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LYSOSOMAL STORAGE DISEASES. MUCOPOLYSACCHARIDOSIS TYPE III, SANFILIPPO SYNDROME

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The review describes the clinical, biochemical and molecular genetic characteristics of autosomal recessive mucopolysaccharidosis type III, or Sanfilippo syndrome. This is a genetically heterogeneous group of rare, but similar in nature, diseases caused by a deficiency of one of the four lysosomal enzymes involved in the degradation of heparan sulfate. All types of mucopolysaccharidosis III are characterized by severe degeneration of the central nervous system in combination with mild somatic manifestations, which is explained by the accumulation of high concentrations of heparan sulfate in the lysosomes of various cells, including the central nervous system. The primary biochemical defect in the most common type of mucopolysaccharidosis IIIA, occurring with a frequency of $1 : 10^5$ and presented in 60% of all cases of the disease, is heparan-N-sulfatase, or sulfamidase deficiency. Mucopolysaccharidosis IIIB type occurs twice less often and accounts for about 30% of all cases of Sanfilippo syndrome. It is caused by the presence of inactivating mutations in the lysosomal α-N-acetylglucosaminidase gene. Mucopolysaccharidosis IIIC and IIID are 4% and 6%, and occur at frequencies of 0.7 and $1.0 : 10^6$. Mucopolysaccharidosis IIIC is caused by inactivating mutations in the gene of membrane-bound lysosomal acetyl-CoA:α-glucosaminid-N-acetyltransferase, or N-acetyltransferase. Mucopolysaccharidosis IIID is based on the deficiency of lysosomal N-acetylglucosamine-6-sulfatase. The role of experimental models in the study of the biochemical basis of the pathogenesis of Sanfilippo syndrome and the development of various therapeutic approaches are discussed. The possibility of neonatal screening, early diagnosis, prevention and pathogenetic therapy of these severe lysosomal diseases are considered. As an example, a clinical case of diagnosis and treatment of a child with type IIIB mucopolysaccharidosis is presented.

Keywords: review; lysosomal storage disorders; mucopolysaccharidosis type III; pathogenesis; diagnostics; therapy.

ЛИЗОСОМНЫЕ БОЛЕЗНИ НАКОПЛЕНИЯ. МУКОПОЛИСАХАРИДОЗ III ТИПА, СИНДРОМ САНФИЛИППО

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Обзор посвящен клинической, биохимической и молекулярно-генетической характеристике аутосомно-рецессивного мукополисахаридоза III типа, или синдрома Санфилиппо. Это генетически гетерогенная группа редких, но сходных по характеру течения заболеваний, обусловленных дефицитом одного из четырех лизосомных ферментов, участвующих в деградации гепарансульфата. Все типы мукополисахаридоза III типа характеризуются тяжелой дегенерацией центральной нервной системы в сочетании с мягкими соматическими проявлениями, что объясняется накоплением высоких концентраций гепарансульфата в лизосомах различных клеток, в том числе и центральной нервной системы. Первичный биохимический дефект при самом распространенном типе мукополисахаридоза IIIA, встречающийся с частотой $1 : 10^5$ и составляющий около 60 % всех случаев заболевания, — это недостаточность гепаран-N-сульфатазы, или сульфамидазы. Мукополисахаридоз типа IIIB

встречается в 2 раза реже и составляет около 30 % всех случаев синдрома Санфилиппо. Он обусловлен присутствием инактивирующих мутаций в гене лизосомной α-N-ацетилглюкозаминидазы. Мукополисахаридоз IIIC и IIID составляют 4 и 6 % и встречаются с частотой 0,7 и 1,0 : 10^6 соответственно. Причиной мукополисахаридоза IIIC являются инактивирующие мутации в гене мембраносвязанной лизосомной ацетил-КоА:α-глюкозаминид-N-ацетилтрансферазы, или N-ацетилтрансферазы. В основе мукополисахаридозы IIID лежит недостаточность лизосомной N-ацетилглюкозамин-6-сульфатазы. Обсуждается роль экспериментальных моделей в изучении биохимических основ патогенеза синдрома Санфилиппо и разработке различных терапевтических подходов. Рассматривается возможность неонатального скрининга, ранней диагностики, профилактики и патогенетической терапии этих тяжелых лизосомных болезней. В качестве примера представлен клинический случай диагностики и лечения ребенка с мукополисахаридозом типа IIIB.

