

REVIEW PAPER

A genetic disease under the multiform mask – infantile-onset of Pompe disease

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ABSTRACT

Acid α -glucosidase deficiency – Pompe disease (PD) is a genetic, autosomal recessively inherited disorder leading to impaired glycogen degradation and storage in cells, especially muscles. It occurs with a frequency of 1 : 10,000 – 1 : 40,000 live births. This article presents a currently 14-year-old girl diagnosed with infantile-onset PD. A 15 days old the girl was referred to the hospital due to tachycardia. On examination, reduced muscle tone and hepatomegaly were observed. Electrocardiography showed supraventricular tachycardia. Laboratory tests detected increased hepatic aminotransferase activity. Echocardiography of the heart showed features of hypertrophy of both chambers. The patient was referred to the Children's Memorial Health Institute in Warsaw. Pompe disease was diagnosed. At 4 months of age, therapy with Myozyme, administered intravenously every other week, was started, and it continues to the present day. Early recognition of PD and initiation of substitution therapy allow its course to be slowed and patients' lives to be extended.

KEY WORDS:

Pompe disease, glycogen, α -glucosidase, Myozyme.

INTRODUCTION

Pompe disease (PD, OMIM#232300, ORPHA: 308552), also known as acid maltase deficiency and glycogen storage disease type II, is a rare chronic disease that is genetically determined, autosomal recessively inherited, and has a high mortality rate. The incidence of PD is estimated at 1 in 10,000 to 27 40,000 live births [1]. The same incidence rate is observed in men and women. Symptoms are associated with progressive impairment of muscle function resulting from mutations in the GAA gene (chromosome 17q25.2-q25.3) encoding acid α -1,4-glucosidase (GAA). Partial or complete deficiency of the enzyme leads to glycogen storage in many tissues, especially muscles [2, 3]. The first case of a 7-month-old child with general muscle weakness was described in 1932 by Dutch physi-

cian Joanne Pompe – idiopathic cardiac hypertrophy was linked to glycogen accumulation [4].

Taking into account the age at which the first symptoms are noted, 3 types of the disease can be distinguished, which differ in enzyme activity. In infancy, there is a more severe form that begins within the first few months of life – infantile-onset Pompe Disease (IOPD), and a form that reveals itself at around one year of age – late-onset/non-classic Pompe disease (LOPD). The third type manifests during adolescence, although it can also occur for the first time in adults [5]. In the course of the early form of IOPD, symptoms from many systems are observed, especially the cardiovascular system: cardiomegaly, cardiomyopathy, arrhythmia, heart failure, or the neuromuscular system in the form of a progressive decrease in muscle strength. Problems with the respiratory or digestive

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systems appear. Frequent middle ear infections lead to hearing damage. Laboratory tests show elevated creatine kinase levels. Cardiomyopathy and significant muscle weakness can cause death in the first year of life [6].

Treatment includes enzyme replacement therapy (ERT). Recombinant enzyme α -glucosidase enables glycogen processing. The dose depends on the patient's weight, and without treatment, the disease is fatal.

CASE REPORT

The girl was born from pregnancy II, delivery II, at full term, with a body weight of 3440 g, and with 10 points on the Apgar scale. The neonatal period was complicated by prolonged jaundice. Family history was unencumbered by cardiovascular diseases at the time of admission.

The first hospitalisation occurred in the third week of life (March 2010) due to tachycardia above 200/min diagnosed in the family physician's outpatient clinic. In the history, the parents reported impaired appetite and periodic restlessness. On physical examination, the following abnormalities were found: facial dysmorphic features – bicoronal narrowing and upwardly angled eyelid crevices, jaundice, and tachycardia. Laboratory tests performed showed hyperbilirubinaemia (total bilirubin – 13.8 mg%, direct bilirubin – 0.52 mg/dl, slightly elevated aspartate aminotransferase (AST) – 103 U/l (< 77 U/l), and creatine kinase-myocardial band (CK-MB) – 76 U/l (< 25 U/l).

An electrocardiography showed features of paroxysmal supraventricular tachycardia of about 300/min (Figure 1).

