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Clinical and Genetic Aspects of Pompe Disease: A Review of Current Knowledge

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Abstract:

Introduction:

Pompe disease is classified as a metabolic myopathy and is a glycogen storage disorder inherited in an autosomal recessive manner due to a mutation in the gene encoding the enzyme α-glucosidase. There are two main forms: infantile and late-onset. The disease progresses chronically, with clinical presentation characterized by progressive muscle weakness and varying degrees of respiratory insufficiency. Although incurable, causative treatment is available in the form of enzyme replacement therapy with alglucosidase alfa, a human recombinant α-glucosidase. Early diagnosis, primarily based on enzyme activity assessment, is crucial as timely treatment can extend and improve patients' quality of life.

Purpose of the work: This study aims to review and characterize the clinical and genetic aspects of Pompe disease.

Materials and methods: A comprehensive analysis of research papers available on PubMed, Google Scholar, Web of Science, Embase and Scopus was undertaken using the search terms encompassing the following keywords: Pompe disease / lysosomal storage disease / myopathy / acid alpha-1,4-glucosidase / glycogen / newborn screening / enzyme replacement therapy.

Results: Pompe disease is a life-threatening rare condition where prompt diagnosis is essential due to the availability of causative treatment. It is included in newborn screening programs for inherited metabolic disorders in some countries. Unfortunately, in Poland, routine diagnostic screening does not cover this disease. Implementing screening could simplify diagnosis and reduce the need for extensive differential diagnostics. Diagnosing late-onset Pompe disease can be challenging due to its diverse progression and symptoms. Patients with Pompe disease, even those receiving enzyme replacement therapy, require multidisciplinary care involving cardiology, pulmonology, neurology, and physical therapy.

Keywords: Pompe disease, lysosomal storage disease, myopathy, acid alpha-1,4-glucosidase, glycogen, enzyme replacement therapy

Introduction

Pompe Disease (PD), also known as Glycogen Storage Disease Type II, is an autosomal recessive inherited metabolic myopathy caused by a deficiency of acid alpha-glucosidase (GAA) - an enzyme responsible for the degradation of glycogen in lysosomes. Etiologically, it is classified as a lysosomal storage disease (LSD). Pompe Disease was the first disorder identified as an LSD in 1963, when Hers and his colleagues discovered that the cause was a deficiency of α-glucosidase. They also suggested that other diseases, such as mucopolysaccharidoses, might be caused by similar enzyme deficiencies. The disease is divided into two forms: infantile-onset Pompe disease (IOPD), described by Johannes Pompe, and late-onset Pompe disease (LOPD), described by Andrew Engel [1,2,3].

In the late 1950s and early 1960s, de Duve and his colleagues, using cell fractionation techniques, cytological studies, and biochemical analyses, identified and characterized the lysosome as a cellular organelle responsible for intracellular digestion and recycling of macromolecules. Lysosomes are membrane-bound organelles that contain acid-active enzymes involved in the degradation of complex molecules and are essential for the digestion of intracellular material during autophagy. Among these enzymes, about 50-60 are soluble and located in the lysosomal lumen, while seven are integral membrane proteins. This groundbreaking discovery led to the understanding of the physiological basis of lysosomal storage diseases [4,5].

Lysosomal storage diseases (LSDs) are congenital metabolic disorders that lead to lysosomal dysfunction and the accumulation of undegraded substances in various body tissues, causing damage. These diseases are caused by defects in single genes. Enzyme defects account for nearly seventy percent of LSDs, while the remaining cases are due to defects in enzyme activators or associated proteins. A gene at a specific chromosomal locus codes for a particular enzyme - improper coding results in inactive enzymes. Similarly, defective activators arise from mutations in activator genes. To date, seventy LSDs have been described, and it is likely that more will be discovered in the future. Most LSDs follow an autosomal recessive inheritance pattern. Three LSDs - Hunter syndrome, Fabry disease, and Danon disease - have an X-linked inheritance pattern. Besides genetics, inflammation and oxidative stress also play significant roles in LSDs. LSDs can be classified in various ways, with the most common classification based on the type of accumulated substrate. Many LSDs are named after the individuals who first described them [1,3,6].

