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LYSOSOMAL STORAGE DISEASES: MUCOPOLYSACCHARIDOSIS TYPE I AND II

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Mucopolysaccharidosis (MPS) are a genetically heterogeneous group of rare monogenic metabolic diseases associated with hereditary insufficiency of lysosomal enzymes involved in the catabolism of glycosaminoglycans, or mucopolysaccharides. The pathogenesis of MPS is due to the accumulation of non-cleaved glycosaminoglycans in lysosomes, which can destroy cells. All MPS are characterized by a polysystemic manifestation, the simultaneous involvement of many organs and tissues in the pathological process, first of all, connective tissues, bones and cartilaginous. This review presents the epidemiology, clinical, biochemical, and molecular genetic characteristics of MPS types I and II, caused by the recessive mutations in the alpha-L-iduronidase and iduronate-2-sulfatase genes, respectively, and by the accumulation of dermatan and heparan sulfate. Each of these diseases is characterized by clinical polymorphism, especially observed in MPS I, which often manifests in a severe form of Hurler syndrome, but can also occur in a milder form of Scheie syndrome. Currently, there is an increased interest in MPS in the world due to the identification of the spectrum and frequencies of mutations in the *IDUA* and *IDS* genes in various populations, including in Russia, and the practical availability of methods for individual molecular diagnostics. The description of the existing experimental models, their role in the study of the biochemical basis of the pathogenesis of these severe hereditary diseases and the development of various therapeutic approaches are given. Discusses the possibility of early diagnosis of MPS I and II types based on neonatal screening in order to increase the effectiveness of their prevention and treatment, as well as the advantages and disadvantages of the main approaches to the treatment of these serious diseases, such as hematopoietic stem cell transplantation, enzyme replacement and substrate-reducing therapy. A clinical example of a combination therapy for a severe form of mucopolysaccharidosis type I – Hurler syndrome is presented

Keywords: review; lysosomal storage disorders; mucopolysaccharidosis.

ЛИЗОСОМНЫЕ БОЛЕЗНИ НАКОПЛЕНИЯ: МУКОПОЛИСАХАРИДОЗЫ I И II ТИПОВ

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Мукополисахаридозы (МПС) — это генетически гетерогенная группа редких моногенных болезней обмена, связанных с наследственной недостаточностью лизосомных ферментов, участвующих в катаболизме гликозаминогликанов, или мукополисахаридов. Патогенез МПС обусловлен накоплением в лизосомах нерасщепленных гликозаминогликанов, представляющих угрозу для клеток. Для всех МПС характерна полисистемность поражения, одновременное вовлечение в патологический процесс многих органов и тканей, прежде всего, соединительной, костной и хрящевой. В данном обзоре представлены эпидемиология, клиническая, биохимическая и молекулярно-генетическая ха-

рактеристика МПС типов I и II, обусловленных присутствием рецессивных мутаций в генах альфа-L-идуронидазы и идуронат-2-сульфатазы соответственно, и накоплением дерматан- и гепарансульфата. Для каждого из этих заболеваний характерен клинический полиморфизм, особенно выраженный при МПС I типа, который чаще проявляется в тяжелой форме синдрома Гурлера, но может протекать и в более легкой форме синдрома Шейе. В настоящее время в мире наблюдается повышенный интерес к МПС в связи с идентификацией спектра и частот мутаций в генах *IDUA* и *IDS* в различных популяциях, в том числе и в России, и практической доступностью методов индивидуальной молекулярной диагностики. Дано описание существующих экспериментальных моделей, их роли в изучении биохимических основ патогенеза этих тяжелых наследственных заболеваний и разработке различных терапевтических подходов. В первую очередь обсуждается возможность ранней диагностики МПС типов I и II на базе неонатального скрининга с целью повышения эффективности их профилактики и лечения, во вторую — преимущества и недостатки основных подходов к терапии этих тяжелых заболеваний, таких как трансплантация костного мозга и гемопоэтических стволовых клеток, ферментная заместительная и субстрат-редуцирующая терапия. Представлен клинический пример комбинированной терапии тяжелой формы мукополисахаридоза типа I — синдрома Гурлера.

Ключевые слова: обзор; лизосомные болезни накопления; мукополисахаридозы.

This article in combination with others on lysosomal storage disorders (LSDs), present information on diseases belonging to various classes of LSDs according to a unified scheme. This includes themes such as clinical presentation and epidemiology; biochemical fundamentals of pathogenesis; mapping and identification of the mutant gene; spectra and frequencies of mutations; experimental models; laboratory diagnosis and treatment.

This review is focused on the most common mucopolysaccharidoses (MPS) types I and II [10]. Allelic of Hurler syndrome, Scheie syndrome, and Hurler–Scheie syndrome belong to MPS I. They are due to the presence of autosomal recessive mutations in the *IDUA* gene for alpha-L-iduronidase. MPS II, or Hunter syndrome [24], is X-linked inherited recessive disorder which is caused by mutations in the *IDS* gene of iduronate 2-sulfatase. Alpha-L-iduronidase and iduronate 2-sulfatase are lysosomal enzymes involved in the degradation of glycosaminoglycans (GAGs).