Non-pharmacological methods were used to treat the arrhythmia, as well as intravenous bolus of adenosine

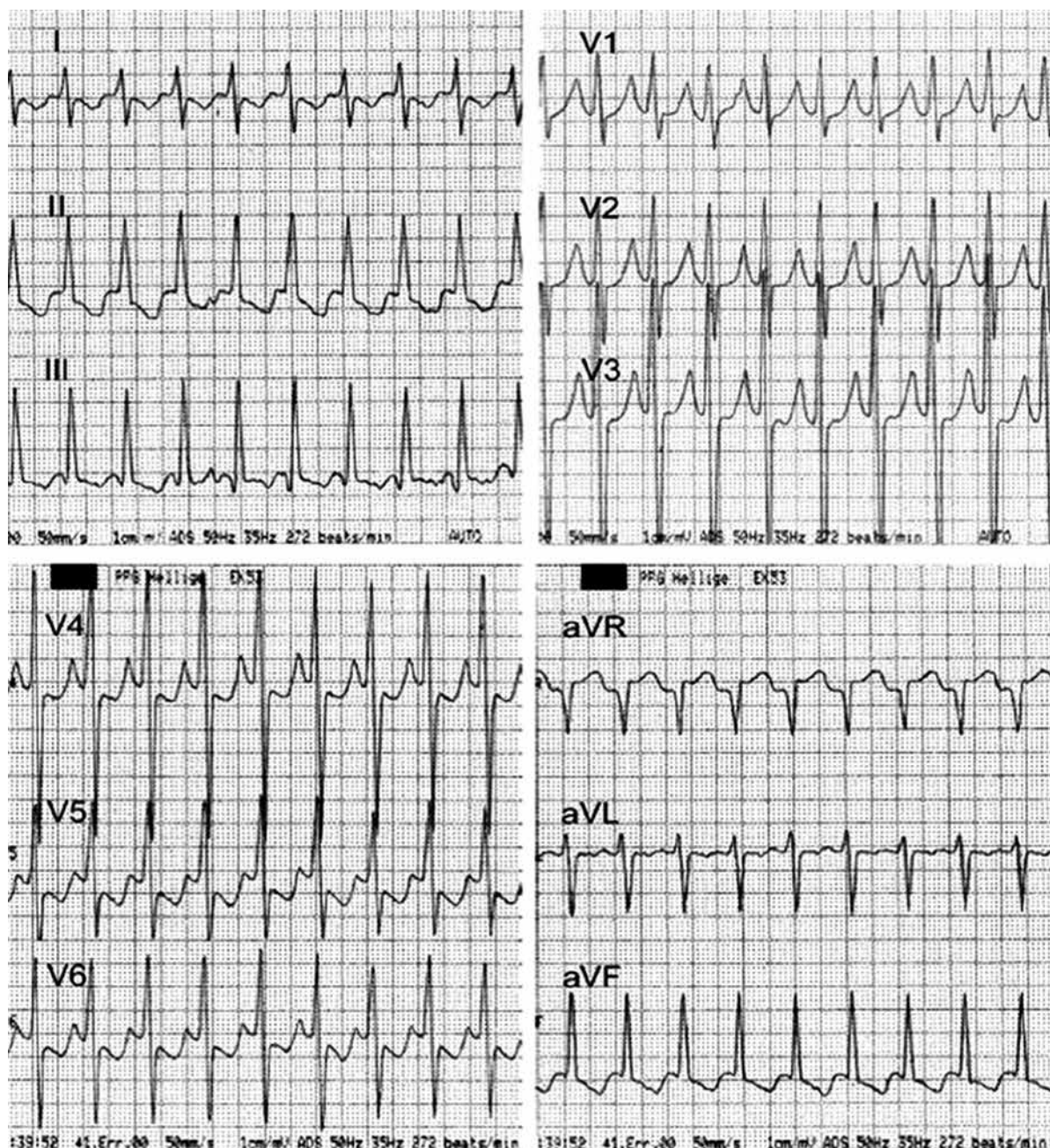


FIGURE 1. Electrocardiography – supraventricular tachycardia of about 300/min

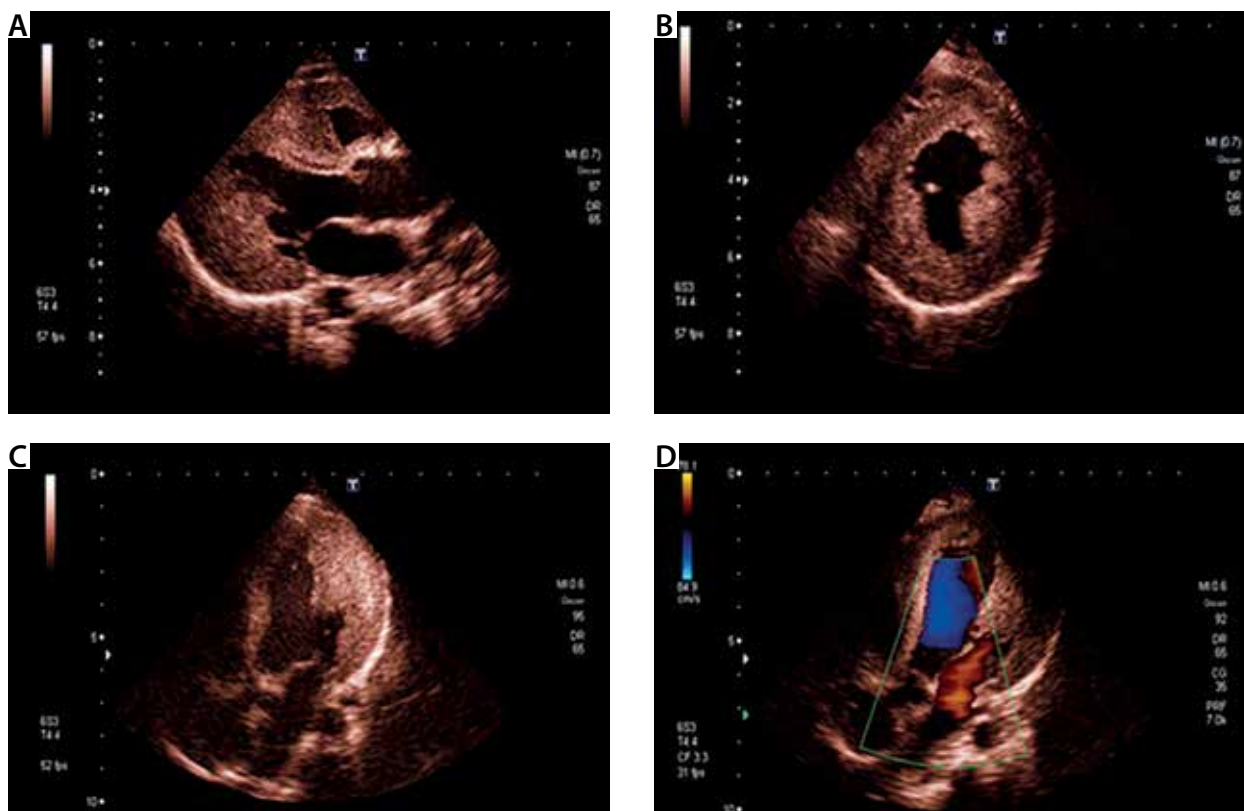


FIGURE 2. Cardiac echocardiography (ECHO). **A)** ECHO long-axis view. **B)** ECHO short-axis view. **C)** ECHO 4-chamber view. **D)** ECHO 4-chamber view with colour-doppler – massive myocardial hypertrophy visible: interventricular septum – 250% of normal, posterior wall of the left ventricle – 200% of normal, no narrowing in the right and left outflow tract

– twice (0.1 mg/kg/dose, 0.2 mg/kg/dose successively), with no effect. Due to the persistence of tachycardia, an infusion of 20% magnesium sulphate was given, followed by amiodarone (15 mg/kg/day in 3 doses) in an hourly infusion. A gradual deterioration of the patient's general condition with features of circulatory failure was observed. Another dose of amiodarone with a subsequent bolus of adenosine (0.2 mg/kg/dose) was administered, resulting in resolution of tachycardia symptoms and slowing of heart rate (HR) to 140/min.

However, in the following hours of hospitalisation, deterioration of the general condition was observed with features of circulatory centralisation and increased dyspnoea, with drops in saturation to 40% and slowing of HR to 70/min. The electrocardiography showed hypertrophy of left ventricle, confirmed by echocardiography. The girl was transferred to the intensive care unit. Fifteen days after the acute incident of cardiopulmonary failure, the girl was admitted to the paediatric ward for further diagnosis and treatment. On physical examination, the following features were observed: decreased muscle tension, liver enlargement (+ 3 cm below the costal arch), and signs of circulatory failure: grey shadow around the mouth, oedema on the feet, hands, and eyelids, and HR of 110/min. Laboratory tests showed persistently elevated liver enzymes. TORCH syndrome was excluded. Abdominal ultrasound and trans-temporal ultrasound did not reveal any abnormalities. In repeated echocardiogram, gener-

alised hypertrophy of the myocardium was found and the presence of a patent foramen ovale with left-right flow was noticed (Figure 2). Electrocardiography showed sinus rhythm 130/min, levogram, features of significant ventricular hypertrophy, mainly of the left side of the heart, and features of left bundle branch block.

