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CONGENITAL METABOLIC DISEASES. LYSOSOMAL STORAGE DISEASES

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The classification and epidemiology of hereditary metabolic disorders are presented. That is a large group consisting from more them 800 monogenic diseases, each of which caused by inherited deficiency of certain metabolic fate. Many of these disorders are extremely rare, but their total incidence in the population is close to 1:1000–5000. Lysosomal storage diseases (LSD) resulting from inherited deficiency in lysosomal functions occupy a special place among hereditary metabolic disorders. The defects of catabolism cause the accumulation of undigested or partially digested macromolecules in lysosomes (that is, 'storage'), which can result in cellular damage. About 60 diseases take part in this group with total incidence of about 1:7000–8000. LSDs typically present in infancy and childhood, although adult-onset forms also occur. Most of them have a progressive neurodegenerative clinical course, although symptoms in other organ systems are frequent. The etiology and pathogenetic aspects of their main clinical entities: mucopolysaccharidosis, glycolipidosis, mucolipidosis, glycoproteinosis, etc, are presented. Mucopolysaccharidoses caused by malfunctioning of lysosomal enzymes needed to break down glycosaminoglycans are more frequent among LSD. Sphingolipidoses caused by defects of lipid catabolism are second for frequency group of LSD. The state-of-art in field of newborn screening. clinical, biochemical and molecular diagnostics of these grave diseases are discussed. The main directions of modern lysosomal storage diseases therapy are characterized: transplantation of hematopoietic stem cells; enzyme replacement therapy; therapy with limitation of substrate synthesis (substrate-reducing therapy); pharmacological chaperone therapy. Perspective directions for LSD therapy are gene therapy and genome editing which are at advanced preclinical stages.

Keywords: inborn errors of metabolism; lysosomal storage disorders; diagnosis; newborn screening; enzyme replacement therapy.

НАСЛЕДСТВЕННЫЕ БОЛЕЗНИ ОБМЕНА. ЛИЗОСОМНЫЕ БОЛЕЗНИ НАКОПЛЕНИЯ

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В статье представлена классификация и эпидемиология наследственных болезней обмена (НБО). НБО — это большая группа из более чем 800 моногенных заболеваний, обусловленных наследственной недостаточностью определенного метаболического пути. Многие из этих болезней встречаются крайне редко, однако их общая частота в популяции приближается к 1 : 1000–5000. Среди НБО особое положение занимают лизосомные болезни накопления (ЛБН), обусловленные наследственной дисфункцией лизосом. Дефекты лизосомного катаболизма приводят к накоплению в лизосомах не расщепленных или частично расщепленных макромолекул, представляющих угрозу для клеток. В группу ЛБН входит более 60 заболеваний, их суммарная частота составляет 1 : 7000–8000. ЛБН чаще всего дебютируют в младенчестве или детстве, хотя описаны и взрослые формы заболевания. Для многих ЛБН характерно одновременное вовлечение в патологический процесс многих органов и систем, при этом частыми являются прогрессирующие нейродегенеративные расстройства. Обсуждается этиология и патогенез главных групп ЛБН, таких как мукополисахаридозы, сфинголипидозы, муколипидозы, гликопротеинозы и др.

Наиболее частыми среди ЛБН являются мукополисахаридозы — генетически гетерогенная группа заболеваний, обусловленных мутациями в генах ферментов, участвующих в деградации гликозаминогликанов. Вторые по значимости — сфинголипидозы, причиной развития которых становится нарушение катаболизма липидов. Обсуждается современное состояние в области неонатального скрининга, клинической, биохимической и молекулярной диагностики ЛБН. Охарактеризованы основные направления современной терапии этих тяжелых заболеваний: трансплантация гемопоэтических стволовых клеток, ферментная заместительная терапия; терапия с ограничением синтеза субстратов (субстратредуцирующая терапия); фармакологическая шаперонотерапия. Перспективными подходами для лечения ЛБН являются генная терапия и геномное редактирование, которые находятся на стадии преклинических испытаний.

Ключевые слова: наследственные болезни обмена; лизосомные болезни накопления; диагностика; неонатальный скрининг; ферментная заместительная терапия.