Ключевые слова: обзор; лизосомные болезни накопления; мукополисахаридоз III типа; патогенез; диагностика; терапия.

Previous issues of the journal presented a classification of lysosomal storage diseases [2] and a more detailed description of types I and II mucopolysaccharidoses (MPS) [4]. This article continues the description of MPS and presents the characteristics of MPS type III or Sanfilippo syndrome. This is a genetically heterogeneous MPS group consisting of four autosomal recessive diseases, types IIIA, IIIB, IIIC, and IIID. These diseases are caused by a deficiency of various lysosomal enzymes involved in heparan sulfate degradation. The primary biochemical defect in the MPS IIIA type is heparan-N-sulfatase or sulfamidase deficiency [1, 3, 14]. Also, type IIIB MPS is caused by the presence of inactivating mutations in the lysosomal α-N-acetylglucosaminidase gene [53, 54]. However, type IIIC MPS is caused by inactivating mutations in the gene of membrane-bound lysosomal acetyl-CoA:α-glucosaminide-N-acetyltransferase or N-acetyltransferase [21]. The deficiency of lysosomal N-acetylglucosamine-6-sulfatase underlies MPS IIID [24].

MPS IIIA is registered with a frequency of 1:100,000 and accounts for approximately 60% of all disease cases. The second most frequent (1:200,000) is MPS IIIB, accounting for about 30% of all cases of Sanfilippo syndrome. Finally, MPS IIIC and IIID are 4% and 6%, respectively, and are registered with a frequency of 0.7 and $1.0:10^6$, respectively [6].

Clinical presentation and epidemiology

The disease is characterized by severe central nervous system (CNS) degeneration with mild somatic manifestations. Children do not have abnormalities at birth, and unlike other MPS forms, they rarely have hernias. In year 2 of their life, there may be slight mental retardation, which is rarely given a diagnostic value. Usually, disease onset is registered at 2–6 years with a change in behavior, such as hyperactivity, aggressiveness, pronounced mental retardation, developmental speech delay, and sleep disturbance combined with relatively mild somatic signs, such as wide thick eyebrows (synophrys is possible), coarse hair, hirsutism, moderate hepatosplenomegaly, minimal changes in heart valves, and frequent infections of ear, nose, and throat organs [7]. The most notable aspects of the phenotype are manifested in fair-haired children with thick, dark eyebrows. Sanfilippo syndrome is manifested by progressive dementia, hyperactivity with signs of aggressive behavior, severe sleep disturbances (night sleep less than 2 h), progressive sensorineural hearing loss, mild skeletal abnormalities characterized by radiographically biconvex vertebrae, thick cranial vault, hydrocephalus accompanied by ventriculomegaly, and possible development of femoral head necrosis. Also, signs of cerebral cortex atrophy are noted on computed tomography, and patients rarely develop independent speech, and sometimes it is entirely absent. As the disease progresses, mental retardation progresses, patients lose their previously acquired skills, and most develop seizures. At 6–10 years, severe degradation develops with the loss of social skills and possible self-service. Additionally, there is a decrease in motor activity at the disease's terminal stage up to complete immobility, cachexia, and a lack of response to the environment. Notably, death occurs in the second or third decade of life from progressive encephalopathy [5, 6, 11].

The literature describes adult patients with mild MPS III, mild cognitive impairment, and normal intelligence. Thus, 12 patients with MPS III (11 with MPS IIIA and 1 with MPS IIIB) were selected from three expert centers for lysosomal storage diseases, with an average age at diagnosis of 43 years [35]. In this group of patients, primary manifestations at disease onset were retinal dystrophy in two cases, cardiomyopathy in one case, and decreased intelligence in one case; some patients were identified based on the results of family screening. Further-

more, in 9/12 cases, cognitive impairment was not diagnosed, on average, by the age of 47 years (19–74 years).