Suspecting a metabolic or genetic basis of the disease, a urinary organic acid profile by gas chromatography/mass spectrometry was performed, but the result did not indicate an inborn metabolic defect associated with the profiles studied. The results of the consultations are shown in Table 1.

Antiarrhythmic treatment, diuretics, antibiotic therapy, and supportive treatment (proton pump inhibitor, vitamins B₆, K, D₃, folic acid) were administered, with improvement in general condition. Rehabilitation exercises using the Vojta method were recommended due to reduced muscle tone. The girl was referred to the Children's Memorial Health Institute in Warsaw (CMHI).

In April 2010, during hospitalisation in the CMHI, a dry drop test was performed to assess GAA activity. Based on the result, IOPD was diagnosed. The patient was admitted to the PD therapeutic program with ERT consisting of Myozyme – human acid α -glucosidase (rhGAA) – dose of 20 mg/kg per kg body weight. From that time, intravenous infusions of the enzyme Myozyme have been administered at 2-week intervals in Warsaw, and from June 2010 during hospitalisations in the De-

TABLE 1. Results of consultations (March 2010)

Genetic consultation	Rehabilitation consultation	Neurological consultation	Ophthalmic consultation
Morphological phenotype	Completely reduced muscle tone spastic motility	Limb motility symmetrical, very lazy	Normal fundus examination
Facial dysmorphic features	MORO reflex (–)	Primary reflexes: lazy, weakly expressed	
Abdomen arched above the level of the chest	Galant reflex (+) Symmetrical deep reflexes Recommended Stimulation by Volta method 4 times a day		

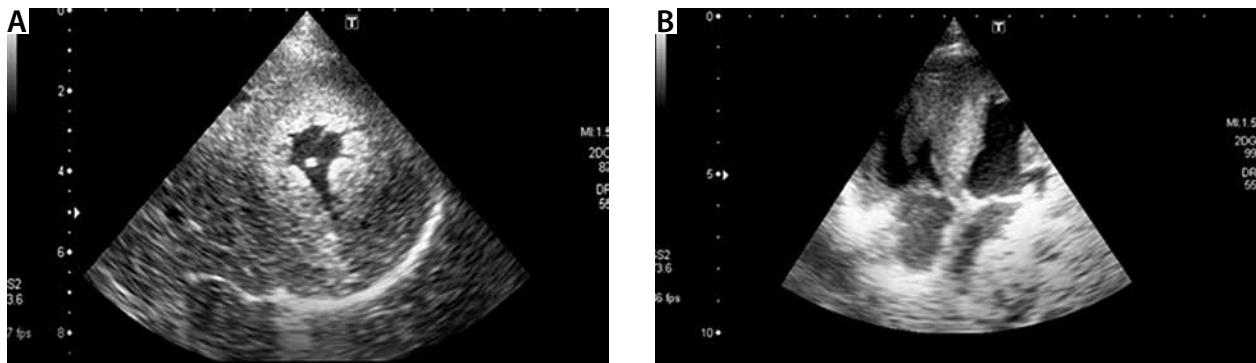


FIGURE 3. Echocardiography. A) Short axis – hypertrophy of the apex of the heart. B) Apical 4-chamber view. Hypertrophy of both heart cavities

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There were numerous respiratory and middle ear infections that required hospitalisations. Delayed motor development and decreased muscle tone were observed. In May 2012, the girl was diagnosed with spina bifida at the level of the fifth lumbar vertebra and gastroesophageal reflux, the cause of wet cough. Bioprazole, Hepatil, and Gastrotuss were added to the treatment. Progression of hypertrophic cardiomyopathy was observed. Wolff-Parkinson-White syndrome was diagnosed. In 2013, a tracheotomy tube was inserted due to an episode of cardiopulmonary failure. An echocardiogram showed progression of hypertrophy of the heart cavities (Figure 3). The girl required passive oxygen therapy, and periodically ventilator therapy. Decreases in saturation levels were observed. Due to hearing loss and frequent ear infections, a bilateral tympanostomy was placed and hearing aids were recommended.