MUCOPOLYSACCHARIDOSIS TYPE I, HURLER SYNDROME, SCHEIE SYNDROME, AND HURLER–SCHEIE SYNDROME

Clinical presentation and epidemiology

Hurler syndrome is the most common and severe form of MPS I [13]. At birth, affected patients look normal, but later they develop symptoms characteristic of MPS of which hernias and hepatosplenomegaly are often the first clinical manifestations. Moreover, the disease is often diagnosed at the age of 9–18 months.

All types of MPS I are characterized by Hurler-like phenotypes: coarse grotesque facial features, or “gargoilism,” high forehead, broad eyebrows, synophrys, hypertelorism, a short saddle nose, full lips, macroglossia, a low-set ears, and a short neck (Fig. 1). In the skeletal system, there is dysostosis multiplex which includes changes in the skull (macrocephaly, often combined with hydrocephalus, thickening of the diploe), skeleton (wide clavicles, short and wide ribs

Fig. 1. Monozygotic twins with Hurler syndrome
Рис. 1. Монозиготные близнецы с синдромом Гурлера

located horizontally), spine (C2 hypoplasia, dysplasia of the thoracolumbar spine vertebrae with kyphosis; in severe forms kyphosis occurs at the age of 6–8 months, when the child begins to sit), limbs (short and wide diaphysis of tubular bones, dysplastic metaphyzes, flattened epiphyzes), hands (bullet-shaped phalanges), pelvis (rounded iliac wings, sloping acetabular roofs, *coxa valga*, dysplasia of the femoral heads), malformations of the lower extremities (*genu valgum*), and joint stiffness. Growth usually at the age of 2 and the height of patients usually does not exceed 110 cm. Involvement of the cardiovascular system in the form of hypertrophic cardiomyopathy and myxomatous degeneration of the valves is often observed. Due to GAG deposits in the interatrial and interventricular septa, arrythmias are often encountered. Patients are prone to frequent otitis media and respiratory infections due to narrowing of the upper and lower respiratory tracts as a result of thickening of the mucous membranes, accumulation of viscous secretions, and hypertrophy of the lymphoepithelial pharyngeal ring. Sleep apnea is a common complaint from parents. Furthermore, corneal opacity, and glaucomas are often encountered. Most children experiences difficulty in speaking due to developmental regression, hearing loss and macroglossia, and they have hoarse voices. Delay in psychomotor development in the first year of life is typical for children with Hurler syndrome, but development is progressive in the next six months. The child experiences a gradual regression of the acquired skills in the future, in the absence of therapy [1, 2, 5].

Death can occur from 1 to 12 years of age due to airway obstruction, respiratory infections, and heart failure.

Scheie syndrome, which was previously referred to as MPS V [51], is the mildest form of MPS I [13]. The diagnosis is often made late, at the age of 10–20 years. The typical phenotype usually develops after the age of 5 years [53]. Intellectual disorders are usually absent or mild despite the persistence of many external manifestations of Hurler syndrome. It is characterized by joint stiffness, corneal opacity, thickening of the mitral and aortic valves, and carpal tunnel syndrome that often develops in the form of numbness, tingling, or weakness of the fingers. The prognosis is favorable for life. In the middle age, patients may experience disabilities due to progressive joint damage (stiffness, contractures, degenerative and destructive changes in the joints), decreased visual acuity (corneal opacity), or cardiac surgery [9].

The Hurler–Scheie syndrome occupies an intermediate position in terms of disease progression and severity [13]. The main clinical manifestations are dwarfism, corneal opacity, joint stiffness, umbilical and inguinal hernias, recurrent hernias after hernia repair, dysostosis multiplex, hepatosplenomegaly, and moderate oligophrenia (a decrease in intelligence is registered in some patients). A detailed phenotypic presentation of the disease is formed at the age of 3–8 years. The prognosis for life is satisfactory [9, 53].

Rare cases of a "pseudo-deficiency" have been described where the activity of alpha-L-iduronidase is reduced, and the GAG metabolism remains within normal limits. At the same time, clinical manifestations of MPS I are not noted in carriers of "pseudo-deficient" alleles of the *IDUA* gene [72].

The incidence of MPS I is 1 per 100,000 newborns. The incidence is less in adults (1:500,000 newborns) [10].

Biochemical base of pathogenesis

Using monoclonal antibodies, was performed the immunoprecipitation of alpha-L-iduronidase from human liver; were explored the biochemical and catalytic properties of the enzyme, which functions in the cleavage of the terminal residues of alpha-L-iduronic acid from two GAGs, dermatan sulfate and heparan sulfate [31]. With insufficient catalytic activity of alpha-L-iduronidase in MPS I patients, abnormally high concentrations of GAGs accumulate in the lysosomes of all cells of mesenchymal origin, which explains the highly pleiotropic nature of the disease. The severity of the course of various forms of MPS I depends directly on the residual activity of the enzyme, which is almost completely absent in Hurler syndrome and can reach 5–7% compared with the norm in adult forms of the disease.