There is an accumulation of high heparan sulfate concentrations in the lysosomes of almost all body cells with all types of MPS III. This explains the simultaneous involvement of many systems, organs, and tissues in the pathological process and similar nature of various genetic variants of Sanfilippo syndrome. A characteristic diagnostic sign of all MPS III types is increased urinary excretion of heparan sulfate and other glycosaminoglycans (GAGs). Simultaneously, cases of false-negative results in determining GAG in urine are often registered, requiring repeated analysis of GAG excretion and enzymatic diagnostics with an appropriate clinical presentation [15]. Early MPS III diagnosis are based on studying a combination of clinical and biochemical manifestations of the disease [21]. However, the most objective differential diagnosis of various types of Sanfilippo syndrome is possible only with data from biochemical and molecular genetic analysis.

The highest incidence of Sanfilippo syndrome is registered in Germany and the Netherlands (1:20,000 and 1:24,000, respectively) [11, 39, 46]. Also, approximately half of 73 MPS III patients studied in the Netherlands had type IIIA, 30% had type IIIB, and 19% had type IIIC. In Australia, the incidence is 1:56,000–58,000 newborns [49], and in other populations, the incidence of Sanfilippo syndrome does not exceed 1:300,000 newborns [32].

Furthermore, Sanfilippo A syndrome is the most severe and common MPS III type [6]. It is characterized by an earlier onset of the disease with rapid symptoms and a shorter life expectancy. However, type B is clinically considered the most polymorphic, and regarding severity, Sanfilippo C syndrome occupies an intermediate position between MPS IIIA and IIIB (a rarer type of disease). The incidence of MPS IIIC in Australia, the Netherlands, and Portugal is estimated at 0.07, 0.12, and 0.21 per 100,000 newborns, respectively [22]. Finally, Sanfilippo D syndrome is the rarest type of MPS III.

Biochemical aspects of MPS III pathogenesis

Sulfamidase, defective in MPS IIIA, is the first enzyme involved in heparan sulfate degradation. It cleves sulfate from the amino group of the terminal glucosamine residue in the heparan sulfate molecule [29]. As a result, α-glucosaminide residues are formed, separated into two stages. First, their N-acetylation occurs in the presence of acetyl-CoA:α-glucosaminide-N-acetyltransferase, which is deficient in MPS IIIC. Then, these residues are hydrolyzed under the action of α-N-acetylglucosaminidase, absent in patients with MPS IIIB. In type IIID, N-acetylglucosamine-6-sulfatase is defective and involved in releasing sulfate from N-acetylglucosamine-6-sulfate bonds in heparan sulfate-derived oligosaccharides. Mature sulfamidase consists of 482 amino acids containing five potential N-glycosylation sites.

Alpha-N-acetylglucosaminidase, defective in MPS IIIB, catalyzes the cleavage of terminal N-acetylglucosamine in the heparan sulfate molecule. Also, a mature protein with a molecular weight of approximately 80 kDa consists of 720 amino acids [54].

The primary function of acetyl-CoA: α-glucosaminide-N-acetyltransferase, also called N-acetyltransferase, which is defective in MPS IIIC, acetylates the amino group of the terminal glucosamine residue in the heparan sulfate molecule after desulfation with sulfamidase and before hydrolysis with alpha-N-acetylglucosaminidase. Furthermore, it is the only lysosomal enzyme that does not function as a hydrolase. The reaction can be divided into two parts: enzyme acetylation and the transfer of the acetyl group to glucosamine. Acetyl-coenzyme A (acetyl-CoA) is the donor of the acetyl group in this reaction; however, it is unlikely that this cofactor can exist stably in the acidic and hydrolytic medium of lysosomes. N-acetyltransferase enables cells to use the cytoplasmic cofactor to degrade heparan sulfate without transferring an intact molecule across the lysosomal membrane. Thus, the substrate and cofactor are separated with a lysosomal membrane; membrane-associated proteins are challenging to obtain in pure form. N-acetyltransferase is assumed to be a dimer consisting of two subunits with a molecular weight of 120 kDa containing asparagine-linked oligosaccharides [21]. Moreover, only one of these subunits has catalytic properties.