Even within the same disease, the clinical presentation can be heterogeneous. Some lysosomal storage diseases manifest prenatally or very early after birth, while others become apparent in childhood or adulthood. Infantile forms are often much more severe than those observed in adults, with certain organs, such as the central nervous system, being more affected early in life. If prenatal diagnosis of an LSD is available, vigilant monitoring after birth can enable early detection of symptoms and prompt initiation of treatment. Recurrent fetal or neonatal deaths among older siblings or other relatives should raise suspicion of an LSD as a potential cause. Some LSDs that manifest later in life may be incidentally detected in specialized ophthalmology clinics, lipid clinics, and dialysis centers [1,3,7].

Epidemiology

The overall incidence of these diseases ranges from 1 in 5,000 to 1 in 8,000 births [1]. Pompe disease was the first condition classified as a lysosomal storage disease (LSD) [2]. Data on its incidence are limited due to the absence of a patient registry and official epidemiological data. It occurs in approximately 1 in 40,000 births. Traditionally, it is estimated that about 75% of cases are late-onset Pompe disease, while 25% are infantile onset. The incidence can vary significantly among different ethnic groups and has historically been based on retrospective data from carrier frequencies. Populations at higher risk include individuals of African American, Taiwanese, Dutch, and Israeli descent. With the implementation of newborn screening protocols, more precise incidence rates are now being obtained [8]. Pompe disease is present worldwide but is more common among African Americans (1 in 14,000 births) compared to Caucasians (1 in 60,000 adults and 1 in 100,000 children). In Europe, approximately 5,000 to 10,000 people suffer from Pompe disease, and in Poland, it may affect up to 400 individuals [3,9,10].

Pathophysiology

Glycogen is a homopolysaccharide composed of α-D-glucose residues and has a highly branched structure. In the linear chains, glucose residues are linked by α-1,4-glycosidic bonds, while branches are formed by α-1,6-glycosidic bonds. Glycogen serves as a reservoir of glucose, the main energy substrate in the body's cells. It is synthesized from excess glucose present in the blood during the fed state and is stored primarily in the liver and skeletal muscles. The degradation of liver glycogen during fasting helps maintain normal blood glucose levels (normoglycemia) [11]. Muscle glycogen is utilized within the muscle cells and is the primary source of glucose needed to generate energy for contraction [11,12].

The synthesis and breakdown of glycogen are continuous processes requiring the coordinated action of multiple enzymes. Glycogen degradation occurs in both the cytosol and lysosomes. In Pompe disease, lysosomal breakdown is impaired due to a deficiency of the enzyme α-glucosidase (GAA), also known as acid maltase. This enzyme is responsible for hydrolyzing the α-1,4-glycosidic bonds in glycogen [13].

The gene encoding GAA is located on the long arm of chromosome 17 (17q25.2-q25.3) and comprises 20 exons, including one non-coding exon and 19 coding exons [14]. The enzyme is synthesized as an inactive, membrane-bound precursor with a mass of 110 kD and undergoes several post-translational modifications. In the rough endoplasmic reticulum, it undergoes glycosylation, followed by phosphorylation of mannose residues in the Golgi apparatus. The presence of mannose-6-phosphate (M6P) residues induces transport to lysosomes via the mannose-6-phosphate receptor in this organelle. The enzyme undergoes further proteolytic processing, leading to the formation of two mature lysosomal forms with masses of 70 and 76 kD [14,15,16]. Some of the precursor protein may be secreted and taken up by M6P receptors on the cell surface and delivered to lysosomes via the endocytic pathway, which forms the basis for enzyme replacement therapy [15].

The occurrence of the disease is conditioned by the presence of pathogenic mutations in both alleles of the GAA gene. Over 500 mutations have been identified, including insertions, deletions, splice site mutations, nonsense mutations, and missense changes.

These mutations can affect various stages of GAA production, including protein synthesis, post-translational modifications, lysosomal transport, and maturation. Depending on the type of mutation, enzyme activity may be reduced to varying degrees, or may be completely absent. Most mutations are characteristic of individual families, while some are common in certain ethnic groups. In Caucasian patients, the most common defect is the c.-32-13T>G mutation in intron 1, which reduces the expression of the normal enzyme [15,16]. Other frequently occurring mutations include the c.525delT variant and the deletion of exon 18, which, depending on the variant present on the second allele, can cause varying degrees of GAA activity reduction [17].