***IDUA* gene mapping and identification**

Somatic hybridization of the *IDUA* gene reveals that the alpha-L-iduronidase is located in the 4p16.3 region, which was further confirmed by *in situ* hybridization [60]. The *IDUA* gene consists of 14 exons distributed over an area of 19 kb of genomic DNA, with 13 kb being occupied by the huge intron 2 of this gene [60, 61]. The *IDUA* gene is expressed in many tissues (fibroblasts, liver, kidney, and placenta), thereby forming tissue-specific isoforms of the enzyme through alternative splicing.

Mutations in the *IDUA* gene

The spectra of mutations in the alpha-L-iduronidase gene in patients with Hurler and Scheie syndromes differ significantly. In the former, nonsense

mutations are most often identified, two of which (W402X and Q70X) are major ones [12, 59, 61, 62]. They are found in all European countries and together account for more than half of all known mutant alleles of the *IDUA* gene. However, their frequencies vary considerably, ranging from 37% and 35% in the North of Europe to 11% and 13% in Italy, respectively [25, 41]. Moreover, the W402X mutation is registered approximately 2.5 times more often than the Q70X mutation in the Netherlands and Germany (48% and 19%) and in the Scandinavian countries (17% and 62%). In the USA, the incidence of the W402X and Q70X mutations in the *IDUA* gene in patients with MPS I are 39% and 30% [48]. In Russia, the ratio of these frequencies is closer to that registered in the Scandinavian countries, namely 4% and 44%, respectively [12, 13].

Along with nonsense mutations in patients with Hurler syndrome, deletions with a shift in the reading frame and missense mutations (to a lesser extent) have been found. However, the frequency of one of the severe missense mutations, P533R, is about 3%. In a homozygous state, each of these three major mutations (W402X, Q70X, and P533R) occurred in patients with the most severe clinical forms of the disease. In this case, the activity of alpha-L-iduronidase is almost completely absent. Severe mutations, accompanied by premature translation termination, combined with other mutations could occur in patients with any forms of MPS I and even be detected in "pseudo-deficiency" conditions [67, 71]. For example, in one family, a sister of a patient with MPS I, who had no clinical manifestations of the disease, had a heteroallelic combination of the major nonsense mutation, W402X, and the missense mutation, A300T [18].

Missense mutations are frequent in Scheie and Hurler–Scheie syndromes. However, the first specific mutation identified in a patient with a typical Scheie syndrome presentation is a G-T transition in intron 5 of the *IDUA* gene. This creates an additional splice site, resulting in the insertion of additional five nucleotides into a specific mRNA [52, 62]. Such alteration is compatible with the formation of a small number of functionally active mRNAs, while the complete inhibition of the synthesis of alpha-L-iduronidase does not occur. Therefore, even in a compound with nonsense-type mutations, this splicing defect is implemented in the form of Scheie syndrome. In addition, several missense mutations in the *IDUA* gene have been identified in patients with Scheie syndrome. Thus, the Hurler and Scheie syndromes represent a classic example of phenotypic polymorphism due to the existence of allelic series [49].

In Japan, major European nonsense mutations were not revealed in most patients, but two other mutations in the IDUA gene were frequent (an insertion of five nucleotides 704ins5 and a missense mutation R89Q). They are registered with frequencies of 18% and 24%, respectively [78]. The 704ins5 mutation was found in Korean patients with MPS I [48]. Homozygotes for 704ins5 were detected in patients with Hurler syndrome, and the R89Q mutation in patients with Scheie syndrome.

Experimental models

Hereditary diseases of cats and dogs similar in clinical and biochemical manifestations to MPS I, have been described [64, 65]. The homologous canine alpha-L-iduronidase gene has been cloned, and molecular identification of a defect in this gene leading to enzyme deficiency in mutant animals has been performed.

The transgenic knockout line *Idua*–/– simulating Hurler syndrome was constructed by targeted disruption of the mouse *Idua* gene [29]. The (*Idua*–/–) mutants have no alpha-L-iduronidase activity, and increased urinary GAG levels. Starting at week 4, these animals show radiographic signs of dysostosis, which become evident by week 15. Progressive lysosomal accumulations first appear in reticuloendothelial cells, then in hepatocytes, chondrocytes, neurons, and tubular cells of the liver by Week 8, and later in all studied cells. In the cerebellum of mutant animals, a progressive loss of neurons was observed; in the brain tissues, the levels of GM2 and GM3 gangliosides were increased.

All these models are widely used not only to study the biochemical base of the MPS I pathogenesis, but also to develop specific treatment methods for this condition, such as bone marrow transplantation (BMT), immunosuppressive therapy, as well as enzyme replacement therapy (ERT), and gene therapy [27, 34, 45, 46, 79].

Laboratory diagnostics and treatment

Diagnosis of MPS I is based on data obtained from clinical examination, biochemical, and molecular genetic analysis of a patient. One of the earliest diagnostic signs of MPS I is considered to be an increased urinary excretion of GAG, first of all dermatan sulfate and heparan sulfate. To confirm the diagnosis and determine the clinical form of MPS I, an analysis of the enzymatic activity of alpha-L-iduronidase in the blood and mo-

lecular diagnosis of major (W402X, Q70X, P533R, G-T transition in intron 5) and other mutations in the *IDUA* gene are performed.

