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Case Report

Vimizin (Elosulfatasealpfa) in an Adult Patient with Mucopolysaccharidosis Type IV Ð

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ABSTRACT

Lysosomal diseases include a group of over 40 inherited metabolic diseases due to enzyme deficiency. In them, the accumulation of undegraded substrate in the cells is observed. They are chronic diseases with a heterogeneous clinical picture. Mucopolysaccharidosis type IVA (Morquio syndrome) is a rare form of these diseases and occurs in a frequency of 1: 200,000 patients. Treating this condition is difficult, expensiveÑ€, and often ineffective. We report a patient, a 22-year-old man suffering from Morquio syndrome, who was admitted to the hospital in a serious condition with an inability to move due to musculoskeletal problems (the patient walks 0 meters in a 6-minute walking test) and inability to climb stairs. In 2018, treatment with Vimizin (elosulfatasealfa) was started at a dosage of 2 mg/kg body weight every week. The patient's condition was monitored weekly, and the level of glycosaminoglycans in the urine was examined every 30 days (normal 0.9-6.7 mg/mmol). Serious side effects include an allergic reaction during the 8. infusion, which has been affected by the administration of antihistamines and muscle pain. At 12 weeks the patient walks 18 meters alone, at 24 months - 51 meters. In the 1st year, the patient walks independently 650 meters and climbs 10 stairs, in the second year 900 meters and climbs 15 stairs. Gradually, the level of glycosaminoglycans in the urine returns to normal. Conclusion: VIMIZIN (Elosulfatasealfa) is a suitable and effective enzyme replacement in patients with Mucopolysaccharidosis type IVA, regardless of the initial condition of the patient.

Key words: Vimizin (elosulfatasealfa); Morquio syndrome; 6-minute walking test

INTRODUCTION

Lysosomal diseases include a group of over 40 inherited metabolic diseases [1,2]. They are due to an enzyme deficiency, leading to the accumulation of undegraded substrate in the cells. The overall incidence of these diseases as a group is 1: 7700. They are chronic diseases with a heterogeneous clinical picture [1-4]. Mucopolysaccharides are composed of glucosaminoglycans bound to a protein with a hyaluronic acid core. Lysosomal enzymes break down these glucose-aminoglycans into macromolecules to heparansulphate, dermatansulphate and keratansulphate [5,6]. Enzyme deficiency blocks their degradation and leads to the accumulation of these products in the cells and disruption of their function. The description of these diseases - mucopolysaccharidosis, began in the early 20th century [5,6].

To date, more than 5 types of mucopolysaccharidosis have been described. Mucopolysaccharidosis type IVA (Morquio syndrome) is a very rare form of this disease. It occurs in a frequency of 1: 200,000 patients. Two subtypes are known - type A - Mucopolysaccharidosis (MPS) 4A, in which there is a deficiency of N-acetylgalactosamine-6-sulfate, sulfatase-chondroitin 6 sulfate and keratan sulfate and type B - Mucopolysaccharidosis (MPS) 4B - β-deβ -keratansulphate [2,7]. In Morquio's syndrome, glucosaminoglycans accumulate - chondroitin 6 sulfate and keratan sulfate in the lysosomes of cartilage and its extracellular matrix, where they are mainly produced. As a result of this accumulation, cellular function, ossification, change in growth and as a result skeletal dysplasia occurs. Accumulated glucosaminoglycans are secreted into the blood and excreted in the urine [1,6]. The clinical presentation of Morquio's Syndrome includes a wide phenotypic spectrum of manifestations, including early onset with severe complaints of spinal cord compression, respiratory problems, heart valve involvement, severe bone changes - kyphosis, scoliosis, pectuscarinatu, abnormalities of the spinal cord. Development of disproportionately low growth with age [8,9]. There is no system or organ that is not involved in the disease process. On the part of the cardiovascular system there is thickening of the heart valves, left ventricular hypertrophy, arrhythmias, regurgitation of the aortic valve, sclerosis of the coronary intima [8-10]. On the part of the respiratory system, there are changes in the adenoids, tonsils, pharynx, larynx, trachea, due

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to the accumulation of glucose aminoglycans in them, impaired breathing due to abnormalities of the spine, obstruction of the large airways due to deviation of the trachea. Development of respiratory failure, pulmonary hypertension [8-11]. Very often in patients with Morquio 's syndrome there is a slowly progressive and varying in severity corneal opacity, optic nerve edema and atrophy, increased intraocular pressure, glaucoma, blindness. Hearing loss in patients correlates with their short stature Patients with Morquio syndrome are usually dysmorphicfacies, short stature, genu valgum, pectuscarinatum, kyphosis. They have impaired gait due to contractures in the large joints - shoulder, elbow, hip and immobilization, but have normal mental development [5,9].