N-acetyltransferase has no structural similarity to any other known prokaryotic or eukaryotic acetyltransferases. Therefore, the enzyme is assumed to belong to a new structural class of proteins capable of transporting activated acetyl residues across the cell membrane. It is a transmembrane protein with an estimated molecular weight of 73 kDa and 656 amino acids, including an N-terminal signal peptide. The protein contains four N-glycosylation sites and 11 transmembrane domains. According to topological modeling, the N-terminal region of this protein is located in the lysosome, and the C-terminal region is located inside the cytoplasm.

Lysosomal N-acetylglucosamine-6-sulfatase, which deficiency underlies MPS IIID, catalyzes sulfate

elimination from the carbon atom 6 of the terminal glucosamine residue in the heparan sulfate molecule [30]. Although N-acetylglucosamine-6-sulfate is part of heparan sulfate and keratan sulfate, in this disease, only heparan sulfate degradation is impaired since β-hexosaminidase A bypasses the block in keratan sulfate degradation. Also, isolation and purification of N-acetylglucosamine-6-sulfatase from the human liver enabled the determination of the enzyme structure and its catalytic properties [24]. Four isoforms of the enzyme have been identified, presumably differing like the large subunit processing. N-acetylglucosamine-6-sulfatase with a molecular weight of 72 kDa is homologous to steroid sulfatases [40]. In addition, the enzyme contains several N-glycosylation sites and a hydrophilic region rich in basic amino acids, where an internal proteolytic cleavage site can be located. During processing, the primary protein product of the gene is split into two subunits: the N-terminal one with a molecular weight of 32 kDa and the C-terminal one with a molecular weight of 48 kDa.

Mapping and identification of *SGSH*, *NAGLU*, *HGSNAT*, and *GNS* genes

The full-length cDNA of the sulfamidase gene (*SGSH*) was isolated from a tissue-specific library of human kidney genes using synthesized oligonucleotide probes [43]. Also, the *SGSH* gene was mapped in the 17q25.3 region by fluorescence *in situ* hybridization. It consists of eight exons distributed over 11 kb of genomic DNA [28]. The *SGSH* gene is expressed in all tissues to form three alternatively spliced transcripts (3.1, 4.3, and 7.1 kb).

The full-length cDNA of the alpha-N-acetylglucosaminidase (*NAGLU*) gene was isolated from various tissue-specific human gene libraries using synthesized oligonucleotide probes [48, 54]. Also, the *NAGLU* gene is located in the 17q21.2 region and consists of six exons distributed over an area of 8.3 kb of genomic DNA.

Genome-wide scanning was performed using cytogenetic index markers and evenly distributed over all chromosomes in 31 families from ten countries. In the 44 patients with Sanfilippo C syndrome, the *HGSNAT* gene of lysosomal acetyl-CoA: α-glucosaminide-N-acetyltransferase is localized on chromosome 8 [10]. Using positional cloning, a coding sequence was isolated from an interval of 2.6 cM (centiMorgan), located between the two nearest markers surrounding the desired gene, which the authors named *TMEM76* [48]. Also, proteomic studies of murine lysosomal membrane proteins revealed an unknown protein homologous to the human protein encoded by the *TMEM76* gene [21]. The full-length expression sequence, *Tmem76*, was isolated, encoding this unknown murine protein. After administering the murine *Tmem76* sequence into the cultured fibroblasts of patients with MPS IIIC, a correction of the enzymatic defect inherent in patients' cells was noted. Thus, *Tmem76* performs the functions of lysosomal acetyl-CoA: α-glucosaminide-N-acetyltransferase, and the genes, *TMEM76* and *HGSNAT*, are identical. The expressed murine *Tmem76* sequence was used to screen tissue-specific human gene libraries and isolate full-length cDNA. Furthermore, the *HGSNAT* gene is located in the 8p11.1 region and contains 18 exons [21]. It is ubiquitously expressed with two mRNAs of 4.5 and 2.1 kb and spliced alternatively with the formation of a deleted protein isoform lacking 64 amino acids in transmembrane domains 3 and 4. This is due to the alternative excision of exons 9 and 10 from mRNA [48], and this protein isoform appears to be catalytically inactive.

