DOI: https://doi.org/10.1186/s13023-017-0662-9.
6. Krovetz L.J., Lorincz A.E., Schiebler G.L. Cardiovascular manifestations of the Hurler syndrome. Hemodynamic andangiocardiographic observations in 15 patients. Circulation. 1965. Vol. 31. P. 132-141. DOI: https://doi.org/10.1161/01.cir.31.1.132.
7. Renteria V.G., Ferrans V.J., Roberts W.C. The heart in theHurler syndrome. Gross, histologic and ultrastructuralobservations in five necropsy cases. American Journal Cardiology. 1976; Vol. 38. No. 4. P. 487-501. URL: https://www.ajconline.org/article/0002-9149(76)90468-9/abstract

8. Ayuna A., Stepien K.L., Hendriksz C.H. et al. Cardiac rhythm abnormalities - An underestimated cardiovascular risk in adult patients with Mucopolysaccharidoses. Mol. Genet. Metab. 2020. Vol. 130. No. 2. P. 133-139. DOI: https://doi.org/ 10.1016/ j.ymgme.2020.03.005
9. Chen M.R., Lin S.P., Hwang H.K., et al. Cardiovascularchanges in mucopolysaccharidoses in Taiwan. Acta Cardiol. 2005. Vol. 60. No. 1. P. 51-53. URL: https://pubmed.ncbi.nlm.nih.gov/ 15779852/
10. Poletto E., Baldo G., Gomez-Ospina N. Genome Editing for Mucopolysaccharidoses. Int. J. Mol. Sci. 2020. Vol. 13, No. 21(2). P. 500-509. DOI: https://doi.org/10.3390/ijms21020500
11. Jones S.A., Almássy Z., Beck M. et al. Mortality and cause of death in mucopolysaccharidosis type II - a historical review based on data from the Hunter Outcome Survey (HOS). J. Inherit. Metab. Dis. 2009. Vol.32. No. 5. P. 534-543. DOI: https://doi.org/10.1007/s10545-009-1119-7.
12. Jameson E., Jones S. Remmington Enzyme replacement therapy with laronidase (Aldurazyme ®) for treating mucopolysaccharidosis type I Cochrane Database Syst. Rev. 2019. Vol. 18. No. 6(6). P. CD009354. DOI: https://doi.org/10.1002/14651858.CD009354.pub5.
13. Leal G.N., Paula A.C., Leone C., et al. Echocardiographic study of paediatric patients with mucopolysaccharidosis. Cardiol. Young. 2010. Vol. 20. P. 254-261. DOI: https://doi.org/10.1017/S104795110999062X.
14. Braunlin E., Steinberger J., DeFor T., et al. Metabolic Syndrome and Cardiovascular Risk Factors after Hematopoietic Cell Transplantation in Severe Mucopolysaccharidosis Type I (Hurler Syndrome). Biol. Blood Marrow Transplant. 2018. Vol. 24. No. 6. P. 1289-1293. DOI:https://doi.org/10.1016/j.bbmt.2018.01.028.
15. Hirth A., Berg A., Greve G. Successful treatment of severe heart failure in an infant with Hurler syndrome. J. Inherit. Metab. Dis. 2007. Vol. 30. No. 4. P. 820-834. DOI: https://doi.org/10.1007/s10545-007-0613-z.