Various approaches to the treatment of patients with MPS I are being developed [11, 16]. One of the first tested methods is BMT from healthy HLA-compatible donors. The results of such treatment 54 children with MPS I, performed as part of a collaborative study of storage diseases, have been published [55]. For better compatibility of the transplanted tissues, all patients received high doses of chemotherapy with or without subsequent radiation. The 5-year survival rate after the procedure was 64%, and it turned out to be higher when the donors were siblings genotypically identical in the HLA-system compared with haploidentical donors. The mental development index of children after treatment, on average, was 78 if BMT was performed before 2 years of age (group 1), and 63 if BMT was performed later (group 2). In 64% of the surviving children in group 1 and only 25% of the children in group 2, the general development was close to normal or a little slowed down. Thus, allogeneic BMT performed before the age of 2 years can slow down or even prevent the development of severe clinical manifestations of Hurler syndrome. However, this procedure is not available to all patients, primarily due to the difficulty of finding compatible donors.

Alternative technologies could be cord blood transfusion from unrelated patients [32, 66] or hematopoietic stem cell transplantation [42, 70]. It has been revealed that these procedures can increase the patient's life expectancy if performed before the age of 2 years, but their success in preventing the development of neurological abnormalities depends significantly on the child's age [50, 56, 58, 68]. After such transplantations in patients younger than 9 months of age, their cognitive development and adaptive behavior remain within the normal range. However, MPS I is rarely diagnosed at this time. The Union of Pediatricians of Russia developed recommendations for the early detection of MPS patients [14]. In some countries, neonatal screening for MPS I is performed [30, 54] based on the levels of GAG and alpha-L-iduronidase in dried blood spots of newborns [47, 57].

Great efforts are aimed all over the world at the development of methods of gene therapy for MPS I. Various recombinant vectors for the targeted transfer of the normal human *IDUA* gene into mutant cells with alpha-L-iduronidase deficiency have been designed and tested in *in vitro* systems and in experimental models [35, 38]. In addition, successful clinical trials of gene therapy methods have been performed in many cases as many pathological parameters were adjusted [45]. However, improvements are registered not in all patients. In addition, gene therapy methods cannot prevent the development of severe disabling manifestations of MPS.

ERT of MPS I was more successful, as it is able to improve many neurological parameters [1, 2, 4, 36, 37], as well as treatment methods combining different approaches such as cell transplantation and ERT [45, 70]. Successful clinical trials of treatment of MPS I patients using the enzyme laronidase (Aldurazyme) after transplantation of hematopoietic stem cells have been performed [57].

Clinical example of a combination of BMT and ERT

A male patient was first time at the hospital at the age of 11 months. Clinical findings in this patient included delayed psychomotor development, deformation of the spine (kyphosis), noisy nasal breathing, sleep apnea, frequent purulent rhinitis, otitis media, hepatosplenomegaly.

Anamnestic findings: this boy was from the third pregnancy, which proceeded in a mother who presented with pyelonephritis, adnexitis, oligohydramnion, and ended in delivery at term. Birth weight was 4120 g, length was 56 cm, the head circumference was 37 cm, the chest circumference was 32 cm, and APGAR score was 7/8 points. Ultrasound examination (US) of the brain revealed no pathology.

Case history showed that a hepatomegaly was detected at the age of 1.5 months, which was confirmed by an abdominal US. Serum virology was performed for a group of hepatotropic viruses and showed negative results. Moreover, a noisy nasal breathing was noticed, and the child was examined by otolaryngologists. He received antibiotic therapy repeatedly for purulent rhinitis (8 episodes in the first year of life). At the age of 2 months, neurosonography for the first time revealed a slight expansion of the lateral and occipital horns of the lateral ventricles of the brain without impairment of cerebrospinal fluid circulation. Dehydrating therapy was administered. As from month 3, there was a delay in psychomotor development. At the age of 6 months, the boy was examined by a geneticist where an MPS II (Hunter disease) was suspected. The diagnosis was concluded to be unlikely. At the time of examination, the delayed psychomotor development, hepatosplenomegaly (liver +4 cm, spleen +1 cm from under the costal arch),

linear ear lobe creases, narrow palate, hernia of the white line of the abdomen, wide umbilical ring, hydrocele, and suspected neurosensory hearing loss were observed. Beckwith–Wiedemann syndrome was posed as the probable diagnosis, and he was closely monitored. At the age of 9 months, a 1–2-degree bilateral sensorineural hearing loss was observed. Grade 1–2 scoliosis of the lumbar spine and kyphosis of the thoracic spine were equally noticed.