Hereditary metabolic diseases (HMD) are caused by disorders of the catalytic function of various enzymes. This is one of the most and well-studied groups of monogenic human diseases inherited most often in an autosomal recessive mode. Approximately 800 types of HMDs are identified [33, 37], and each disease is characterized by a set of specific biochemical disorders associated with hereditary insufficiency of a certain metabolic pathway. Most often, patients have inactivating mutations in the genes of the corresponding enzymes, and sometimes, other proteins are involved in their activation or transport. The pathogenetic mechanisms of HMDs are associated with either the accumulation of toxic concentrations of substances preceding the enzymatic block or a deficiency of the end products of the reaction. Additionally, blockage of the metabolic chain may be accompanied by pronounced "secondary" biochemical disorders.

Incidence rates of various nosological forms of HMDs vary from 1 : 10,000 newborns to $1:10^5$–10^6, and many of them are characterized by pronounced differences in this parameter in different ethnic groups and populations [7]. In some isolated populations, HMDs can occur in 1 per 3000–5000 newborns. The total incidence of HMD is 1 per 1000–5000 newborns.

Generally, HMDs represent serious conditions with quite diverse clinical manifestations. They often include psychomotor retardation, seizure syndrome, myopathy, skeletal abnormalities, recurrent coma, ketoacidosis, hepatosplenomegaly, malabsorption, ataxia, and sudden death syndrome. For most HMDs, neonatal, childhood, adult, and in some cases even asymptomatic disease forms have been described. Differences in disease onset and severity are determined by the enzyme residual activity, which in turn depends on the type of the corresponding mutation. In neonatal and childhood forms, which often end in early lethal outcomes, the enzyme activity is not determined or is significantly less than 1% of the norm; in juvenile forms, it varies from 0.5% to higher rates, and in the case of adult forms, it usually exceeds 5%, sometimes reaching several tens of percent with subclinical disease forms. However, in some cases, significant phenotypic polymorphism is registered in patients who are consanguineous and have identical mutations, which indicates the potential influence of the environmental and/or genotypic background on the manifestation of the mutation [10, 18].

HMDs are divided into 22 groups depending on the intracellular localization of the disorder (i.e., lysosomal, mitochondrial, and peroxisomal) or the type of the damaged metabolic pathway (aminoacidopathy, organic aciduria, metabolic disorders of carbohydrates, lipids, steroids and other hormones, purines and pyrimidines, bilirubin, porphyrin, among others). However, the classification of HMDs is not always unambiguous because some metabolic pathways intersect. The groups with numerous nosological forms are those that combine metabolic disorders of organic acids and amino acids, lysosomal storage diseases (LSDs), mitochondrial diseases, and disorders of carbohydrate and glycogen metabolism.

At the clinical level, HMDs can only be suspected. Biochemical methods are the first options in the diagnostics of HMD. At stage 1, the corresponding metabolites were analyzed, and at the next stage, the dysfunction of the mutant protein is identified by assessing its activity and/or amount. The determination of the concentration of metabolites in biological fluids, primarily in urine and blood, as well as their qualitative or semiquantitative analysis, often enables suspicion of a certain group of HMDs or even a nosological form with high accuracy. In this case, various spectrophotometry and chromatography types are usually used, such as primarily tandem mass spectrometry, which enable characterization of the structure within a few minutes, determine the

molecular weight, and quantify various substances. In biochemical diagnostics of HMD, approximately 50 compounds are determined in one sample.

The most complete biochemical diagnostics of HMD in Russia is performed at the Medical Genetic Scientific Center (MGSC) of the Russian Academy of Medical Sciences in the laboratory of HMDs, which was headed by K.D. Krasnopolskaya for many years. The laboratory has collected and characterized a large sample of patients. Throughout her life, Ksenia Dmitrievna has attracted the attention of doctors, medical geneticists, and specialists from other medical genetic centers of Russia to the problem of HMD, publishing articles and speaking at various conferences, meetings, and congresses. The results of this long-term work are summarized in a unique monograph by K.D. Krasnopolskaya [10], released by her students, who continue successfully the work started under the supervision of E.Yu. Zakharova [7].

Objective diagnosis of HMDs is achieved by identifying inactivating mutations in the corresponding genes. Currently, in several Russian molecular diagnostic centers, and, first of all, in the N.P. Bochkov MGSC, DNA diagnostics of HMDs is performed using "new-generation sequencing" methods. Another example is the GenoMed Center, created in the molecular pathology laboratory of the Moscow Medical Genetic Center, which offers a molecular diagnostic panel for the simultaneous assessment of the state of 500 HMD-associated genes.