Ineffective hydrolysis leads to the gradual accumulation of glycogen in lysosomes, which enlarge and rupture, causing the release of hydrolytic material into the cytoplasm and damage to the contractile units [14,16]. Secondary events resulting from the accumulation of unmetabolized lysosomal substrates include disruptions in autophagy and calcium homeostasis, mitochondrial abnormalities, and oxidative stress. Autophagy is the primary intracellular degradation pathway and involves the formation of an autophagosome - a double-membrane vesicle containing cellular components destined for degradation - which then fuses with the lysosome. The contents are subsequently broken down by lysosomal enzymes. In Pompe disease and many other lysosomal storage diseases, there is ineffective fusion of the autophagosome with the lysosome, resulting in impaired autophagy and the formation of large areas of accumulated autophagosomes, lysosomes, undigested autophagic substrates, and ubiquitinated protein aggregates [16,18]. This is also associated with the presence of abnormal mitochondria, which are not removed from the cell due to disrupted autophagy. The presence of dysfunctional mitochondria leads to the production and accumulation of reactive oxygen species, which damage the cell [19]. Ineffective lysosomal degradation also causes the accumulation of lipofuscin unrelated to aging [14]. Due to the high amounts of glycogen in striated muscles, skeletal muscles are primarily affected, and in children, the heart muscle is also involved. Glycogen synthesis occurs to a lesser extent in other tissues of the body as well. The disease process also affects smooth muscles of the gastrointestinal tract, blood vessels, bones, the central nervous system (CNS), and peripheral nerves [20].

Clinical Manifestations

Pompe disease affects individuals of different ages and with varying degrees of severity. This variation includes the timing of the onset of the first symptoms, the severity of the disease, and the specific organs involved. The two main types are the infantile form and the late-onset form, which can appear at any time after 12 months of age [21,22].

The most severe form occurs during infancy, where the activity of the enzyme alpha-glucosidase in this group of patients is less than 1% of normal levels. The first signs of the disease can be observed in utero. However, it is usually around the fourth month of life that the child’s clinical condition becomes concerning. Significant hypotonia and generalized muscle weakness become noticeable, resulting in abnormal motor development and respiratory failure. In infantile-onset Pompe disease, up to 100% of children exhibit cardiomegaly and hypertrophic cardiomyopathy, which can be detected by echocardiography within the first few weeks of life. If untreated, these conditions lead to left ventricular outflow obstruction. Subsequently, there is a reduction in lung volume, atelectasis, and sometimes bronchial compression.

Cardiac arrhythmias may be visible on an ECG as a shortened PR interval. Imaging studies often reveal an enlarged liver. Hearing loss is also common and can be cochlear, conductive, or mixed in origin. Feeding and swallowing difficulties arise from several overlapping factors, such as hypotonia, macroglossia, and tongue muscle weakness, which result in poor weight gain [14,21,23]. Major motor development milestones, such as the ability to roll over, sit, or stand, are not achieved. Although this most devastating form is clinically homogeneous, there is an important distinction among patients: some produce a non-functional enzyme (CRIM-positive), while others do not produce the enzyme at all (CRIM-negative). Additionally, a subgroup of patients with a similar age of onset and clinical presentation, but without or with less severe cardiomyopathies and without left ventricular outflow tract obstruction, is classified as non-classic IOPD. In this subgroup, the main features of the disease are delayed motor development and severe progressive muscle weakness leading to respiratory failure in early childhood [15]. The most common cause of death in children with IOPD is cardiorespiratory failure or aspiration pneumonia. If left untreated, the disease can lead to death before the age of 2 [9].
Common clinical presentations of infantile-onset Pompe disease [24]:

a) Musculoskeletal:
    - Progressive muscle weakness
    - Hypotonia
    - Motor delay
    - Macroglossia
    - Reduced reflexes
b) Heart:
    - Cardiomegaly
    - Left ventricle hypertrophy
c) Lungs:
    - Progressive respiratory symptoms
    - Respiratory infections
d) Others:
    - Difficulty in swallowing, eating and breastfeeding
    - Psychomotor development delay
    - Hepatomegaly

Symptoms of limb-girdle muscle weakness, respiratory dysfunction, and elevated CK levels at any time after 12 months of age are the main features of late-onset Pompe disease. Early symptoms such as exercise intolerance, muscle pain, and fatigue are often overlooked or ignored, leading to delayed diagnosis. Later, the slow, progressive degradation of axial muscles, limb-girdle muscles, and respiratory muscles, especially the diaphragm, ultimately leads to dependence on a wheelchair and assisted ventilation [15]. The late-onset form of Pompe disease is divided into two subtypes. The juvenile form is characterized by a slower progression than infantile-onset Pompe disease (IOPD). It typically presents with delayed motor development, limited walking ability due to proximal muscle weakness, swallowing difficulties, and respiratory disorders. Calf muscle hypertrophy and the appearance of Gowers' sign may suggest Duchenne muscular dystrophy. Cardiomyopathy in this form is much milder and rarely leads to left ventricular outflow tract obstruction.

