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RESEARCH **CASE REPORT**

Pompe Disease, A Rare Condition in Two Patients: Case Report

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ABSTRACT

Pompe disease, or type II glycogen storage disease, is a lysosomal storage disorder in which a deficiency in acid alpha-glucosidase (GAA) results in the accumulation of glycogen, which eventually causes progressive weakness and heart enlargement. Infantile-onset and late-onset forms of Pompe disease are distinguished. The heart is the organ most impacted by glycogen buildup in infantile-onset Pompe illness. A late-onset form, however, often presents as a weakening of the skeletal muscles that worsens over time. The key assay used to make the diagnosis of Pompe illness is enzymology, which shows a lack of lysosomal GAA activity, although molecular genetic testing for GAA mutations can also be used to confirm the diagnosis. The administration of recombinant human acid alpha-glucosidase and a large multidisciplinary team are needed for the treatment of Pompe disease.

Two patients with Pompe disease are presented in this case report. A 13-year-old female patient who is still alive and receiving enzyme replacement therapy, and a five-month-old newborn who died from cardiomyopathy.

KEYWORDS- Pompe disease; genetic disorders; cardiomyopathy; enzyme replacement therapy

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List of Abbreviations

GAA: acid alpha-glucosidase

RhGAA: recombinant human acid α-Glucosidase.

ERT: enzyme replacement therapy.

LVOT: left ventricular outflow tract.

GSD: glycogen storage disease.

CRIM: cross reactive immunologic material.

INTRODUCTION

Pompe disease, often known as glycogen storage disease (GSD) type II, is a rare, debilitating neuromuscular condition that causes chronic muscle weakness. Joanne Pompe, a Dutch physician, initially described the disease in a seven-month-old baby with generalized muscle weakness who died from idiopathic cardiac hypertrophy in 1932 [1].

The lack of acid alpha-glucosidase (GAA) results in the buildup of glycogen and, ultimately, the breakdown of muscle tissue in this autosomal recessive metabolic condition. Infantile-onset Pompe disease, a fatal progressive cardiac and skeletal muscle disorder is brought on by a complete deficiency of GAA. The nonclassical infancy, childhood, adolescent, and adult forms of Pompe disease are characterized by partial deficiency of GAA, which results in a

milder late-onset phenotype that can manifest at any age.

Pompe disease typically manifests as deteriorating cardiac function and skeletal muscle weakness, particularly the respiratory muscles. The tongue and liver may also be enlarged [2]. Respiratory insufficiency, which presents at various ages in late-onset type, is the most common cause of mortality for both onsets. Another compelling cause of mortality in the infantile-onset form is left ventricular outflow tract obstruction.
Maintaining a current immunization regimen, respiratory syncytial virus prophylaxis, and enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase (rhGAA), which was licensed for treating patients with Pompe disease in 2006, are the mainstay for the treatment [3].

The incidence of Pompe disease is 1:40000 births [4]. There are few studies conducted for this disease in the Middle East region. In a study done in the United Arab Emirates, the prevalence of infantile-onset type was reported to be 2.66 per 100,000 [5]. In the case report, we present two patients diagnosed with Pompe disease.

CASE PRESENTATION

FIRST CASE - The first patient is a 13-year-old female who was first evaluated at the age of eight months for sudden onset of dyspnea, cough, and facial cyanosis. On physical examination, the patient had no hepatomegaly but prognathism and a protruded tongue were noted. Routine blood tests were normal. Chest X-ray revealed cardiomegaly and echocardiogram revealed non-obstructive hypertrophic cardiomyopathy. The patient was started on β-blocker agent (carvedilol). Further investigations revealed a diagnosis of Pompe disease based on low GAA activity of 0.1 nmol/ml/hr (normal range: 2.2-21.5 nmol/ml/hr) and the sequence analysis of GAA gene revealed the presence of one GAA missense mutation [c.2015G>A P. (Arg672Gln)] classified as (class 1 mutation - pathogenic) using the American Collage of Medical Genetics and Genomics (ACMG) recommendations. Her older brother died at age two and a half years because of Pompe disease, and a younger sister died at age one week with no known cause of death.

The patient started to walk at age one and a half years, but the family reported increased incidence of falling and being hypotonic at age two with waddling-like gait.
An echocardiography was done in 2010, 2012 and 2013. Data are described in table 1 and reveal a clear left ventricular outflow tract (LVOT) obstruction with grade one mitral regurgitation. The patient started on rhGAA 20 mg/kg at age three years. Five years after initiating ERT, evaluation revealed less dyspnea on exertion and normal sleep pattern. She could run and had better ambulation, but still had waddling-like gait and frequent falls. Cardiac examination revealed no tachycardia or gallops, and chest X-ray revealed no cardiomegaly [Figure 1]. The patient also had scoliosis which was evaluated at age 11 by CT scan of the cervical and thoracic spine, it showed S-shaped idiopathic thoracolumbar scoliosis with a curve at level T7 to the right side and a second curve at level T12-L1 to the left. She was planned for corrective surgery after puberty. The patient's quality of life was affected as she was not attending school.