LSDs hold a special place among HMDs, which represent a heterogeneous group of recessive diseases, including approximately 60 nosological forms [4, 33]. All LSDs are caused by genetic disorders of the functions of lysosomes that control intracellular cleavage processes of most biological macromolecules, such as glycolipids, glycosaminoglycans (GAGs), and glycoproteins. LSDs occur in 1 per 7–8 thousand newborns [7]. Each disease type occurs in 1 per 10,000–100,000 populations, but it can be much lower in most cases. In the laboratory of HMDs of the MGSC of the Russian Academy of Medical Sciences, from 1992 to 2009, more than 900 patients with 25 nosological forms of LSDs were identified and characterized, which enabled assessment of the range and incidence of these diseases in Russia [7, 10].

Primary lysosomes are formed from the Golgi apparatus. By merging with other membrane vesicles, secondary lysosomes are formed and contained materials that entered the cells as a result of endocytosis or are absorbed during autophagy. Lysosomes are a central component of the endosomal–lysosomal system which functions in conjunction with the chaperone-mediator system of autophagy.

Lysosomal enzymes belong to the class of acidic hydrolases which mainly break down macromolecules into their primary components, namely, amino acids, monosaccharides, and fatty and nucleic acids. Lysosomal enzymes include acid and alkaline phosphatases, glucose 6-phosphatase, lipase, cholinesterase, protease, urease, among others. Hydrolases are synthesized in the endoplasmic reticulum and then undergo post-translational processing when they are glycosylated by the addition of oligosaccharides and acquire the terminal residue of mannose 6-phosphate. In this form, hydrolases are transported to primary lysosomes. Genetic disorders at any stage of the synthesis and maturation of these enzymes lead to the accumulation of the corresponding specific substrates such as mucopolysaccharides, gangliosides, lipids, and glycoproteins, in the lysosomes. This increases the number of lysosomes, which is morphologically revealed in the appearance of so-called foam cells. The accumulation of non-cleaved macromolecules can reach significant amounts, especially in tissues and organs characterized by an increased rate of regeneration. Some LSDs are caused by genetic disorders of proteins involved in the biogenesis of lysosomes, as well as activator proteins that solubilize insoluble substrates (glycolipids), and proteins that control the vesicular transport of lysosomal enzymes or substrates subject to hydrolysis [5, 33].

Mononuclear phagocytic system cells are rich in lysosomes and thus are often involved in the pathological process in LSD. The target organs are the natural sites of the corresponding macromolecule destruction. Thus, when myelin catabolism is impaired, the white matter of the brain is involved in the process, and the accumulation of unsplit macromolecules in central nervous system (CNS) tissues generally stimulates the development of neurodegenerative processes and mental retardation. With the accumulation of metabolites in parenchymal organs, hepatosplenomegaly, anemia, and thrombocytopenia occur; the accumulation of pathological material in bone tissue contributes to the development of multiple dysostosis; and the accumulation of mucopolysaccharides present in most tissues leads to generalized damage to various organs and systems [33].

Neurological disorders are often combined with signs of dysmorphogenesis (such as coarse facial features and macroglossia), hepatosplenomegaly, skeletal disorders, contractures, umbilical hernia,

cardiovascular system pathologies (such as arrhythmia and cardiomegaly), and visual damage (corneal haze or cherry-red spot) [9, 11–14, 17]. Currently, several groups of LSDs are identified, namely mucopolysaccharidoses (MPS), lipidoses, mucolipidoses, oligosaccharidoses, neuronal ceroid lipofuscinosis [3, 6, 15].

MPS are the most common lysosomal diseases and represent a genetically heterogeneous group of recessive diseases with a high level of clinical polymorphism [9, 13, 14]. All MPS are caused by mutations in the genes of lysosomal enzymes involved in the degradation of GAGs or mucopolysaccharides. Owing to the deficiency of these enzymes in many organs and systems, an excessive amount of partially degraded GAGs (carbohydrate structures linked covalently to the core proteins of proteoglycans) accumulate. By chemical structure, GAGs are linear polymers containing amino sugar (N-acetylated or N-sulfated) and uronic or iduronic acid, which forms disaccharidase units specific for each type. GAGs include hyaluronic acid, type A, B, and C chondroitin sulfates, keratin sulfate, heparan sulfate, and heparin.

The most abundant chondroitin sulfate and dermatan sulfate proteoglycans are distributed in the extracellular space. Their interactions with collagen and elastic fibers provide the mechanical properties of many connective tissues. By contrast, heparan sulfate proteoglycans are transmembrane proteins and act as receptors for extracellular matrix proteins, growth factors, and angiogenic peptides.