Alpha-glucosidase enzyme activity levels are less than 10% of normal. Death in this group of patients typically occurs in the second decade of life [3,9,22].

The slowest progression is observed in adults, whose alpha-glucosidase activity levels are below 40% [9]. The primary symptom is weakness of the proximal muscles, causing difficulty climbing stairs, lifting arms, and getting up from a chair. In addition to the limb-girdle muscles, the disease also affects the paraspinal muscles and diaphragm. Respiratory failure develops slowly and chronically. Initially, it manifests as post-exertional shortness of breath, increased daytime sleepiness, morning headaches, and symptoms of obstructive sleep apnea. Imaging studies reveal hepatomegaly and, less frequently, macroglossia. Cardiac symptoms are rare in adults, unlike in other forms of Pompe disease. Occasionally, changes in the central nervous system are also observed. Patients may exhibit various additional symptoms, such as dysarthria, dysphagia, osteoporosis, scoliosis, and involvement of the urinary tract and anal sphincter [3,9,14,16]. In the untreated group of individuals with late-onset Pompe disease, the median age of onset was 38 years, the median survival after diagnosis was 27 years, and the median age at death was 55 years (range 23–77 years) [21].

Common clinical presentations of late-onset Pompe disease [24]:

a) Musculoskeletal:
   - Progressive muscle weakness
   - Unstable walking
   - Tiptoe
   - Low back pain
   - Reduced reflex
   - Difficulties in climbing stairs
   - Scapula alata
   - Gowers sign (dystrophy as result of proximal muscle weakness)
   - Psychomotor development delay
   - Lordosis/scoliosis

b) Lungs:
   - Respiratory insufficiency
   - Orthopnea
   - Sleep apnea
   - Effort dyspnea
   - Exercise intolerance
   - Respiratory infections

c) Others:
   - Difficulty in swallowing and eating
   - Tongue atrophy
   - Hepatomegaly
   - Morning headache
   - Night somnolence

The impact of Pompe disease primarily depends on the level of residual GAA activity; lower residual activity results in earlier onset and a more aggressive course of the disease, which is associated with a poorer prognosis.

It is important to note that the age of symptom onset does not always accurately reflect PD subtypes, as late-infantile or non-classical forms of PD can also present during infancy. The variety of overlapping clinical symptoms of PD complicates timely diagnosis and the initiation of treatment [24].

Examinations and Diagnosis of Pompe Disease

Early diagnosis plays a crucial role in the management of Pompe disease due to the availability of effective treatment. It is especially important not to delay when Pompe disease is suspected in newborns, as without treatment, death often occurs within the first year of life [23]. There is a screening test that assesses GAA activity in a dried blood spot (DBS), but it may yield false-positive results. The diagnosis should be confirmed by testing enzyme activity in leukocytes, fibroblasts, or skeletal muscle cells, or through genetic testing to confirm the presence of pathogenic mutations in both alleles of the GAA gene [25,26].

Physicians diagnose Pompe disease after excluding more common pathologies, which often leads to diagnostic delays. Early diagnosis in newborns is crucial, as untreated cases can result in death within the first year of life. Analysis of Pompe disease registry data indicates diagnostic delays in all patients. The average diagnostic delay is 1.4 months for newborns with infantile-onset Pompe disease. For patients who develop symptoms after the age of 12, the average delay extends to 6 years. According to European consensus guidelines on Pompe disease, the gold standard for diagnosis is a combination of enzymatic tests and gene sequencing [14].