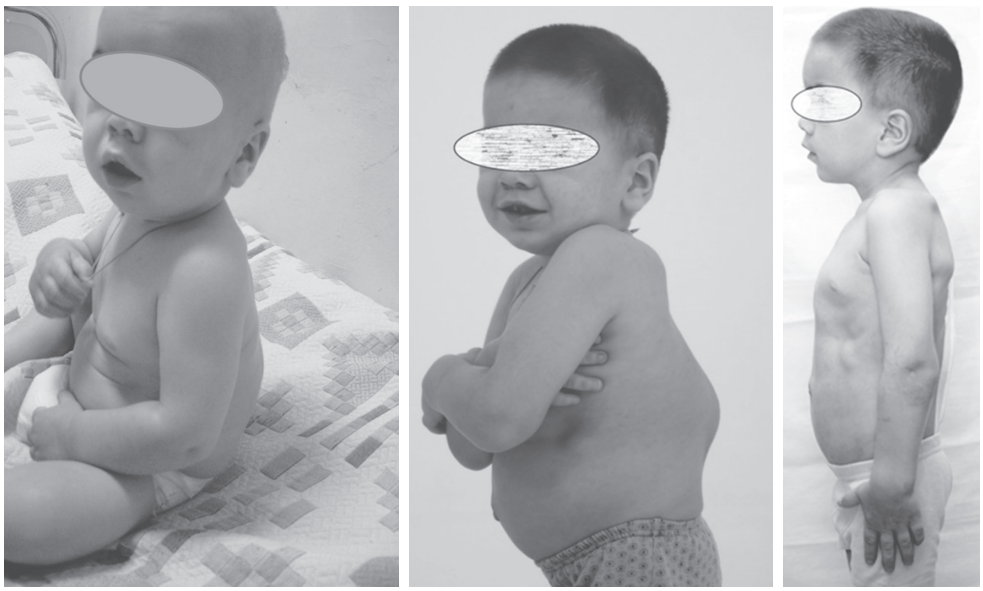
Due to multiple pathological changes in all organs and systems, the child was re-examined by a geneticist. A study of the activity of the enzymes, alpha-L-iduronidase and iduronate sulfatase, as the most common causes of MPS, was performed. Based on the results, the type I mucopolysaccharidosis was diagnosed (alpha-L-iduronidase activity 1.73 nM/mg for 18 hours in blood leukocytes, normal ranges 61.00–175.50), and was confirmed by molecular and genetic tests. Two nonsense mutations were revealed in the compound heterozygous state, characteristic of the severe phenotype of type I MPS (W47X/Q70X).

At the age of 11 months, his height was 78 cm, weight was 10.4 kg, and head circumference was 47.5 cm. Physical development was harmonious, with mesosomatotype. The patient could sit independently and walk with support. There was diffuse muscle hypotension. Hurler-like phenotype was registered, as well as corneal clouding; stiffness of small joints of the hands and the knee joints; and pronounced thoracolumbar kyphosis. Nasal breathing was difficult, with profuse mucous discharge from the nose. Heart sounds were sonorous, regular, with systolic murmurs along the left edge of the sternum. Hypotension of the muscles of the anterior abdominal wall was observed. Liver +4.5 cm from under the costal margin, spleen +1 cm. The abdominal ultrasound revealed hepatosplenomegaly; neurosonography showed triventriculomegaly; cerebrospinal fluid occlusion; echo-CG showed dilatation of the cavities of the heart (mostly the left ventricle), moderate hypertrophy of the interventricular septum; myocardial contractility was normal; with thickening of both cusps of the mitral valve, the movement of the cusps was hypokinetic. The diagnosis was: MPS I (Hurler syndrome). Delayed psychomotor and speech development; organic brain damage, internal hydrocephalus; a 1–2-degree bilateral sensorineural hearing loss; corneal clouding; secondary cardiopathy (left ventricular myocardial hypertrophy, degree 2 mitral valve insufficiency); hepatosplenomegaly.

To prevent the disease progression, as well as to improve the somatic state of the child during the search for a donor, ERT was initiated at a dose of 100 U/kg intravenously once a week with the drug Laronidase. The ERT was well tolerated. Infusion reactions on the administrations 7, 8, and 10 of the drug were vomiting and low-grade fever. The reactions were considered mild and did not require therapy discontinuation. Subsequently, premedication with prokinetics and antipyretic drugs was performed. Adverse reactions did not recur. ERT (8 months of therapy) resulted in the reduction of liver size (up to +1.5 cm from under the costal arch), normalization of spleen size, improvement of nasal breathing, disappearing of sleep apnea, as well as stabilization of heart disease.

At the age of 20 months, the patient underwent an allogeneic bone marrow transplant (BMT) from an unrelated donor. The transplantation was successful, and the graft was rejected on day 12. After BMT, the enzyme activity was within the normal range. The enzyme activity on day 102 after BMT was 118 nm/mg for 18 hours (norm 61–175.5 nm/mg), with urine GAG concentration of 31.2 nm/mM (norm 5.6–10.6 nm/mM).

Dynamics of the underlying disease showed progressive psychomotor development of the child: speech production (phrasal speech by 4.5 years), maintenance of normal liver and spleen sizes, normalization of motor skills in the fingers, stabilization of hearing loss and corneal clouding. There was a progression of kyphotic deformity in the thoracolumbar spine with narrowing of the spinal canal (the changes were verified by X-ray, computed tomography and magnetic resonance imaging), and appearance of mild spastic paraparesis. The indication for surgical treatment was a rapidly progressing severe spine deformity and an increase in the occurrence of neurological symptoms. In order to correct the defect the surgical treatment was performed. It was a posterior instrumental fixation of the thoracolumbar region with a multi-support transpedicular system. The postoperative period was uneventful. The muscle tonus of the lower extremities and exercise tolerance improved. The follow-up examination a year after treatment showed no progression in the deformity, a correct implant position, and stable neurological status. Photographs of the patient with type I MPS at the age of 11 months, 3 years and 5 months (before surgical treatment); 4 years and 5 months (result of surgical correction of deformity) are presented (Fig. 2).