In the course of the disease, hypertrophy of the tongue and regurgitation of the eyelid crevices due to weakness of the circular muscles of the eyes results in recurrent inflammation of the eyelid margins were observed. The development of astigmatism, horse feet, stiff, abolished deep reflexes in the limbs, joint contractures, especially of the ankle and knee joint, and generalised reduced muscle tone were observed. Mental, social, and emotional ma-

turity is normal. The girl assumes a lying/sitting position with assistance and does not verticalise. In 2017, a percutaneous endoscopic gastrostomy was placed, which was replaced with a balloon gastrostomy in 2018 due to retention of significant amounts of food content in the oesophagus; permanent ventilator therapy was also started. Anthropometric measurements taken in 2022 (12 years 1 month): height: 128 cm, weight: 19 kg, body mass index: 11.4 (all 3 measurements 0.1 centile). A gradual regression of hepatomegaly after the treatment was observed. Antibodies to glucosidase alfa were determined in 2012, 2013, and 2015. The results were positive – the level of antibodies was respectively 51200, 800, and 12,800.

Currently, the girl is 14 years old. The last intelligence test took place at the age of 3 years, earlier every 6 months. Since then, the girl's parents have stopped assessing intelligence. The parents are very involved in the treatment process, looking for new therapeutic options. The patient continues treatment with Myozyme, propranolol, and trimebutin. She remains under the care of the Department of Paediatrics, Endocrinology, and Diabetology with Cardiology Division at the Children's Clinical Hospital in Białystok. Within the framework of the drug program, the patient undergoes periodic check-ups and consultations (Figures 4, 5) for further qualification for treatment with Myozyme, including a psychological one, during which psychomotor performance is assessed. The girl communicates with her par-

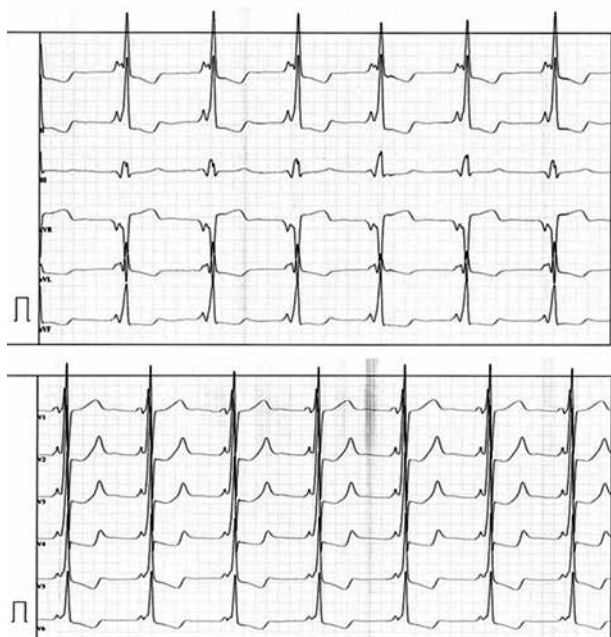


FIGURE 4. Current electrocardiography, 50 mm/sec – nomogram, features of: preexcitation syndrome – Wolff-Parkinson-White syndrome and hypertrophy of both ventricles

ents using words and sounds, and with her friends with gestures. The girl cannot read, but she is very intelligent. She has an individual course of study from fourth grade. The girl has flaccid quadriplegia with areflexia of the upper and lower limbs and joint contractures. She does not sit on her own and does not walk. She requires her parents' assistance in daily activities.

DISCUSSION

Early implementation of treatment is important to reduce the likelihood of developing multiple organ failure. It is necessary to reduce the time from the manifestation of the first symptoms to the correct diagnosis. However, this is challenging due to the non-specific complaints [7]. Without treatment of the classic form of IOPD, death occurs within the first year of life [8]. This is the reason for the widespread inclusion of PD in newborn screening (NBS) in the United States (US), among others [9]. Due to the various manifestations of the disease, making an appropriate diagnosis can be challenging.

For this reason, characteristic test abnormalities are still being sought to facilitate diagnosis. Currently, the gold standard in the diagnosis of PD is the determination of the enzymatic activity of GAA. A reliable test used to diagnose PD is the dry blood drop test for the presence of this enzyme [10]. More recently, due to the need to confirm the low GAA activity found in the dry blood drop test, biochemical tests from various tissues, and/or genetic analysis have been advocated [11]. Attention is also drawn to the biomarker of glycogen storage diseases, which is the tetrasaccharide 6- α -D-glucopyranosyl



FIGURE 5. Current X-ray – visible dilated cardiac silhouette, increased cardiopulmonary index of about 0.71, tracheostomy tube, scoliosis

-maltotriose. Its urinary excretion is increased when large amounts of glycogen are stored. Despite the high sensitivity of the test used for initial diagnosis, it does not allow differentiation of storage disease types [12]. There have been research papers indicating periodic acid Schiff-positive lymphocyte vacuoles as a screening test for PD among people at risk for myopathy [13].