GAG synthesis starts with transferring xylose to serine residues in the core protein of proteoglycans. When two residues of galactose and glucuronic acid are sequentially added, a common linked structure is formed, which is present in most types of proteoglycans. Alternative addition to this structure of N-acetylglucose or N-acetylgalactose residues leads to the formation of heparan sulfate or chondroitin sulfate, respectively. Proteoglycans degradation is a normal physiological process. It is implemented by two classes of enzymes, namely, proteinases (exo- and endopeptidases) that break down the core protein and glycosidases that break down GAG chains and oligosaccharides [33].

All MPSs are characterized by the multiplicity of lesions and simultaneous involvement of many organs and systems in the pathological process. The main clinical manifestations of MPS are considered coarse, grotesque facial features (gargoylism), significant growth retardation, multiple dysostosis, joint stiffness, hernias, hepatosplenomegaly, corneal opacity and glaucoma, hypertelorism, decreased intelligence, and bradyacuasia, and, in the cardiovascular system, hypertrophic cardiomyopathy and myxomatous degeneration of valves, more often aortic and mitral valves, with the development of their insufficiency or stenosis in the disease outcome. Typically, a clinical diagnosis cannot be established at birth. The disease manifestations are formed gradually during the first several months or even years of life and further progress. In clinical practice, MPS are often divided into two groups, namely, Hurler-like and Morquio-like phenotypes. There is a high genetic heterogeneity of the MPS. At present, genes mutated in 11 hereditary types of these diseases have been identified [15]. The Morquio-like phenotype is a characteristic of types A and B Morquio syndromes, and the remaining types constitute the MPS group with a Hurler-like phenotype.

Table 1 presents primary biochemical defects, mutant genes, and accumulation products in different MPS.

Worldwide, MPS occur in 1.56 per 100,000 newborns [24]. The most common type is MPS II which accounts for approximately 30% of all MPS cases in European countries and more than 50% in Japan. MPS types I, III, and IV account for 12%, 24%, and 24% in Europe and 15%, 16%, and 10% in Japan, respectively. MPS types VI and VII are less common; in Europe, they account for 7.3% and 2.4% of all MPS cases and in Japan 1.7% and 1.3%, respectively. The ratio of incidence of different types of MPS in Russia is approaching European values [7].

Hereditary **glycolipidoses** are caused by the deficiency of lysosomal enzymes involved in lipid catabolism, or a disorder of one of the stages of synthesis, transport, and degradation of lipoproteins, which include all the main plasma lipids, namely, triglycerides, phospholipids, cholesterol, and free fatty acids [1, 11, 12, 17]. These diseases are characterized by the abnormal deposition of large amounts of unsplit products of fat metabolism in various organs and tissues.

The majority of glycolipids are represented by sphingolipids, mainly including sphingomyelins, cerebrosides, glycosphingolipids, gangliosides, and sulfatides. Sphingomyelins are composed of sphingosine that can be combined with phosphocholine or phosphoethanolamine. These phospholipids are located on the outside of the lipid layer of the cell membrane and are especially abundant in the myelin sheath of axons. Cerebrosides, or glycosphingolipids, are also components of cell membranes. They include sphingosines, fatty acids, and carbohydrates, which can be represented by galactose or, less often,

Table 1 / Таблица 1

Molecular genetic description of the mucopolysaccharidoses (MPS)
Молекулярно-генетическая характеристика мукополисахаридоза (МПС)

