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MUCOPOLYSACCHARIDOSIS TYPE VI: WHY EARLY DIAGNOSIS AND TIMELY TREATMENT IS EXTREMELY IMPORTANT?

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Abstract

Mucopolysaccharidosis (MPS) is a group of hereditary metabolic diseases caused by impaired metabolism of glycosaminoglycans (acidic mucopolysaccharides) due to a deficiency of enzymes required for their degradation (cleavage) in the lysosome. Accumulation of glycosaminoglycans in lysosomes causes significant cellular changes and the emergence of a characteristic clinical picture. We present a case of MPS VI in a 12-year-old girl. The disease was diagnosed at the age of 1 year and 4 months, but the opportunity to receive enzyme replacement therapy became possible when the patient was 6 year old. Despite the replacement therapy, the disease course was severe and rapidly progressing progressing, which led to irreversible clinical manifestations. The patient presented with severe recurrent respiratory tract infections, heart valve disease, hepatosplenomegaly, visual and hearing impairment, coarse facial features, abdominal hernia, joint and skeletal involvement. The described case demonstrates that not only early diagnosis but also timely treatment are extremely important for improving the quality and life expectancy of children with mucopolysaccharidosis type VI. It is extremely important to recognize disease as soon as possible and prescribe a specific drug.

Keywords: *lysosomal storage diseases, arylsulfatase b, enzyme replacement therapy, Maroteaux–Lamy syndrome.*

Introduction

Mucopolysaccharidosis (MPS) is a group of hereditary metabolic diseases caused by impaired metabolism of glycosaminoglycans (acidic mucopolysaccharides) due to a deficiency of enzymes required for their degradation (cleavage) in the lysosome [1]. Accumulation of glycosaminoglycans in lysosomes causes significant cellular changes and the emergence of a characteristic clinical picture. Among diseases, the accumulation of mucopolysaccharidosis is one of the most common [2].

According to the modern classification, there are 9 types of MPS, each of which occurs due to a deficiency of a specific enzyme involved in the sequential breakdown of a particular glycosaminoglycan (chondroitin, dermatan, heparan and keratan sulfates).

Mucopolysaccharidosis type VI (MPS VI), also known as Maroto-Lamy syndrome, is a heterogeneous hereditary multisystem lysosomal disease characterized by deficiency of the enzyme N-acetylgalactosamine-4-sulfatase (arylsulfatase B) [3]. The gradual accumulation of dermatan sulfate breakdown products in lysosomes, cells and tissues is responsible for various clinical manifestations: valvular heart disease, large liver and spleen, joint immobility, growth retardation, multiple dysostosis and corneal opacity [4]. It is also accompanied by irreversible damage to organs, which in turn causes their dysfunction.

MPS VI is inherited by autosomal recessive type. The arylsulfatase B gene (ARSB) is located on the long arm of chromosome 5 at the q14.1 locus. [5]. The disease manifests itself only if both parents are carriers of the disease and, although they themselves are not sick, pass on to the child two damaged genes. The risk of rebirth in a family where there are already such children is 25% for each subsequent pregnancy [6]. As a rule, MPS type VI is manifested only in patients with severe deficiency of the enzymatic activity of arylsulfatase B (usually less than 10% of the lower limit of normal). Carriers of one abnormal allele retain sufficient enzyme activity, which makes it possible to avoid the manifestations of the disease [7].

MPS type VI was first described in 1963 by French physicians Pierre Marotto and Maris Lamy as Gurler syndrome (MPS I). The prevalence of the disease in the population varies considerably depending on the geographical location of the country and population groups and is: in Northern Ireland - no cases, 2.3 - in Turkish immigrants living in Germany, 20 per 100,000 live births - in the county of Monte Santo in the northeast Brazil [8]. In Central and Eastern Europe, the incidence rate ranges from 0.0363 to 0.64 per 100,000 live births in Poland and Lithuania, respectively [7].

Currently there are 3 forms of mucopolysaccharidosis type VI: severe - with a debut in children from 1 to 3 years, moderate - onset at 6 years, mild - beginning after 20 years.

Here we report a case of MPS VI in a 12-year-old girl. The disease was diagnosed at the age of 1 year and 4 months, but the opportunity to receive enzyme replacement therapy became possible when the patient was 6 year old.

Case presentation

A 12-year-old girl was admitted to the intensive care unit of the regional hospital in a serious condition due to respiratory disorders. Her mother complained of reduced saturation up to 35-50%, cyanosis of the lips, shortness of breath, cough, and weakness.