a *b* *c*

Fig. 2. Boy with mucopolysaccharidosis type I in age: *a* – of 11 months; *b* – 3 years 5 months (before surgeon); *c* – in age of 4 years 5 months (after correction of spine deformity) [6]

Рис. 2. Мальчик с мукополисахаридозом I типа в возрасте: *a* — 11 мес.; *b* — в 3 г. 5 мес. (перед оперативным лечением); *c* — в 4 г. 5 мес. (результат оперативной коррекции деформации) [6]

MUCOPOLYSACCHARIDOSIS TYPE II, HUNTER SYNDROME

Clinical presentation and epidemiology

At birth, males with MPS II do not have any clinical manifestations of the disease. At the age of 2–4 years, they develop some craniofacial features such as full lips, large round cheeks, wide nose bridge, macroglossia, and macrocephaly in combination with hydrocephalus. Thickening of the vocal cords induces coarse voice. Corneal clouding is uncommon, although retinal degeneration sometimes develops. Patients are prone to frequent otitis media and respiratory infections. Umbilical and inguinal hernias, as well as hepatosplenomegaly are the early symptoms [7, 8].

Later the main clinical manifestations of MPS II are observed: grotesque facial features, multiple dysostosis in combination with dwarfism, hepatosplenomegaly, hypertrophic cardiomyopathy, and myxomatous degeneration of the valves, resulting in the development of cardiovascular insufficiency and a high risk of cardiac arrhythmias, excretion of large amounts of dermatan sulfate and heparan sulfate with urine. Some patients have a characteristic diagnostic sign, local ivory-white formations in the form of sea pebbles appear on the skin of the back or lateral surface of the thighs.

The Figure 3 shows the age-related phenotypic features of two brothers with Hunter syndrome.

MPS II is characterized by wide clinical polymorphism. There are two forms of the disease, a severe infantile form A with progressive mental retardation and a milder, adult form B, in which intelligence is usually not affected [51]. However, there is no clear boundary between these forms, and there is a continuous series of intermediate conditions. Form A in its clinical manifestations differs little from Hurler syndrome, although it develops more slowly. Progressive encephalopathy at the end of the disease leads to severe neurological symptoms, decreased motor activity up to complete immobility, cachexy, and lack of response to the environment. These patients are prone to chronic diarrhea. Severe diffuse coronary circulation insufficiency may develop. MPS II patients aged 10–15 years die most often from respiratory or heart failure [7, 8].

Form B MPS II is more similar to Scheie syndrome. The disease is usually diagnosed at the end of the first or at the second decade of life. Inguinal and umbilical hernias formed early, as well as damage to the cardiovascular system; gargoilism-like facial changes occur, as well as signs of dysostosis multiplex (Fig. 4), joint stiffness (Fig. 5), sensorineural hearing loss, retinopathy, possible obstruction of the airways, sleep apnea, and carpal tunnel syndrome [9]. The course of the disease is slowly progressive. Life expectancy varies widely. One of the typical

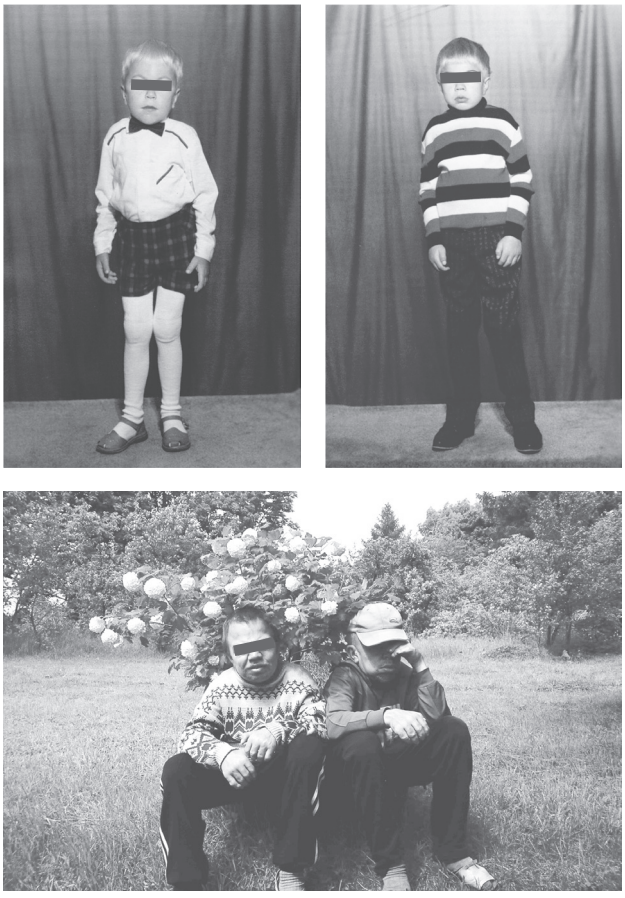


Fig. 3. Two brothers with Hunter syndrome at different ages
Рис. 3. Фенотип братьев с синдромом Хантера в разном возрасте