Using the data on the amino acid sequence of N-acetylglucosamine-6-sulfatase, oligonucleotide probes were constructed using the cDNA of the *G6S* gene (referred to as *GNS*), isolated from a tissue-specific library of human liver genes [40]. First, the isolated cDNA was used as a probe for mapping the *GNS* gene in the 12q14 region by *in situ* hybridization [38]. Subsequently, the data were confirmed by somatic hybridization. The *GNS* gene contains 14 exons.

Mutations in genes *SGSH*, *NAGLU*, *HGSNAT*, and *GNS*

In patients with MPS IIIA, missense mutations in the *SGSH* gene are often revealed [16, 43], and the R245H substitution is the most frequent and has been repeatedly identified in different populations [14]. Its frequency in patients with Sanfilippo A syndrome is 31% in Australia, 19% in the USA, and exceeds 50% in the Netherlands [34, 41]. Differences in the range and frequencies of mutations in the *SGSH* gene are registered in European populations [49]. Thus, the incidence of the R245H mutation in German patients reaches 35%, whereas, in Polish patients, it is found only in 3% of cases. The missense mutation, R74C, which changes the evolutionarily-conserved amino acid in the active site of sulfamidase, accounts for 56% of all mutant alleles in patients of Polish origin, whereas it is only 21% in German patients. In Italy, the S66W substitution is frequent, accounting for 33% of all mutant alleles of the *SGSH* gene [18]. Furthermore, all six patients from Sardinia had this mutation,

and it was in a homozygous state in five of them, indicating its common ancestor. Mutations with high frequencies in various populations, such as R245H, Q380R, S66W, and 1080delC, are associated with the classic severe phenotype [45, 46]. Simultaneously, the S298P mutation in a homozygous or compound heterozygous state is more often registered in patients with a milder course of MPS IIIA, long-term preservation of psychomotor functions, and a longer life expectancy.

Furthermore, in patients with MPS IIIB, missense mutations in the *NAGLU* gene are most often registered. A frequent missense mutation replaces arginine with cysteine at position 674 of the enzyme [50, 55]. Mutations with premature translation termination, nonsense type, and minor deletions and insertions accompanied by a shift in the reading frame have also been described. Additionally, two mutations, R643C, associated with a milder clinical phenotype, and R297X, account for about 20% of all mutant alleles in Danish patients. Each of the four mutations (R297X, P521L, R565W, and R626X) occurs in Australian patients with frequencies of approximately 6%. Sanfilippo B syndrome is the most common MPS III type in Portugal [33]. This is due to the spread in this population because of the founder effect of the R234C missense mutation, making up approximately 32% of all mutant alleles in this population. Also, haplotype analysis showed that this mutation is of relatively recent origin.

Furthermore, many studies have noted the heterogeneous nature of mutations in the *HGSNAT* gene and the absence of a correlation between the genotype and nature of the course of MPS IIIC [21, 22, 26]. Specific mutations in the *HGSNAT* gene are common in some populations. Thus, in patients with MPS IIIC from Spain and Morocco, two structural mutations (372–2A-G and 234+1G-A) are common [17]. However, in Denmark, the incidence of two missense mutations, R344C and S518F, is 22% and 29%, respectively [41].

All mutations identified in the *GNS* gene in patients with the rare Sanfilippo D syndrome are accompanied by premature translation termination. In addition, these mutations were found in patients only in a homozygous state [19, 27]. Therefore, these are two nonsense mutations and three minor structural rearrangements, accompanied by a shift in the reading frame.