Syndrome / Синдром OMIM [37]	Protein, gene, localization / Белок, ген, локализация	Storage product / Продукт накопления
MPS type I: Hurler syndrome, 607014; Scheie syndrome, 607016; Hurler–Scheie syndrome, 607015 / МПС тип I: синдром Гурлера, 607014; синдром Шейе, 607016; синдром Гурлера–Шейе, 607015	Alpha-L-iduronidase / Альфа-L-идуронидаза *IDUA*; 4p16.3	Dermatan sulfate, heparan sulfate / Дерматансульфат, гепарансульфат
MPS type II Hunter syndrome МПС тип II: синдром Хантера / 309900	Iduronate 2-sulfatase / Идуронат-2-сульфатаза *IDS*; Xq28	Dermatan sulfate, heparan sulfate / Дерматансульфат, гепарансульфат
MPS type IIIA: Sanfilippo syndrome A / МПС тип IIIA: синдром Санфилиппо, тип A 252900	Heparan N-sulfatase, or sulfamidase / Гепаран-N-сульфатаза или сульфамидаза *SGSH*; 17q25.3	Heparan sulfate / Гепарансульфат
MPS type IIIB: Sanfilippo syndrome B / МПС тип IIIB: синдром Санфилиппо, тип B 252920	Alpha-N-acetylglucosaminidase / A-N-ацетил-глюкозаминидаза*NAGLU*; 17q21.1	Heparan sulfate / Гепарансульфат
MPS type IIIC: Sanfilippo syndrome C / МПС тип IIIC: синдром Санфилиппо, тип C 252930	Aacetyl CoA: alpha-glucosaminide acetyltransferase / Ацетил-КоА: α-глюкозаминидаза-N-ацетилтрансфераза *HGSNAT*; 8p11.1	Heparan sulfate / Гепарансульфат
MPS type IIID: Sanfilippo syndrome D / МПС тип IIID: синдром Санфилиппо, тип D 252940	N-acetylglucosamine-6-sulfatase / N-ацетилглюкозамин-6-сульфатаза *GNS*; 12q14	Heparan sulfate / Гепарансульфат
MPS type IVA: Morquio syndrome A / МПС тип IVA: синдром Моркио, тип A 253000	Galactosamine-6-sulfate sulfatase / Галактозамин-6-сульфат-сульфатаза *GALNS*; 16q24.3	Keratan sulfate, chondroitin-6-sulfate / Кератансульфат, хондроитин-6-сульфат
MPS type IVB: Morquio syndrome B / МПС тип IVB: синдром Моркио, тип B 253010	Beta-galactosidase-1 / Бета-галактозидаза-1 *GLBI*; 3p21.33	Keratan sulfate / Кератансульфат
MPS type VI: Maroteaux–Lamy syndrome / МПС тип VI: синдром Марото–Лами 253200	Arylsulfatase B / Арилсульфатаза B *ARSB*; 5q11-q13	Dermatan sulfate / Дерматансульфат
MPS type VII: Sly syndrome / МПС тип VII: синдром Слая 253220	Beta-glucuronidase / Бета-глюкуронидаза *GUSB*; 7q21.11	Heparan sulfate, dermatan sulfate / Гепарансульфат, дерматансульфат
MPS type IX / МПС тип IX 601492	Hyaluronidase / Гиалуронидаза *HYAL1*; 3p21.31	Keratan sulfate, heparan sulfate / Кератансульфат, гепарансульфат

glucose (galactocerebrosides and glucocerebrosides, respectively). Gangliosides (GM1, GM2, and GA2) are an integral part of glycosphingolipids located on the outer surface of most cell membranes. They are especially abundant in cells of the nervous system. Sulfatides are involved in the construction of the myelin sheath of nerve fibers [33].

Lysosomal diseases caused by hereditary insufficiency of sphingolipids are called **sphingolipidosis**. Sphingolipid catabolism occurs in lysosomes, where glycohydrolases degrade them by sequential separation of terminal sugars to the core ceramide. Sphingolipidoses include disease groups such as glycosphingolipidosis, cerebrozidosis, gangliosidosis, and leukodystrophy. Cerebrosidosis includes Fabry disease [17], glucosylceramide lipidosis (or Gaucher disease) [12], lipogranulomatosis (or Farber disease), and sphingomyelin lipidosis (or Niemann–Pick disease) [11].

Gangliosidosis includes GM1 gangliosidosis and three GM2 gangliosidoses, namely, types I and II (or Tay–Sachs disease and Sandhoff disease,

respectively), as well as type AB. Hereditary leukodystrophies include Krabbe disease (or globoid cell leukodystrophy), metachromatic leukodystrophy, combined deficiency of prosopasine, a precursor of sphingolipid hydrolysis activator proteins, and multiple sulfatase deficiency.

All sphingolipidoses are characterized by signs related to the intracellular accumulation of certain sphingolipids in the liver, spleen, lungs, bone marrow, and brain. Table 2 shows primary biochemical defects, mutant genes, and accumulation products in different types of glycolipidoses.

Mucolipidosis is based on the deficiency of enzymes involved in the processing of lysosomal hydrolases such as N-acetylglucosamine 1-phosphotransferase, which is an enzyme necessary for the attachment of mannose 6-phosphate to oligosaccharides of lysosomal enzymes. Without mannose 6-phosphate, enzymes cannot enter the lysosomes and are eliminated from the cell. The most famous mucolipidosis is I-cell disease, and its clinical presentation is largely reminiscent of Hurler's syndrome, and pseudo-Hurler polydystrophy, characterized by later onset and mild course. Table 3 presents primary biochemical defects, mutant genes, and accumulation products in different types of mucolipidosis.