16. Soliman O.II., Timmermans R.G.M., Nemes A. et al. Cardiac abnormalities in adults with the attenuated form of mucopolysaccharidosis type I. JIMD. 2007. Vol. 30. No. 5. P. 750-757. DOI: https://doi.org/10.1007/s10545-007-0586-y
17. Braunlin E.A., Harmatz P.R., Scarpa M. et al. Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management. JIMD. 2011. Vol. 34. No. 6. P. 1183-1197. DOI: https://doi.org/10.1007/s10545-011-9359-8
18. Harmatz P., Shediac R. Mucopolysaccharidosis VI: pathophysiology, diagnosis and treatment Front Biosci. (Landmark Ed). 2017. Vol. 1. No. 22. P. 385-406. DOI: https://doi.org/10.2741/4490
19. Thomas J.A., Beck M., Clarke J.T.R., Cox G.F. Childhood onset of Scheie syndrome, the attenuated form of mucopolysaccharidosis I. JIMD. 2010. Vol. 33. No. 4. P. 421-427. DOI: https://doi.org/10.1007/s10545-010-9113-7
20. Wraith J.E., Beck M., Giugliani R. et al. Initial report from the Hunter Outcome Survey. Genet. Med. 2008. Vol. 10. P. 508-516. DOI: https://doi.org/10.1097/gim.0b013e31817701e6
21. Yano S., Moseley K., Pavlova Z. Postmortem studies on a patientwith mucopolysaccharidosis type I: Histopathological findingsafter one year of enzyme

replacement therapy. JIMD. 2009. Vol. 32. No. S. P. 53-57. DOI: https://doi.org/10.1007/s10545-009-1057-4
22. Johnson G.L., Vine D.L., Cottrill C.M., et al. Echocardiographic mitral valve deformity in the mucopolysaccharidoses. Pediatrics 1981. Vol. 67. P. 401-406. PMID: 6787559. URL: https://pubmed.ncbi.nlm.nih.gov/6787559/
23. Maganti K., Rigolin V.H., Sarano M.E., et al. Valvular heart disease: diagnosis and management. Mayo Clin. Proc. 2010. Vol. 85. P. 483-500. DOI: https://doi.org/10.4065/mcp.2009.0706
24. Taylor M., Khan S., Stapleton M. et al. Hematopoietic Stem Cell Transplantation for Mucopolysaccharidoses: Past, Present, and Future. Biol. Blood. Marrow Transplant. 2019. Vol. 25. No. 7. P. e226-e246. URL: https://www.astctjournal.org/article/S1083-8791(19)30137-5/fulltext
25. Kettles D.I., Sheppard M., Liebmann R.D., et al. Left ventricular aneurysm, aortic valve disease and coronary narrowing in a patient with Hunter's syndrome. Cardiovasc Pathol. 2002. Vol. 11. Is. 2. P. 94-96. DOI: https://doi.org/10.1016/S1054-8807(01)00099-0 URL: https://pubmed.ncbi.nlm.nih.gov/11934600/
26. Braunlin E.A., Krivit W., Burke B.A. et al. Radiological case of the month. Arch. Pediatr. Adolesc. Med. 2000. Vol. 154. No. 8. P. 841-842. DOI: https://doi:10.1001/archpedi.154.8.841
27. Burton B.K., Jego V., Mikl J. et al. Survival in idursulfase-treated and untreated patients with mucopolysaccharidosis type II: data from the Hunter Outcome Survey (HOS). JIMD. 2017. Vol. 40. No. 6: 867-874. DOI: https://doi.org/10.1007/s10545-017-0075-x
28. Giugliani R., Harmatz P., Wraith J.E. Management guidelines for mucopolysaccharidosis VI. Pediatrics 2007. Vol. 120. P. 405-418. DOI: https://doi.org/10.1542/peds.2006-2184
29. Nemes A., Timmermans R.G., Wilson J.H. et al. The mild form of mucopolysaccharidosis type I (Scheie syndrome) is associated with increased ascending aortic stiffness. Heart Vessels. 2008. Vol. 23. P. 108-111. DOI: https://doi.org/10.1007/s00380-007-1013-x
30. Hinek A., Wilson S.E. Impaired elastogenesis in Hurler disease. Dermatan sulfate accumulation linked to deficiency in elastin-binding protein and elastic fiber assembly. Am. J. Pathol. 2000. Vol. 156. P. 925-938. DOI: https://doi.org/10.1016/S0002-9440(10)64961-9
31. Ma X., Tittiger M., Knutsen R.H. et al. Upregulation of elastase proteins results in aortic dilatation in mucopolysaccharidosis I mice. Mol. Genet. Metab. 2008. Vol. 94. P. 298-304. DOI: https://doi.org/10.1016/j.ymgme.2008.03.018
32. Fesslová V., Corti P., Sersale G., et al. The natural course and the impact of therapies of cardiac involvement in the mucopolysaccharidoses. Cardiol. Young. 2009. Vol. 19. No. 2. P. 170-178. DOI: https://doi.org/10.1017/S1047951109003576