From the anamnesis of life it is known that the girl from II full-term pregnancy, II physiological childbirth, with a tight umbilical cord around the neck. She was born with a body weight of 3000 g, length – 50 cm. Genetic history was not burdened. For the first time, parents consulted a doctor at the age of 1 year and 3 months with complaints of delayed static functions. At the time of examination by a geneticist found an open big fontanelle, macrocephaly (head circumference - 49 cm), scarocephaly, chest circumference - 50 cm, stiff hair, rough facial features, expanded lower aperture of the chest, deformed toes, brain skull increased in size, lag in growth by 1 sigma. As a result of examination and a sharply positive test for mucopolysaccharides, MPS was suspected. Neurosonography revealed signs of combined hydrocephalus, ventricular dilatation of the III degree. In the study of the activity of lysosomal enzymes, the level of arylsulfatase B was 8.7 mmol/h/kg of plasma protein (at a rate of 110-130). MPS VI (Maroto-Lamy syndrome) was diagnosed.

Despite of early diagnosis (in 1 year and 4 months) the girl did not receive special replacement therapy because the enzyme drugs were not registered in Ukraine. Only since 2014 the problem of orphan diseases in Ukraine has been recognized at the state level. Therefore, from the age of 6, the child began receiving enzyme replacement therapy.

The disease in this girl was severe and rapidly progressing, which led to irreversible clinical manifestations.

The general condition of the child on admission to the regional hospital at the age of 12 years was severe due to the presence of respiratory disorders. The girl occupied a forced position in bed - half-sitting, lying on the abdomen.

Appearance of the child: gargoilism (rough facial features), macrocephaly, large wide nose with wide, flat and sunken nose and large, thick nostrils, large plump lips, short, motionless neck, round face, thick and stiff hair, thick eyebrows, small teeth with wide tooth gaps, macroglossia, narrow and round shoulders (Fig. 1).

Changes in the skeletal system: dwarfism (height - 110 cm, Z-score -5.74), multiple dysostosis, short torso and limbs, wedge-shaped deformity of the chest with an enlarged lower part, congenital dysplasia of the hip joints, change of gait (standing and walking with bent knees and hips), X-shaped curvature of the limbs, feet wide and not bent, toes pressed and shortened, flexion contractures of all joints of I-II degree (Fig. 2). Radiography of the hands and hip joints in 6 years demonstrated fibrous the growth zones of the epiphyses of the nuclear bones, deformation of growth zones of epiphyses of radial bones, disorders of osteogenesis. Computed tomography of the cervical spine in 12 years of age detected straightening of physiological lordosis.

Changes in the respiratory system: oxygen saturation on admission - 35-50%; after stabilization - 87-89%, with a constant oxygen supply - 96%. Respiratory rate - 42 per 1 min, breathing through the nose is difficult. The thorax is enlarged in anterior-posterior size. At percussion of a thorax: shortening of a pulmonary sound paravertebral and in the lower and posterior parts of the lungs; on auscultation crackles were heard in the lower and posterior parts of the lungs. Chest computed tomography at 12 years detected signs of fibrosis in the right lung; calcified fibrous granuloma S6 in the left lung; inflammatory changes of the left S5 and right S6, S10 segments.

Changes in the cardiovascular system: cardiomegaly. The activity of the heart was rhythmic, the tones were weakened. Heart rate was 112 per minute; tachycardia and heart murmur at all points, maximum at the apex was head. Electrocardiography showed overload right ventricular. Echocardiography revealed combined aortic defect with a predominance of insufficiency; combined mitral heart disease with a predominance of stenosis; severe secondary pulmonary hypertension; dilatation of the trunk and branches of the pulmonary artery and right heart.

Changes in the gastrointestinal tract: the abdomen was enlarged, protruding, umbilical hernia of large size (approximately 3 cm) was seen (Fig. 3). The liver was +2 cm below the edge of the costal arch, the spleen was +1 cm. The patient's mother reported prone to constipation in a child. Ultrasound confirmed the moderate increase in the size of the liver, increasing its echogenicity and slightly enlarged spleen.

Changes in the nervous system: intelligence was not impaired. Despite the visual and hearing impairment, the girl could write and retell the text to her parents.

Otorhinolaryngologist revealed adenoid vegetations of the III degree; tonsil hypertrophy; bilateral otitis media; bilateral conductive deafness.

Ophthalmologist detected opacity of the cornea of both eyes; secondary glaucoma; descending atrophy of the optic nerves of both eyes.

Diagnosis: Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome), severe form, progressive course. Combined aortic defect with the advantage of insufficiency. Combined mitral regurgitation with a predominance of stenosis. Minimal insufficiency of aortic and tricuspid valves. Severe secondary pulmonary hypertension. Secondary cardiomyopathy with right ventricular dysfunction, circulatory failure of the IIA degree. Out-of-hospital bilateral focal pneumonia, congestive genesis, IV degree of severity, respiratory failure of the II degree. Keel-shaped deformation of the chest. Flexural contractures of

all joints of the I-II degree. Thoracic scoliosis of the II degree. Opacity of the cornea of both eyes. Secondary glaucoma. Descending atrophy of the optic nerves of both eyes. Adenoid vegetations of the III degree. Bilateral otitis media. Bilateral conductive deafness. Umbilical hernia. Dysfunction of the biliary tract.