The age of symptom onset, the course of the disease, and a family history of muscle diseases should always be thoroughly assessed. Progressive limb-girdle muscle weakness is one of the most commonly reported features by patients with late-onset Pompe disease and often prompts medical consultation. However, red flags include isolated respiratory muscle involvement and isolated elevation of serum creatine kinase levels, which are found in approximately 2.5% of patients in population studies. A neurological examination should assess the trunk muscles, which may be involved in the early stages of late-onset Pompe disease. Evaluating their involvement is challenging because the ability to rise from a supine position or lift the trunk from a prone position requires activating various muscle groups and can be influenced by osteoarticular conditions or respiratory dysfunction. Trunk muscle weakness may be indicated by the presence of scoliosis. Tongue weakness, which can be an early sign of the disease, should always be assessed, as it can help differentiate late-onset Pompe disease from other forms of myopathy. Clinical assessment of tongue weakness can later be confirmed using magnetic resonance imaging (MRI) with the "bright tongue sign," which inexperienced radiologists may unfortunately overlook [28].

Upon detecting symptoms suggestive of Pompe disease (PD), further clinical assessments are required to confirm the diagnosis due to the varied and non-specific nature of clinical presentations [24]. Laboratory parameters that can assist in the diagnosis include serum creatine kinase (CK) activity, as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase. However, these parameters are non-specific and may not be altered in all individuals with PD [14]. Muscle damage leads to increased CK levels, which are a sensitive marker for PD.

Elevated CK levels are observed in all patients with infantile-onset Pompe disease and most patients with late-onset Pompe disease, with levels ranging from 1.5 to 15 times above the upper limit of normal. However, it is important to note that normal CK levels can also occur in LOPD. In IOPD, a chest X-ray may reveal cardiomegaly and reduced lung volume. Respiratory muscle dysfunction is often observed in PD and may develop before limb and other muscles are involved. Therefore, assessing respiratory function is recommended. Clinically, a change in posture during the measurement of forced vital capacity (FVC), from an upright to a supine position, exceeding 20% may indicate diaphragmatic weakness. ECG changes characteristic of hypertrophic cardiomyopathy and rhythm disturbances (short PR interval and wide QRS complexes) may be observed. In LOPD, magnetic resonance imaging (MRI) can be helpful in determining the extent of muscle involvement and in monitoring disease progression. Electromyography (EMG) is a useful test that shows signs of primary muscle damage, particularly in proximal and paraspinal muscles in LOPD. Muscle biopsy may also be useful for establishing the diagnosis. In IOPD, histological signs suggestive of PD include a positive result in periodic acid-Schiff (PAS) staining, the presence of cytoplasmic vacuoles, and a reaction to acid phosphatase. This test is not widely used due to its invasiveness and the limitations of the method, including significant variability in imaging between muscle groups and even within the same muscle group. It is important to confirm biopsy results with a DNA test or by measuring GAA activity [14,23,24].

Newborn Screening for Pompe Disease

Newborn screening (NBS), including pilot studies, is currently being conducted in several countries worldwide. Early diagnosis of Pompe disease is achievable primarily through newborn screening in the absence of a family history. The dried blood spot (DBS) test, known for its non-invasive nature, offers high sensitivity and specificity for identifying individuals with Pompe disease (PD). Earlier studies using mass spectrometry have shown no significant differences between measurements in blood and those in fibroblasts. The initial pilot NBS study began in Taiwan in 2005 using a fluorometric method. From 2005 to 2018, approximately 1 million newborns were screened, revealing a higher-than-expected incidence of PD. Similar findings were reported by the Japanese NBS program, which commenced in 2013 [27].

Advancements in screening technologies for lysosomal storage disorders have led to the development of multiplex enzyme assays utilizing fluorescence-based digital microfluidics (DMF) or tandem mass spectrometry (MS/MS). Several pilot programs worldwide have assessed the feasibility of NBS for PD using these methods. Diagnosis is established based on low GAA activity in dried blood spots, lymphocytes, or fibroblasts, and confirmed by gene analysis. Additionally, urinary glucose tetrasaccharide (Glc4), a byproduct of glycogen breakdown, serves as a specific biomarker indicating reduced GAA activity or other signs and symptoms of PD [27,28,29].

Treatment

As of now, Pompe disease (PD) is an incurable condition. For many years, the only available treatment was symptomatic management of the individual disorders. Since 2006, causative treatment has been available through enzyme replacement therapy (ERT) with alglucosidase alfa, a human recombinant α-glucosidase.

In Europe, it is marketed under the name Myozyme. In Poland, this therapy is covered by a drug program. It is used for both early-onset and late-onset PD patients, with diagnosis based on a deficiency of α-glucosidase activity in peripheral blood leukocytes or skin fibroblasts and confirmed by molecular testing. Patients are evaluated for treatment effectiveness every 6 months [16,26].