Experimental models

Heparan sulfate sulfatase deficiency due to homozygous deletion of three nucleotides in a canine gene homologous to human *SGSH* has been described in two adult Wirehaired Dachshund littermate dogs [9, 23]. At the age of 3 years in both dogs, ataxia of the hind limbs was noted, gradually progressing over 1–2 years to generalized spinocerebellar ataxia. Simultaneously, cognitive abilities of the dogs remained within the normal range. However, according to the results of the CNS examination, moderate atrophy of the cortical layer and dilatation of the brain's lateral ventricles were revealed. Additionally, a positive urinary GAG test, accumulation of heparan sulfate in many tissues, and a decrease in sulfamidase activity in fibroblasts and liver of sick dogs indicate that these animals are adequate models of MPS IIIA in humans.

Furthermore, a genetic line of mice with a spontaneously emerging D31N missense mutation in the *SGSH* gene has been described [12]. Mutant mice die at about 10 months after age and develop hepatosplenomegaly and bladder distension. Histological preparations of the brain show large lysosomes with accumulations of heparan sulfate. Also, sulfamidase activity in the brain, liver, and kidney extracts is reduced, and when studying the behavior of mutant animals, a decrease in locomotor activity is registered at the age of 3 weeks [25]. Other behavioral abnormalities related to gait, pain sensitivity, and response to geotaxis appear after week 15 of life. The order of appearance of these behavioral anomalies sheds light on the chronology of the pathological changes in the brains of diseased mice and the rate of axonal degeneration.

Reports have revealed that the fusion of autophagosomes and lysosomes is disrupted in the brain cells of mutant mice. The ability to degrade aggregated proteins is reduced, the accumulation of ubiquitin-positive inclusions, and an increase in the number of nonfunctional mitochondria were noted [44]. Similar abnormalities have also been revealed in the mouse model of multiple sulfatase deficiency. Furthermore, the authors suggest that autophagy impairment is a common mechanism of neurodegenerative processes in lysosomal storage diseases.

The creation of a transgenic line of mice with an inactivated *NAGLU* gene greatly influenced the understanding of molecular mechanisms of MPS IIIB pathogenesis [31, 35]. (*NAGLU*–/–) mutants are fertile and born without visible phenotypic abnormalities. However, their life expectancy is reduced to 8–12 months, whereas massive accumulations of heparan sulfate are noted in their liver and kidneys. A secondary decrease in the activity of some other lysosomal enzymes occurs along with the complete absence of alpha-N-acetylglucosaminidase activity. Many cells of mutant animals, such as macrophages,

epithelial cells, and neurons, are vacuolated, and these changes increase progressively. There are large pleiomorphic inclusions in vacuoles, along with accumulations of GAGs, which are especially noticeable in brain neurons. Hyperactive behavior of mutants is manifested from the age of 4–5 months. Thus, mice strain with an inactivated *NAGLU* gene is an adequate MPS IIIB model, actively used to develop therapeutic methods for this severe disease [35].

In neurons, along with heparan sulfate, unrelated metabolites accumulate, including the C subunit of mitochondrial adenosine triphosphate synthase (SCMAS), which is detected by peptide fingerprinting [42]. However, this contrasts somatic cells of mutant mice, which predominantly accumulate heparan sulfate. Additionally, GM3-ganglioside accumulates in the lysosomes of microglial cells. In the preparations used for cryoelectron microscopy and prepared further for standard electron microscopy, SCMAS disappears. Still, in the same places, "zebra-bodies" appear, which are known but insufficiently studied inclusions in the brain of MPS patients.

Laboratory diagnostics and treatment

Currently, for diagnosing Sanfilippo syndrome in children with clinical MPS manifestations, at stage 1, GAG levels in the urine are determined, and their qualitative assessment is performed. If abnormal GAG excretion is detected, enzymatic diagnostics are performed at the next stage to determine the MPS III type. The confirmation test identifies mutations in one of the genes *SGSH, NAGLU, HGSNAT*, or *GNS* [5, 8].

An important aspect of care to pediatric patients with MPS III is symptomatic therapy, including psycho-pedagogical and drug correction of behavior, rehabilitation techniques, physiotherapy, and surgical care [6, 37].

Many medical centers have used different approaches for the pathogenetic treatment of MPS III, such as hematopoietic stem cell transplantation, substrate reduction therapy, and much more promising enzyme replacement and gene therapy methods using adeno-associated or lentiviral vectors [36, 47, 51]. Some of these approaches have been successfully tested in preclinical trials.