Hereditary disorders of glycosidases involved in oligosaccharide breakdown can cause the development of **oligosaccharidoses**. Generally, the structure of glycoproteins represents a protein core and oligosaccharide chains attached to it in the process of movement from ribosomes to the Golgi apparatus. In this case, two metabolic pathways can be used, namely, monosaccharide–nucleotide and lipid (dolichol)-mediated pathways. Both pathways ensure attachment of fucose-rich oligosaccharide chains to proteins through the formation of an N-glycosidic bond between N-acetylglucosamine and asparagine and an O-glycosidic bond between N-acetylgalactosamine and serine or threonine. The dolichol-mediated metabolic pathway is used to attach mannose-rich and complex oligosaccharide chains to proteins through the formation of an N-glycosidic bond between N-acetylglucosamine and asparagines.

The catabolism of oligosaccharide chains is implemented by exoglycosidases in lysosomes such that the degradation product of one of the enzymes serves as a substrate for the other. Impairment of these processes leads to oligosaccharidoses, or glycoproteinosis, which include mannosidoses, fucosidosis, and aspartylglucosaminuria. Table 4 presents primary biochemical defects, mutant genes, and accumulation products in different types of glycoproteinoses.

Neuronal ceroid lipofuscinosis represents a group of autosomal recessive neurodegenerative diseases characterized by progressive visual impairment, myoclonus epilepsy, neurodegeneration, and accumulation of autofluorescent lipopigment in neurons and other cells. The neurodegenerative process is accompanied by ataxia, progressive mental retardation, and psychomotor disorders. In classical forms, the disease onset is registered at age 4–7 years. Depending on the time of emergence of the first symptoms and clinical signs, three main disease types are identified, namely, infantile, classic late infantile, and juvenile. Several atypical disease forms with onset in late infancy have also been described, including the "Finnish" variant. The genetic heterogeneity of neuronal ceroid lipofuscinosis is much greater. Currently, genes have been identified in 14 genetic forms of the disease.

Other LSDs have also been described, which biochemical characteristics do not fit into the described disease groups. These are type C Niemann–Pick disease, Wolman disease, cholesterol ester storage disease, cystinosis, Sahl's disease, pycnodysostosis, among others.

Recently, HMD and, especially, LSD has received increased attention worldwide, not only due to the development of effective methods for their early molecular diagnostics, including prenatal, but also the possibility of treating these severe conditions, which until recently were considered completely incurable [8, 15, 16]. The main therapeutic approaches among proposed ones include enzyme replacement therapy [21, 28], therapy with a limited synthesis of substrates (substrate-reducing therapy), pharmacological chaperone therapy, and hematopoietic stem cell transplantation [19, 23, 26, 34, 35]. For some diseases, gene therapy methods have been successfully tested in experimental models.

Enzyme replacement therapy is considered a priority approach in the treatment of patients with LSD, while the necessary drugs, the number of which has been rapidly increasing in recent years, are produced using genetic engineering methods. Experimental studies and clinical trials conducted in some cases have revealed that under the influence of such drugs, patients experience an improvement in the functions of many organs and systems, which pathological changes are the main cause of severe disability and lethal outcomes. The most successful enzyme replacement therapy has proven itself in the treatment of patients with type I Gaucher disease [12] and some forms of MPS [2, 9, 13, 14].

Table 2 / Таблица 2

Molecular genetic description of the lipid storage disorders
Молекулярно-генетическая характеристика болезней накопления липидов