Treatment included oxygen therapy, antibacterial and antifungal therapy, diuretics, angiotensin-converting enzyme inhibitors, enzyme replacement therapy, symptomatic therapy.

As enzyme replacement therapy the patient since 6 years of age received galsulfase at a dose of 1 mg/kg intravenously drip through a lineomat for 4 hours 1 time per week.

Discussion

The peculiarity of this case is an early diagnosis of mucopolysaccharidosis (at the age of 1 year 4 months), but the late start of specific treatment due to the lack of official registration of the enzyme in Ukraine. This in turn has led to disease progression and irreversible changes in many organs and systems.

Important specific features of MPS type VI are rough facial features, which were observed in our case. The first thing that mother noticed was the delay in statokinetic development, and only doctors noted the specific features characteristic of MPS.

The first symptoms of the disease are umbilical hernia and recurrent infections, as well as lack of normal growth from the first year of life [10]. Other authors describe progressive weight gain from 2 months [11]. Among the early signs describe hip dysplasia, delayed physical development from 6 months, recurrent laryngitis, rhinitis, otitis [4, 5]. Recurrent infections, poor weight gain and lack of normal growth require ruling out other diseases, especially primary immunodeficiencies [12-13]. Some authors have shown the presence of knee contractures at 7 months, arm contractures at 14 months, kyphosis, delayed motor development and increased muscle tone [9].

In the clinical case described by us, the first symptoms noted by the mother at the age of 6 months were the lag of the child in body length and increase in head size. At the age of 1 year and 3 months, the mother went to the hospital, due to the presence of shortness of breath and cyanosis of the lips. Shortness of breath, of course, can indicate a significant number of diseases, but is also a typical sign for MPS type 6 and in particular is often observed in infants [14].

Therefore, the first symptoms of MPS VI are quite diverse and also depend on the age of the child, which in turn complicates its early diagnosis. However, in our clinical case, the signs of the disease were common and helped to diagnose in time.

There are several forms of pathology depending on factors such as age of onset, height and level of GAG (glycosaminoglycans) in the urine. In our case, the classic form of mucopolysaccharidosis or severe was diagnosed, because it was detected before the age of 3 years. Skeletal lesions are the most characteristic of the rapidly progressing course. However, among all the characteristic features in our girl abnormal forms of ribs and vertebrae, scoliosis or kyphosis were not detected, on the contrary, there was a straightening of physiological lordosis. Nerve pinching syndromes such as spinal cord compression, nerve root compression, and carpal tunnel syndrome have not been reported in our patient [13].

According to other authors, fibroelastosis in patients with MPS VI has been described mainly in infants, but fibrous and thickened endocardium is found mainly in the left ventricle and usually in middle-aged adult patients [15]. Among other pathologies of the cardiovascular system, scientists also describe lesions of the mitral valves, which are observed in 96% of patients, tricuspid valves - in 71% and aortic valves - in 43% [14], which was also detected in our patient. With the help of serial echocardiography in the dynamics, it was investigated that heart disease gradually worsens with age, even in people with a slowly progressive course [8]. Literature data also indicate the development of cardiomyopathy and heart failure in children under 1 year [8].

Hepatosplenomegaly accompanies the disease in most cases, which confirms the literature [16].

Long-term treatment of mucopolysaccharidosis type VI was limited to symptom relief and palliative care. However, more than 20 years ago treatments were developed that directly address the cause of the disease that is a deficiency of the enzyme arylsulfatase B (ARSB). To date, available methods

of treatment of pathology are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT) [5]. ERT is currently the recommended first-line treatment for MPS VI. Its late onset may be the cause of irreversible changes in organs and systems.

Therapy includes weekly intravenous infusions with recombinant human ARSB or galsulfase to replace the defective enzyme. Numerous studies have shown that early intervention with ERT (until irreversible complications occur) is beneficial, so it is vital that the diagnosis be made quickly and accurately to maximize therapeutic potential [2,3,7,14]. According to other authors, naglazim treatment helps to maintain the respiratory system and increase the volume of movements in some joints as soon as possible after diagnosis [3,5,7]. ERT improves the size of the heart, but has no clear effect on valve regurgitation or dysmorphic features of the valves. Prior to taking the drug, the size of the liver in children was even up to 7 cm, and the spleen up to 6 cm below the edge of the costal arch. Replacement therapy resulted in a reduction in hepatosplenomegaly: liver size in all patients decreased by approximately 0.6 cm/year and in some children (43%) reached the age norm, and spleen size decreased by approximately 0.3 cm/year and in 57% of children reached norms for age [16]. There were also positive changes in the senses. Doctors noted an improvement in hearing in 36.4% of children, deterioration in 9.1% and remained stable in 54.5% of children [16]. Importantly, a decrease glycosaminoglycans in urinary was detected in all patients. After all, it is impossible not to mention the subjective indicators that indicate an improvement in the quality of life of patients. Also parents noted a reduction in lung problems, improved sleep and overall activity of the child, a positive mood of children and their communication skills with peers and the environment [3].