The European Consensus identifies a combination of enzyme test and gene sequencing (usually by Sanger's method) as the gold standard for PD diagnosis [14]. Changes in parameters such as serum CK activity, AST, alanine transaminase, and lactate dehydrogenase have also been reported in PD patients, but are not specific, limiting their use in diagnosis [15]. Although muscle biopsy is used in the diagnosis of muscle diseases, in PD patients its value is limited due to the high variability of fibres within the same muscle group [16]. Electromyography is not a specific test for the diagnosis of PD, but an auxiliary one. The potential role of miRNAs in the pathogenesis and progression of PD and as novel biomarkers has been considered. Expression of miRNAs can be used to assess response to treatment [17].

A breakthrough in the treatment of PD was the introduction in 2006 of ERT with rhGAA in both the US and Europe. It is administered intravenously every 2 weeks. Positive effects on respiratory and cardiovascular func-

tions have been reported. A prolongation of patients' lives has been observed.

However, emerging anti-rhGAA antibodies limit the effectiveness of the treatment [18]. To determine the likelihood of antibody formation, western blot testing for GAA in skin fibroblasts is postulated. This allows detection of specific antigens of the enzyme termed cross-reactive immunologic material (CRIM) before receiving ERT. Patients with IOPD showing residual enzyme activity are CRIM-positive, while patients with IOPD showing no residual enzyme activity, and therefore immune tolerance, are CRIM-negative – they develop inactivating antibodies to rhGAA during ERT [19].

The role of immunomodulatory therapy – rituximab, methotrexate, or intravenous immunoglobulins – is emphasised in preventing the production of antibodies or eliminating those already produced. It has been proven that some CRIM-positive patients are likely to develop neutralising antibodies [20]. For this reason, monitoring antibody levels is recommended in patients undergoing ERT. When their high levels interfere with ERT, immunosuppressive treatment should be considered during ERT administration, or ERT should be discontinued [21].

In patients with worsening clinical condition during therapy with a standard enzyme dose of 20 mg/kg every 2 weeks and significantly high levels of anti-rhGAA antibodies, therapy trials using a higher enzyme dose per kilogram of body weight can be considered, as is being done in the US, among other countries. According to the researchers, the standard dose of the enzyme changed the course of PD but did not permanently prevent the progression of myopathy. Studies have been conducted using a dose of 40 mg/kg per week in both LOPD and IOPD patients. Improvements in gross motor skills, language strength, biochemical markers, and lung function measurements were shown, especially in the early stages of the disease [22].

Patients with IOPD who have been diagnosed by NBS and have received ERT should undergo regular examinations to assess the effectiveness of treatment, the appearance of new symptoms, or worsening of existing ones – monthly for the first 6 months. Particularly important is monthly cardiac evaluation in the first 4 months of life, and every 1–2 months thereafter [23]. To achieve optimal results, ERT treatment should be initiated before the onset of obvious symptoms and the development of irreversible damage, which can improve survival rates and quality of life in patients with IOPD [24].

Due to the production of antibodies by some patients, new treatments are being sought. Among them, gene therapy is mentioned. For this purpose, adenoviruses or retroviruses are used. In studies, vectors were administered into the bloodstream, then into tissues [25]. Among the limitations, however, are the need for large doses of vector [26] and the short persistence time of gene transfer [27].

CONCLUSIONS

Crucial in PD is the earliest possible diagnosis and initiation of ERT, allowing the course of the disease to be slowed and significantly prolonging the life of patients. It is important that in newborns with generalised flaccidity and cardiomyopathy, diagnosis should be expanded to include dry blood drop testing. Genetic testing for PD should also be considered. To prevent complications, it is indispensable to prevent infectious diseases (through vaccination of patients and close contacts – for example, influenza vaccination).

The differential diagnosis should include such diseases as muscular dystrophies, inflammatory joint diseases, congenital myopathies, metabolic myopathies, motor neuron disorders, or neuromuscular junction disorders.

DISCLOSURES

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4. Conflicts of interest: None.

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