Syndrome / Синдром OMIM [37]	Protein, gene, localization / Белок, ген, локализация	Storage product / Продукт накопления
Glycosphingolipidoses / Гликосфинголипидозы		
Fabry disease, alpha-galactosidase A deficiency / Болезнь Фабри, недостаточность α-галактозидазы, тип А 300644	Alpha-galactosidase A / α-Галактозидаза А *GLA*; Xq22.1	Globotriaoslyceramide (Gb3) / Глоботриаозилцерамид
Gaucher disease, types I, II, III / Болезнь Гоше, типы I, II, III 230800	Beta-glucocerebrosidase / β-Глюкоцереброзидаза *GBA*; 1q21	Glucocerebrosid (GlcCer) / Глюкоцереброзид
Sphingomyelin lipidosis, Niemann–Pick disease types A/B / Липидоз сфингомиелиновый, болезнь Ниманна–Пика, тип А/В 257200	Sphingomyelinase / Сфингомиелиназа *SMPD1*; 11p15.4-p15.1	Sphingomyelin / Сфингомиелин
Farber lipogranulomatosis / Болезнь Фарбера, липогранулематоз 228000	Acid ceramidase / Кислая церамидаза *ASAH1*; 8p22	Cerebrosides / Цереброзиды
Gangliosidoses / Ганглиозидозы		
GM1-gangliosidosis, mucopolysaccharidoses IVB / Ганглиозидоз GM1, мукополисахаридоз типа IVB 230500	Beta-galactosidase-1 / Галактозидаза, бета-1 *GLB1*; 3p21.33	GM_1-ganglioside / GM_1-ганглиозид
GM2-gangliosidosis, type I, B, B1 and pseudo-AB variantes, Tay–Sachs disease / GM2-ганглиозидоз тип I, варианты В, В1 и псевдо-АВ, болезнь Тея–Сакса 272800	Hexosaminidase A, alpha / Гексозаминидаза А, альфа *HEXA*; 15q23-q24	GM_2-ganglioside / GM_2-ганглиозид
GM2-gangliosidosis, variant AB / GM2-ганглиозидоз, вариант АВ 272750	Hexosaminidase activator / Активатор гексозаминидазы *GM2A*; 5q31.3-q33.1	GM_2-ganglioside / GM_2-ганглиозид
GM2-gangliosidosis, type II, Sandhoff disease/ GM2-ганглиозидоз, тип II, болезнь Зандхоффа 268800	Hexosaminidase B, beta / Гексозаминидаза В, бета *HEXB*; 5q13	GM_2-ganglioside / GM_2-ганглиозид
Leukodystrophies / Лейкодистрофии		
Vetachromatic leukodystrophy / Лейкодистрофия метахроматическая 250100	Arylsulfatase A / Арилсульфатаза А *ARSA*; 22q13	Sulfatides / Сульфатиды
Globoid cell leukodystrophy, Krabbe disease / Лейкодистрофия глобоидно-клеточная, болезнь Краббе 245200	Galactosylceramidase / Галактозилцерамидаза *GALC*; 14q31	Galactocerebroside / Галактоцереброзид (GalCer)
Combined prosaposin deficiency – precursor of sphingolipid activator proteins (SAPs) / Комбинированная недостаточность просапазина — предшественника сфинголипид-активаторных белков (SAPs) 611721	Prosaposin, Saposin B, C, A / Просапозин, сапозин В, С, А *PRSP*; 10q22.1	Lipides, sulfatides, galucocerebroside, galactocerebroside / Липиды, сульфатиды, глюкоцереброзид, галактоцереброзид
Multiple sulfatase deficiency, or juvenile sulfatidosis, Austin disease / Множественная сульфатазная недостаточность, или сульфатидоз юношеский, болезнь Аустина 272200	Sulfatase-modifying factor-1 / Сульфатазомодифицирующий фактор-1 *SUMF1*; 3p26.1	Sulfatides, dermatan sulfate, heparan sulfate, cholesterol sulfate / Сульфатиды, дерматансульфат, гепарансульфат, холестерилсульфат

Table 3 / Таблица 3

Molecular genetic description of the mucolipidoses
Молекулярно-генетическая характеристика муколипидозов

Syndrome / Синдром OMIM [37]	Protein, gene, localization / Белок, ген, локализация	Storage product / Продукт накопления
Sialidosis, mucolipidosis I / Сиалидоз, муколипидоз I 256550	Neuraminidase / Нейраминидаза *NEU1*; 6p21.33	Salylated glycopeptides, oligosaccharides / Сиалосодержащие гликопротеиды, олигосахариды
Mucolipidosis II alpha/beta, or I-cell disease / Муколипидоз II альфа/бета, или «I-клеточная» болезнь 252500 / Mucolipidosis III alpha/beta, or pseudo-Hurler polydystrophy / Муколипидоз III, альфа/бета, или полидистрофия псевдо-Гурлера 252600	N-acetylglucosamine-1-phosphotransferase, alpha and beta / N-ацетилглюкозаминил-1-фосфотрансфераза, альфа и бета *GNPTAB*; 12q23.2	Sialyl-hexasaccharide / Сиаловые гексосахариды
Mucolipidosis III, gamma / Муколипидоз III, гамма 252605	N-acetylglucosamine-1-phosphotransferase, gamma / N-ацетил-глюкозаминил-1-фосфотрансфераза, гамма *GNPTG*; 16p13.3	Oligosaccharides / Олигосахариды
Mucolipidosis IV, or sialolipidosis / Муколипидоз IV, или сиалолипидоз 252650	Mucolipin I / Муколипин-1 *MCOLN1*; 19p13.2	Phospholipides, sphyngolipides mucopolysacharides, gangliosides / Фосфолипиды, сфинголипиды, мукополисахариды, ганглиозиды