The diagnosis of Morquio's syndrome is biochemical, enzymatic, molecular and imaging. Biochemical diagnosis involves the quantitative and qualitative determination of glucoaminoglycans in the urine, knowing that the level of creatinesulphate in the blood and urine correlates with the severity of the clinical picture at an early age and its reduction is a good prognostic marker for the disease [12]. The study of the amount of creatinesulphate is a biomarker for the pharmacodynamic profile of treatment. Molecular diagnosis involves the detection of the GALNS gene, which is located on chromosome 16q24.3. It should be noted that in 1992 mutations of the classical and attenuated form of MPS IVA were discovered, which by 2018,334 are [13,14]. Analysis of GALNS mutations in MPS IVA showed significant molecular heterogeneity reflecting the diversity of clinical phenotypes. Important for the diagnosis of MPS are the conduct of X-ray, CT, MRI examination due to various skeletal involvement [12-14].

Until recently, the treatment of Morkio's syndrome included only symptomatic treatment - nonsteroidal anti-inflammatory drugs, antibiotics, oxygen therapy, orthopedic treatment for decompression of the cervical brain, femoral osteotomy, correction of skeletal deformities [2,4,6]. A new era in the treatment of patients with Morkio's syndrome began after 2009, when the drug Vimizin was created [15]. Due to the very small number of patients treated with it, the drug is called an "orphan drug". Vimizim is a recombinant enzyme elosulfasealfa, used to treat patients with MPS IVA. In the patient, the enzyme is transported by the mannose 6 - phosphate receptor to lysosomes, where the breakdown of glucose aminoglycans occurs [15].

Vimizim is an enzyme replacement therapy. Enzyme replacement therapy provides patients with the enzyme they lack. The active substance in Vimizim, elosulfasealfa, is a copy of the human enzyme N-acetylgalactosamine-6-sulfatase. The replacement enzyme helps to break down GAGs and stop them from accumulating in the cells, thus improving the symptoms of MPS IVA [15].

Elosulfasealfa is produced by a recombinant DNA technology: it is produced by cells into which a gene (DNA) has been introduced, making them capable of producing the enzyme [15,16]. To date, a total of 235 patients worldwide with MPS IVA have been included in 6 clinical trials. Patients ranged in age from 5 to 57 years and were able to walk more than 30 meters during a 6-minute walking test prior to enrollment in the studies [17].

CASE PRESENTATION

Case 1

Our case is a 22-year-old man with 10-year-old complaints of leg pain and avoidance of exercise. In the following years, the complaints progressed to the point of not being able to stand up and use walking aids. During repeated hospitalizations and imaging studies, a wedge-shaped decrease in T12, spina bifida of L5, thoracolumbar kyphosis, lysis of the femoral heads were demonstrated. Treatment includes nonsteroidal anti-inflammatory drugs, oxygen therapy, crutches and an orthopedic corset. Gradually, the patient develops depression and isolation in the home due to the inability to stand up and anticipate independently. In 2018, due to adynamia, muscle pain, weight reduction and impaired movement of the patient, specific tests were performed and a serum level of galactose6 phosphatase - 1./17h/mg (norm 31-122) was established. The level of glucoaminoglycans in the urine is 10.34 mg/mmol (normal 0.9-6.7) before starting treatment. The performed DNA analysis established two pathological mutations - c.329C>T/c.86°C and the diagnosis of Morquio syndrome type A was accepted.

In 2018, treatment with elosulfasealfa was started (2 mg/kg body weight, a total of 32 vials per week). The general condition gradually improved. The patient had no change in the cardiovascular system, respiratory system, endocrine system. The patient has normal vision and hearing. Pain in the large joints (hip, knee and ankle) decreased, ultrasound imaging of the target joints, as well as MRI showed no changes.

Serious side effects include an allergic reaction during the 8. infusion, which has been affected by the administration of antihistamines and muscle pain. At 12 weeks the patient walks 18 meters alone, at 24 months - 51 meters. In the 1st year the patient walks independently 650 meters and climbs 10 stairs, in the second year 900 meters and climbs 15 stairs. Gradually, the level of glucoaminoglycans in the urine returns to normal.

DISCUSSION AND CONCLUSION

Mucopolysaccharidosis is a common disease. They are mainly treated by pediatricians, rehabilitators and orthopedists, as often patients do not survive to old age. In recent years, this trend has changed and now doctors have a new strategy for action. There are three groups of drugs for this disease on the pharmacological market - enzyme replacement therapy, transplantation and gene therapy. Each of these therapies has advantages and disadvantages. Enzyme replacement therapy is currently very expensive and involves weekly infusions by medical personnel. Transplantation is a one-time procedure, but it involves finding a suitable donor and expensive equipment. Gene therapy is still in the experimental stage, and there are still many unknowns - unclear route of administration, lightning reaction, short-term observations.

At present, enzyme replacement therapy remains the most appropriate. Our patient has been on such therapy for more than 24 months and we have observed recovery of the general condition and absence of serious side effects. In Bulgaria, the drug Vimizin is prescribed by a commission appointed by the Ministry of Health and the drug is completely reimbursed.

VIMIZIN (Elosulfatasealfa) is a suitable and effective enzyme replacement in patients with Mucopolysaccharidosis type IV A, regardless of the initial condition of the patient.

COMPETING INTERESTS

The authors declared that they do not have any conflict of interest.

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