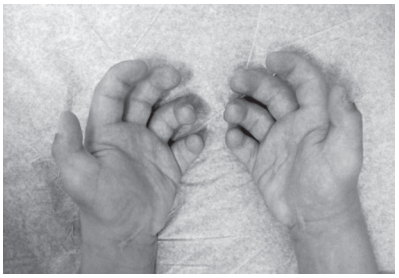


Fig. 4. Hands deformity in MPS II patients
Рис. 4. Поражение кисти при мукополисахаридозе типа II

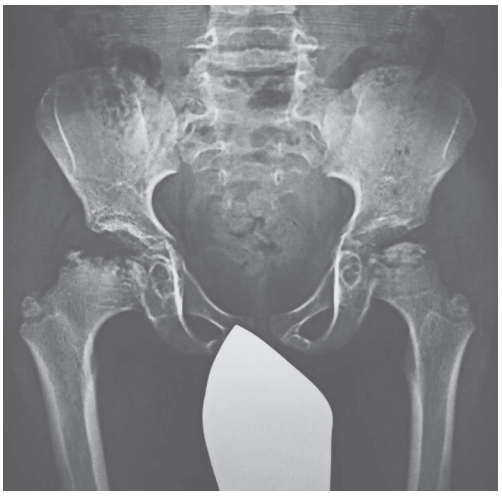


Fig. 5. Hip changes in MPS II patients
Рис. 5. Диспластические и дистрофические изменения тазобедренных суставов при мукополисахаридозе типа II

complications in older patients is narrowing of the tracheal lumen, leading to the need for stenting and/or tracheostomy. The respiratory or heart failure is the most common cause of early death of patients in the second or third decade of life.

In rare cases, Hunter syndrome is diagnosed in girls, while they usually have small heterozygous deletions in the long arm of the X chromosome in the Xq27-q28 region or X-autosomal translocations with break points localized in the same region of the X chromosome [28]. In such girls, the predominant inactivation of the normal X chromosome is registered [24]. The specific nature of lyonization is apparently due to late replication of the deleted or translocated X chromosome. To explain this phenomenon, the hypothesis of chromosomal imprinting is also used. At the moment, in the literature described ten girls diagnosed with Hunter syndrome. There are literature data on minimal manifestations.

The incidence of MPS II ranges from 1 per 100,000 to 1 per 170,000 newborn boys.

Biochemical base of pathogenesis

For the first time, iduronate 2-sulfatase was isolated in pure form from human liver, which enabled to study its biochemical and catalytic properties [20]. In the liver, kidneys, lungs, and placenta, the mature enzyme is represented by two main forms with molecular weights of 42 and 14 kDa. The mature forms of iduronate 2-sulfatase are formed by proteolytic cleavage of the precursor protein. The enzyme is very similar in amino acid sequence to human arylsulfatases A, B, and C and glucosamine 6-sulfatase.

The main function of iduronate 2-sulfatase consists in sulfate cleavage from the terminal 2-sulfoiduronic acid residue in two GAGs, dermatan sulfate and heparan sulfate. As a result of the deficiency of this enzyme in MPS II, the high concentrations of dermatan sulfate and heparan sulfate accumulate in the lysosomes of almost all cells, tissues,

and organs of patients. This explains the pleiotropic phenotype of the disease, that is, the simultaneous involvement of many systems and organs of the patient in the pathological process. The severity of the course of various forms of MPS II depends directly on the residual activity of the enzyme.

IDS gene mapping and identification

For the first time, the full-length cDNA of the iduronate 2-sulfatase (*IDS*) gene was isolated from a tissue-specific library of endothelial cell genes [74], which enabled to localize the *IDS* gene in the long arm of the X chromosome in the Xq28 region [75]. The gene consists of 9 exons distributed over an area of 24 kb [38, 75, 76]. The structure of the gene promoter indicates that it is expressed ubiquitously, so, it belongs to the housekeeping gene class. In the cytogenetic region of about 90 kb, located more along the telomere than the *IDS* gene, its pseudogene, designated *IDS2*, was identified [21, 39]. It has been revealed that the cytogenetic region of the *IDS2* pseudogene localization is involved in recombination with the IDS gene in approximately 13% of patients with Hunter syndrome.

Mutations in the IDS gene. In 20% of patients with Hunter syndrome, the *IDS* gene is completely or partially deleted, or is involved in other structural rearrangements [26, 43]. In about 13% of patients, mutations in *IDS* gene presented by inversions affecting the first 7 exons of the *IDS* gene. These rearrangements occur as a result of homologous recombination between the *IDS* gene and the *IDS2* pseudogene [22]. It has been detected that in this case the "hot spots" of recombination are highly homologous DNA sequences (98% homology) of about a thousand base pairs, located in the intron 7 of the *IDS* gene and distal to exon 3 of the *IDS2* locus, respectively.

In about 23% of patients with Hunter syndrome, relatively small intragenic rearrangements are identified – deletions or insertions that affect several nucleotides. In other cases, point missense or nonsense mutations are revealed in patients, as well as mutations that disrupt the splicing process.

The mutations identified independently in different populations include three nucleotide substitutions in codon 468 of exon 9 of the *IDS* gene, accompanied by amino acid substitutions (R468W, R468Q, and R468L) [33, 44, 72]. The major heterogeneity of mutations in the *IDS* gene complicates the molecular diagnostics of Hunter syndrome.