So, the diagnosis of MPS is important in the early stages of the disease, as it allows for timely existence and adequate symptomatic therapy. It must be understood that the prescription of the enzyme does not cure the disease. The purpose of therapy is to slow the progression of the disease and, consequently, to prolong a full life. Therefore, raising awareness of doctors and early diagnosis are as important as for other rare diseases [17-18].

The prognosis for all forms of MPS VI is unfavorable, because with age the irreversible process of damage to the central and peripheral nervous system progresses, the most promising direction is prevention [8,14]. It is important for parents of children with Maroteaux-Lamy syndrome to undergo medical and genetic consultancy to ensure the possibility of prenatal and preimplantation diagnosis. Prenatal diagnosis of MPS VI is possible by measuring the activity of the lysosomal enzyme arylsulfatase B in the chorionic villus biopsy at 9-11 weeks of pregnancy and / or determining the spectrum of glycosaminoglycans in amniotic fluid at 20-22 weeks of gestation [4,19].

Conclusions

The described case demonstrates that not only early diagnosis but also timely treatment are extremely important for improving the quality and life expectancy of children with MPS VI. Enzyme replacement therapy is currently the only method of treating this disease in Ukraine, so it is extremely important to recognize it as soon as possible and prescribe a specific drug.

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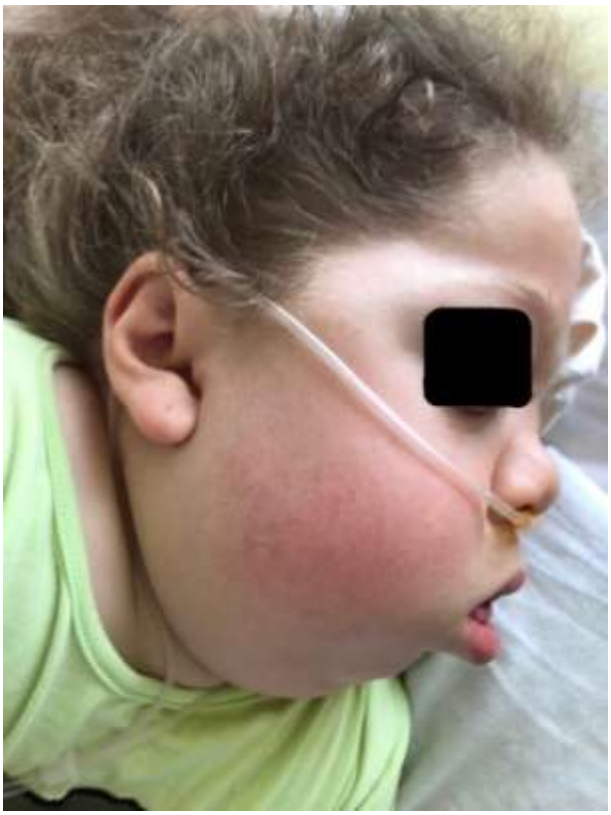

Figure 1. Appearance of a child

Figure 2. Features of the hand of a child with MPS VI

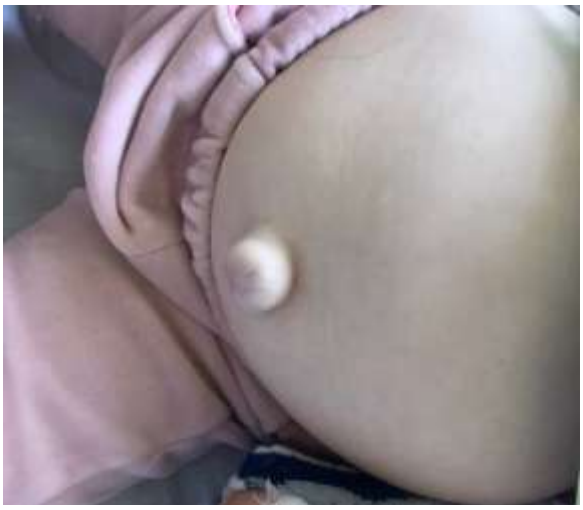

Figure 3. Umbilical hernia in a child with MPS VI