Table 4 / Таблица 4

Molecular genetic description of the glycoproteinoses
Молекулярно-генетическая характеристика гликопротеинозов

Syndrome / Синдром OMIM [37]	Protein, gene, localization / Белок, ген, локализация	Storage product / Продукт накопления
Alpha-mannosidosis / Альфа-маннозидоз 248500	Alpha-D-mannosidase / Альфа-D-маннозидаза *MAN2B1*; 19p13.2	Alpha-mannose 6-phosphate-containing oligosaccharides / Альфа-маннозо-6-фосфат-содержащие олигосахариды
Beta-mannosidosis / Бета-маннозидоз 248510	Beta-D-mannosidase / Бета-D-маннозидаза *MAN2B1*; 4q24	Beta-mannose-6-phosphate-containing oligosaccharides / Бета-маннозо-6-фосфат-содержащие олигосахариды
Fucosidosis / Фукозидоз 230000	Alpha-L-mannosidase / Альфа-L-маннозидаза *FUCA*; 1p36.11	Fucopolysaccharides, fucosphyngolipides / Фукополисахариды, фукосфинголипиды
Aspartylglucosaminuria / Аспартилглюкозаминурия 208400	Aspartylglucosaminidase / Аспартилглюкозаминидаза *AGA*; 4q34.3	Asparagine, aspartylglucosamin / Аспарагин, аспартилглюкозамин

However, it is an expensive drug, which patients usually need to take for life.

The most complete data on the efficacy, limitations, and safety of enzyme replacement therapy have been obtained in types I, II, IVA, VI, and VII MPS [28]. These studies have now passed phase III of clinical trials, and the corresponding drugs have been registered in the USA and some European countries, including Russia [2, 9, 13, 14]. The results of these trials, conducted in different centers, are often contradictory and depend on the disease severity, involvement of various organs and systems in the pathological process, patient's age at the start of treatment, and production of antidrug antibodies. Antidrug antibodies develop in all patients, but their role in resistance to enzyme replacement therapy is less investigated. In general, the therapy is effective in reducing the level of GAGs in the

urine and reducing the liver and spleen volumes. However, such a treatment has a relatively small effect on cardiological, skeletal, and bronchopulmonary manifestations of diseases as well as hearing and vision of patients, which is apparently due to the limited penetration of drugs into specific tissues. When administered intravenously, the drugs do not pass through the blood–brain barrier and are therefore not able to influence the pathological processes occurring in the CNS. To overcome these difficulties, methods are being developed for the administration of medicinal preparations into the cerebrospinal fluid and CNS, using viral vectors as carriers of genetically engineered enzyme preparations [8].

Substrate-reducing therapy is based on restricting the synthesis of metabolites that serve as a source of toxic compounds by selective suppression of the corresponding enzymes. This approach was proven successful in the treatment of patients with type C Niemann–Pick disease. Pharmacological chaperone therapy is based on the ability of certain chemical compounds to have a stabilizing effect on the residual activity of enzymes, the deficiency of which leads to HMD development. The work in this direction is still experimental in nature.

Umbilical cord blood transfusion from unrelated donors and hematopoietic stem cell transplantation for the treatment of patients with HMDs can be used only if they are diagnosed early, i.e., before the development of gross morphological changes in the brain and other organs and systems [30]. In this regard, the issues of including LSD in neonatal screening programs, which are already being introduced into the clinical practice in several countries, are essential [20, 25, 29, 36]. In this case, the most commonly used method is liquid chromatography and tandem mass spectrometry on dried blood stains of newborns. The results of biochemical screening require further confirmation by molecular genetic methods. This approach has already proved its effectiveness in the early diagnostics of types II, IIIB, IVA, VI, and VII MPS [22, 26, 31]. A similar strategy can be used to develop neonatal screening programs for Gaucher disease, Fabry disease, Pompe disease, Krabbe disease, type B Niemann–Pick disease, metachromatic leucodystrophy, and other lysosomal diseases [27, 32].

Thus, in recent years, significant progress has been made in the field of biochemical and molecular diagnostics of HMDs, including LSDs, as a basis for their prevention and prenatal diagnostics. Moreover, treatment algorithms for these severe diseases have been outlined, and the first successful clinical trials have been conducted. Although this work is still at the very beginning, its prospects inspire some optimism.

In further reviews, we will consider in more detail individual diseases included in various groups of LSDs.

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