The preparation is administered as an intravenous infusion every two weeks at a dose of 20 mg/kg body weight. The infusion should be started gradually, beginning at a rate of 1 mg/kg body weight/hour and increasing by 2 mg/kg body weight/hour every 30 minutes, up to a maximum rate of 7 mg/kg body weight/hour. There is a possibility of adverse effects related to the infusion, including the risk of shock [30]. Therefore, the preparation should be administered in a hospital setting with access to life-saving medications and equipment.

The effectiveness of enzyme replacement therapy (ERT) can be negatively impacted by the immune system's response. Before starting ERT, it is crucial to determine whether the patient produces cross-reactive immunologic material (CRIM), as this affects the treatment's efficacy. In CRIM-negative patients, who do not produce any endogenous acid α-glucosidase, the exogenous enzyme may be recognized as a foreign protein, potentially leading to the production of high levels of neutralizing antibodies. This often correlates with worsening clinical status and may lead to death despite treatment. Immunomodulatory treatments, such as a combination of rituximab with methotrexate and, if necessary, intravenous gamma globulins, may be used. In CRIM-positive patients, who produce some amount of GAA, antibody levels typically remain low, which enhances the effectiveness of the treatment [16,23]. Other factors influencing the outcome and effectiveness of ERT include the degree of muscle damage, age, and clinical status at the time treatment begins [20].

While the treatment does not eliminate the disease, it can extend patients' lifespan and improve their quality of life. The response to treatment varies among individual patients. In infants, ERT generally improves cardiovascular and respiratory function, as well as motor skills. In older children and adults, it often results in the improvement or stabilization of skeletal muscle strength. For patients with late-onset Pompe disease (LOPD), improvements in walking distance, as measured by the 6-minute walk test, have been observed. Respiratory function initially improves during the first few months of treatment, but may then gradually return to baseline levels. Deterioration of lung function remains a major cause of mortality in patients with LOPD. Thus, treatment significantly impacts patients' survival by preventing or slowing the decline in respiratory function [31].

Conclusions

Pompe disease is a life-threatening rare condition where prompt diagnosis is crucial due to the availability of causative treatment. In some countries, it is included in newborn screening programs for inherited metabolic disorders. Unfortunately, in Poland, routine diagnostic screening does not include this disease [3]. The introduction of screening would enable diagnosis without the need for extensive differential diagnostics. Key conditions to consider when suspecting infantile-onset Pompe disease include: spinal muscular atrophy, Danon disease, glycogen storage diseases types IIIa and IV, nemaline myopathy, myofibrillar myopathy, and mitochondrial myopathies [3,16,21].

Diagnosing late-onset Pompe disease can be challenging due to its diverse progression and the multitude of additional symptoms. In the differential diagnosis of symptoms within the spectrum of LOPD, it is crucial to primarily consider: limb-girdle dystrophy, Duchenne-Becker muscular dystrophy, polymyositis, pseudohypertrophic myasthenia, and glycogen storage diseases types V and VI [16,21,23]. Patients with Pompe disease, even those receiving enzyme replacement therapy (ERT), are severely ill and require multidisciplinary care, including cardiological, pulmonological, neurological, and physical therapy. Many patients need mobility support and respiratory assistance [20].

Genetic counseling plays a crucial role at the time of diagnosis, encompassing the assessment of genetic risk, carrier status, and preconception counseling. In most cases, the parents of affected children are heterozygous carriers. The sibling of the proband has a 25% chance of being healthy and not a carrier, a 25% chance of being affected by the disease, and a 50% chance of being an asymptomatic carrier at the time of conception. The risk of being a carrier of a pathogenic GAA gene variant for the proband's parents' siblings is 50% [21,32].

If newborn screening is implemented, it will be important to examine older siblings of newborns diagnosed with LOPD, as they may also have the condition. Carrier testing should be offered to adult family members at risk, so they can give informed consent. Testing for carrier status in minors is not recommended [1,2,16].

The offspring of a person with Pompe disease will invariably be carriers of the pathogenic gene variant. Comprehensive GAA gene sequencing for carrier status should be offered to every partner of an individual diagnosed as a carrier of the condition [1,3,16].

Disclosure:

Authors' contribution:

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