Substrate-reducing therapy for MPS III is based on soy preparation (Soyfem, or genistein), and the main effect is to reduce GAG synthesis. Genistein [4',5,7-trihydroxyisoflavone or 5,7-dihydroxy3 (4-hydroxyphenyl)-4*H*1-benzopyran4-one] is a plant estrogen. Follicle-stimulating hormone or epidermal growth factor (EGF) is required to synthesize heparan and dermatan sulfate. EGF triggers a cascade of reactions leading to GAG synthesis, and genistein inhibits this factor, thus reducing GAG production. The efficiency of this method was demonstrated in a study on cell cultures of fibroblasts from MPS patients. As a control group, fibroblasts from MPS patients who received enzyme replacement therapy with α-L-iduronidase were used. Consequently, similar results were obtained, as GAG levels decreased in both cases [38]. In addition, some patients noted a pronounced increase in body weight while taking the drug.

A promising drug for enzyme replacement therapy for MPS IIIA is a genetically engineered recombinant sulfamidase, with the same kinetic properties as the native enzyme [13]. In cell culture, recombinant and native sulfamidases function as a 115 kDa dimer consisting of major and minor subunits with molecular weights of 63 and 57 kDa, respectively, and identical N-terminal residues. Their endocytosis in the culture of fibroblasts from patients with MPS IIIA is implemented using mannose 6-phosphate receptor [52].

Furthermore, experimental therapies are being developed based on mRNA strategy and gene editing. However, MPS III treatment efficiency using any strategy is determined by the early diagnosis of the disease before severe neurological disorders. Therefore, recently, in many laboratories worldwide, much attention has been paid to developing algorithms for the early MPS III diagnosis [20] and creating new screening programs for detecting the disease during the neonatal period or in the first year of life [51, 52].

Description of the clinical case of MPS IIIB

The anamnesis presented a girl from the first pregnancy, which proceeded without complications and first-term birth. There was a premature rupture of membranes. At birth, weight was 3050 g, length was 48 cm, and Apgar score was 8/9 points. On day 1 of life, respiratory failure was gradually developed; she was transferred to the neonatal pathology unit at day 4 of life. Hypoxic-ischemic encephalopathy of mixed genesis, syndrome of motor disorders, vegetative-visceral syndrome, and subacute period was diagnosed. Concomitant diagnosis was hemolytic disease of newborns according to the Rh factor, mild course, anemic form, early neonatal hypoglycemia, hymomegalia, and open foramen ovale.

In the first month of life, neurosonography revealed induration of the periventricular zones, and the neurosonography presentation was normalized

by three months. During the examination at the age of 1 month, large facial features were noted (Fig. 1)

Up to the age of 1 year, psychomotor development corresponded to the age; the patient started walking at 11 months. At 1 year 9 months, the girl's mother noted her increased moodiness and disturbed night sleep. Clinician-observed findings were a hydrocephalic head (circumference 50 cm), slight asymmetry of the nasolabial folds, and ingrown eyelashes. The neurologist concluded on the residual organic lesion of the CNS, hypertensive-hydrocephalic syndrome, and syndrome of movement disorders. At 2 years, adenotomy was performed, and at 2 years 2 months, the patient was examined by a neurologist, who revealed speech as separate words (about ten words), a good understanding of speech, but communication only with her mother. The neurologist concluded on motor alalia in the presence of residual organic lesions of the CNS. At 2.5 years, the vocabulary was about 20 words, with absent phrasal speech. The patient was motorically awkward; she often stumbled and fell. At the age of 2 years 11 months, regression of speech development (not speaking) was registered, and partial understanding of addressed speech, reappearance of disturbances in night sleep, and her self-care skills were partially developed. At 3 years old, she had objectively rough facial features, wide eyebrows, broad hands, but joint contractures were not revealed (Fig. 2).