Experimental models

A natural experimental model of MPS II is labrador retriever males with hereditary iduronate 2-sulfatase deficiency [73]. This deficiency is due to mutations in the canine iduronate 2-sulfatase gene, which is homologous to the human *IDS* gene. Dogs have large heads with coarse features of the muzzle, macrodactyly, generalized osteopenia, progressive neurological disorder, unilateral retinal degeneration, and a positive urinary GAG test.

A transgenic knockout line of mice without iduronate 2-sulfatase activity in males, *Ids*-null, was created [40]. From week 4 of age and throughout life, mutant males showed increased urinary excretion of GAG and accumulation of GAG in tissues starting from week 7. Null mutants developed hepatosplenomegaly and enlargement of other organs. Other phenotypic features were coarse fur, sporadic alopecia, deformation of the dactyls, abnormalities in the development of the skull, decreased motor activity, and a significant reduction of the life expectancy. Histological examination revealed diffusely distributed foamy vacuolated cells in many organs.

These models can be used to study the molecular mechanisms of the pathogenesis of Hunter syndrome and conduct preclinical trials of therapies for this severe disease, including BMT, ERT, and gene therapy.

Laboratory diagnosis and treatment

Diagnosis of MPS II is based on data obtained from the patient's clinical examination, as well as biochemical and molecular genetic analysis. One of the earliest diagnostic signs of MPS II is an increased urinary excretion of GAG, dermatan sulfate and heparan sulfate. To confirm the diagnosis, an analysis of the enzymatic activity of iduronate 2-sulfatase in leukocytes or dried blood spots is performed, as well as molecular analysis of extended deletions, inversions, and other mutations in the *IDUA* gene.

During retroviral transduction of the cDNA sequence of the *IDS* gene into lymphoblastosis cell lines of patients with Hunter syndrome, the metabolic defect was corrected [23]. The expression level of iduronate 2-sulfatase in transduced cells was very high, exceeding the norm by 10–70 times. It has been established that the recombinant enzyme is actively involved in GAG metabolism. These studies can be considered as an initial step in the development of MPS II gene therapy programs.

The results of BMT performed in ten patients with Hunter syndrome have been published [69].

Only three of them survived more than 7 years after the transplantation, and one of them died 11 years after the procedure. This occurred most probably due to poor selection of donors. In one of the surviving patients, the mental capacity was fully preserved, but there was a slight delay in physical development. Currently, BMT in MPS II is not used in Russia, but there are recommendations of the Association of Medical Geneticists for performing BMT in severe MPS II variants associated with missense mutations [15].

In the USA and some European countries, the drug idursulfase (recombinant human iduranate 2-sulfatase), or Elaprase, proposed for the treatment of Hunter syndrome, has been licensed and clinically tested [77]. Equally, Hunterase is also successfully used in the world and in Russian practice. Both drugs are registered in the Russian Federation. It is possible to switch from one drug to the other in case of intolerance and/or severe allergic reactions in patients. With the early start of ERT, an improvement in many pathological manifestations of the disease is guaranteed. The sizes of the liver and spleen are normalized, the degree of cardiovascular involvement are stabilized, and the range of motion in the affected joints are increased [2, 3]. To relieve intravenous infusion in MPS patients, implantable venous systems can be used, which facilitate significantly venous access [17]. But the disadvantage of Elaprase consists in that it does not penetrate the blood-brain barrier. To overcome this difficulty, the drug was modified by adding specific antibodies (AGT-182). The results of treatment of MPS II patients using this modified drug are still unknown. Hematopoietic stem cell transplantation in patients with MPS II also proves to be successful only with early diagnosis at the age of 2 years or earlier [19, 63].

Substrate-reducing therapy based on suppression of GAG production may be promising for treatment of types I and II MPS. For this purpose, the drug Genistein (Soyfem) was developed, which showed good results on experimental models. With an early start of treatment in animals, it was possible to stop the destruction of cells of the central nervous system.

Some of the first patients in Russia who received ERT for MPS I also received Genistein. The drug is well tolerated, but often leads to excess weight as it is analogous in structure to female sex hormones. It is the drug of choice for MPS III, for which there is currently no drug available for ERT.

Currently, about 80 patients with types I and II MPS are receiving treatment in Russia. Most of them are undergoing life-long ERT, and 25 patients have undergone BMT. Due to the high cost of the drugs that must be administered to patients on a weekly basis, the expenses are incurred by the state for the treatment of orphan diseases. Thus, the cost of one bottle of Elaprase ranges from 175 to 185 thousand rubles. For the treatment of one patient with Hunter syndrome, 300–500 thousand rubles are required weekly. Nevertheless, there is no doubt that in the coming years, alternative therapeutic approaches in the prevention and treatment of MPS patients as well as cheaper methods for the production of new and better drugs will be developed.

Mucopolysaccharidoses of types I and II currently occupy a significant niche in the range of orphan diseases. Despite the rarity of the pathology, knowledge about these diseases is relevant for primary care physicians to facilitate early diagnosis which is an important stage in the therapy; thus, improving the long-term results and quality of life of MPS patients.

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