33. Keller C., Briner J., Schneider J.. et al. Mucopolysaccharidosis 6-A (Maroteaux-Lamy disease): comparison of clinical and pathologico-anatomic findings in a 27-year-old patient. Helv Paediatr Acta 1987. Vol. 42. P. 317-333. PMID: 3127360 https://pubmed.ncbi.nlm.nih.gov/3127360/

34. Bush D., Sremba L., Lomax K. et al. Neonatal Onset Interstitial Lung Disease as a Primary Presenting Manifestation of Mucopolysaccharidosis Type I. JIMD. 2019. Vol. 43. P. 71-77. URL: https://pubmed.ncbi.nlm.nih.gov/29654546/ https://link.springer.com/chapter/10.1007/8904_2018_101
35. Hishitani T., Wakita S., Isoda T. et al. Sudden death in Hunter syndrome caused by complete atrioventricular block. J. Pediatr. 2000. Vol. 136. Is. 2. P. 268-269. DOI: https://doi.org/ 10.1016/s0022-3476(00)70117-x URL: https://www.jpeds.com/article/S0022-3476(00)70117-X/abstract
36. Gupta V., Barzilla J.E., Mendez J.S. et al. Abundance and location of proteoglycans and hyaluronan within normal and myxomatous mitral valves. Cardiovasc. Pathol. 2009. Vol. 18. No. 4. P. 191-197. DOI: https://doi.org/10.1016/j.carpath.2008.05.001
37. Latif N., Sarathchandra P., Taylor P.M. et al. Localization and pattern of expression of extracellular matrix components in human heart valves. J. Heart Valve Dis. 2005. Vol. 14. P. 218-227. URL: https://pubmed.ncbi.nlm.nih.gov/15792183/
38. Grande-Allen K.J., Griffin B.P., Ratliff N.B. et al. Glycosaminoglycan profiles of myxomatous mitral leaflets and chordae parallel the severity of mechanical alterations. J. Am. Coll. Cardiol. 2003. Vol. 42. Vol. 2. P. 271-277. DOI: https://doi.org/10.1016/S0735-1097(03)00626-0
39. Nakashima Y., Wight T.N., Sueishi K. Early atherosclerosis in humans: role of diffuse intimal thickening and extracellular matrix proteoglycans. Cardiovasc. Res. 2008. Vol. 79. P. 14-23. DOI: https://doi.org/10.1093/cvr/cvn099
40. Braunlin E., Tolar J., Mackey-Bojack S. et al. Clear cells in the atrioventricular valves of infants with severe human mucopolysaccharidosis (Hurler syndrome) are activated valvular interstitial cells. Cardiovasc. Pathol. 2011. Vol. 20. No. 5. P. 315-321. DOI: https://doi.org/10.1016/j.carpath.2010.06.004
41. Theocharis A.D., Tsolakis I., Hjerpe A., et al. Versican undergoes specific alterations in the fine molecular structure and organization in human aneurysmal abdominal aortas. Biomed. Chromatogr. 2003. Vol. 17. No. 6. P. 411-416. DOI: https://doi.org/10.1002/bmc.263
42. Simonaro C.M. Cartilage and chondrocyte pathology in the mucopolysaccharidoses: the role of glycosaminoglycanmediated inflammation. JPRM. 2010. Vol. 3. No. 2. P. 85-88. DOI: https://doi.org/10.3233/PRM-2010-0120
43. Mathew R.C., Löffler A.I., Salerno M. Role of Cardiac Magnetic Resonance Imaging in Valvular Heart Disease: Diagnosis, Assessment, and Management. Curr. Cardiol. Rep. 2018. Vol. 26. No. 20 (11). P. 119. DOI: https://doi.org/10.1007/s11886-018-1057-9
44. Wolk M.J., Bailey S.R., Doherty J.U. et al. ACCF/ SCCT/ ACR/ AHA/ ASE/ ASNC/ NASCI/ SCAI/SCMR 2013 appropriateuse criteria for cardiac computed tomography. A report of theAmerican College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the AmericanHeart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the NorthAmerican Society for Cardiovascular Imaging, the Society forCardiovascular Angiography and Interventions, and the Societyfor Cardiovascular Magnetic

Resonance. J. Am. Coll. Cardiol. 2014. Vol. 63. No. 4. P. 380-406. DOI: https://doi.org/10.1016/j.jacc.2013.11.009
45. Kakkis E., Marsden D. Urinary glycosaminoglycans as a potential biomarker for evaluating treatment efficacy in subjects with mucopolysaccharidoses. Mol. Genet. Metab. 2020. Vol. 130. No. 2. P. 7-15. DOI: https://doi.org/10.1016/j.ymgme.2020.02.006