At the age of 3 years 9 months, the girl was examined by a geneticist for the first time. MPS diagnosis was suspected and confirmed based on increased urinary GAG excretion (increased excretion of heparan sulfate) and the phenotype typical of the disease. Furthermore, enzymatic diagnosis was performed and revealed a deficiency of N-acetyl-α-D-glucosaminidase of 17.30 nM/ml (normal 257.90–611 nM/ml/24 h), which was a result of MPS IIIB. However, molecular genetic research was not performed.

After 4.5 years, further regression of skills was noted (she stopped dressing independently, washing, and going to the toilet). At 5 years, 2 months, inguinal and umbilical hernia repair was performed, and at 6 years old, she became more excitable, often screamed, and sleep disturbances persisted. Since the age of 6.5 years, convulsions were periodically noted; a neurologist diagnosed symptomatic epilepsy. A specific phenotype was retained on examination, and the combination of light hair and wide dark eyebrows was noted; the patient was motor-awkward, emotionally labile, and did not understand the addressed speech (Fig. 3).

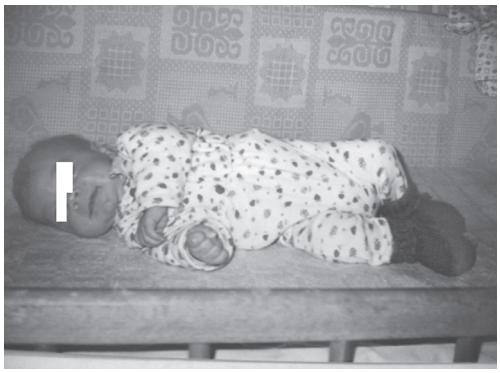

Fig. 1. Girl with mucopolysaccharidosis type III at the age of 1 month

Рис. 1. Фото девочки с мукополисахаридозом IIIB типа в возрасте 1 мес.

Fig. 2. Girl with mucopolysaccharidosis type III at the age of 3 years

Рис. 2. Фото девочки с мукополисахаридозом IIIB в возрасте 3 лет

Fig. 3. Girl with mucopolysaccharidosis type III at the age of 6 years

Рис. 3. Фото девочки с мукополисахаридозом IIIB в возрасте 6 лет

When examined at 8 years old (hospitalized for a comprehensive examination), her height was 118 cm and weight was 19 kg. Contact with the child was complicated; she had a negative attitude toward examination, and did not respond to requests. Furthermore, psychomotor development included walking,

sitting, speaking individual syllables and sounds, recognizing her mother, having no aggression, and the behavior was field. The girl had a phenotype characteristic of MPS, with a large hydrocephalic head, hypertelorism, wide eyebrows, high forehead, low ears, macroglossia, gothic palate, tooth deformity, wide diastemas, short neck, and a wide chest. Flexion-extension contractures were noted in the elbow joints and minimal in the knee joints. The hands were wide, and movements in the wrist and interphalangeal joints were not limited. Also, the skin was clean, heart sounds were clear and regular, the abdomen was soft, and there was a small umbilical hernia (1.5 cm in diameter). Fortunately, the liver and spleen were not enlarged, and the patient was discharged with MPS IIIB type (Sanfilippo syndrome), mixed hydrocephalus of atrophic type, *Coxae valgum*, flexion contractures of the elbow and knee joints, and minor anomaly of the heart with an additional chord of the left ventricle.

Soyfem, five tablets once a day for a long time, was prescribed to the girl as a substrate-reducing therapy, and the patient's mother followed the recommendations. During therapy, slow disease progression was noted. Finally, at 12 years old, the child died of neurological disorders in the structure of the underlying disease.

CONCLUSION

Type III MPS is an example of an orphan disease on the verge of active development and implementation of specific and effective therapy. The previously developed approaches of substrate-reducing therapy recede gradually into the background, giving way to more effective treatment methods. Currently, active attention is paid to the early diagnosis of the disease, screening programs, and disseminating knowledge about the disease in the medical environment. This will help in the future for more effective application, development of new therapy methods, and providing timely and adequate assistance to patients with type III MPS.

ADDITIONAL INFORMATION

Author contributions. All authors confirm the compliance of their authorship with the international ICMJE criteria (all authors made a significant contribution to the development of the concept, research, and preparation of the article, read, and approved the final version before its publication).

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