SECOND CASE - The second patient is a five-month-old male, who was admitted for sudden onset of dyspnea and cough. On physical examination, the patient was hypoactive and hypotonic. The patient had stable vital signs and no hepatomegaly. However, prognathism and tongue protrusion were noted. He was the first live birth in his family and no family history of Pompe disease was known.

Routine blood tests were normal. A chest X-ray revealed cardiomegaly [Figure 2] and an echocardiogram revealed severe non-obstructive hypertrophic cardiomyopathy and a small patent ductus arteriosus. The patient was prescribed furosemide. The diagnosis of Pompe disease was confirmed based on low GAA activity of 0.0 nmol/ml/hr and sequence analysis of GAA gene revealed the presence of two homozygous GAA nonsense mutations, c.[2560C>T]; [2560C>T] and p. [Arg 854Ter]; [Arg854Ter].

Several days later, the patient developed sudden cardiac arrest and a three-cycle cardiopulmonary resuscitation was done, however, the patient passed away.

DISCUSSION

The metabolic illnesses known collectively as Glycogen Storage Diseases (GSDs) are brought on by enzyme shortages that impair glycogen production, glycogen breakdown, or glycolysis, typically in skeletal muscles and/or hepatocytes [6]. At least 15 different types of GSD have been identified, all of which cause aberrant glycogen metabolism and glycogen buildup in these cells [7,8]. Ninety percent of cases of GSD are Von Gierke disease, which is the most prevalent type. Other types include acid maltase deficiency (Pompe disease) and Type III (Cori's disease).

Table 1. Shows the results of serial echocardiography that was done for case one. It shows a clear left ventricular outflow tract (LVOT) obstruction with grade one mitral regurgitation.

	LVEDD (3.5-5.6 mm)	LVESD (2.5-4.1 mm)	IVSD (0.7-1.1 mm)	PLVWD (0.7-1.1 mm)	FS
2010	3.6 mm	2.7 mm	1.8 mm	1.5 mm	24%
2011	-	-	-	-	-
2012	3 mm	2.3 mm	2.1 mm	1.8 mm	25%
2013	2.6 mm	1.4 mm	2.1 mm	2.5 mm	30%

LVEDD: left ventricular end-diastolic diameter

LVESD: left ventricular end-systolic diameter

IVSD: Interventricular septal diameter

PLVWD: left ventricular posterior wall diameter

FS: fractional shortening

Figure 1. Shows a chest X-ray after five years of starting enzyme replacement therapy in case one. It revealed no cardiomegaly which indicates response to treatment.

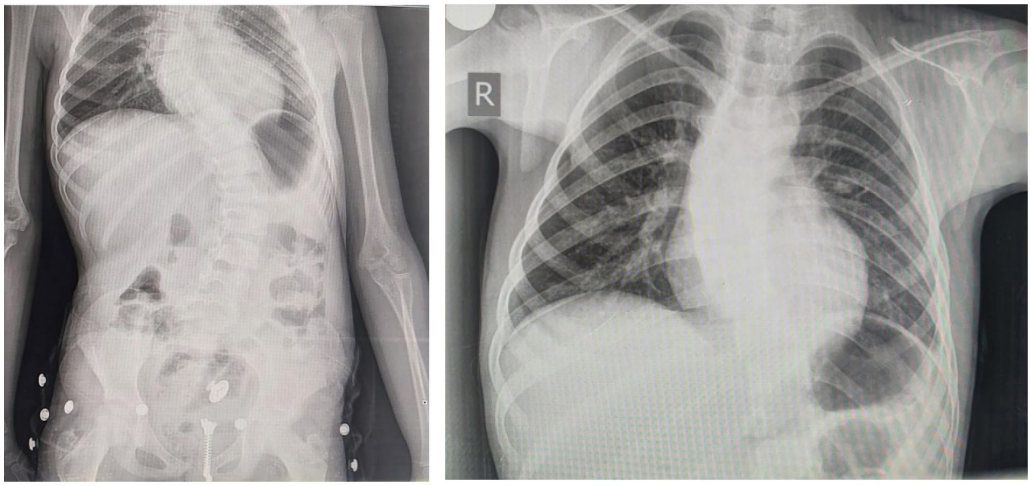
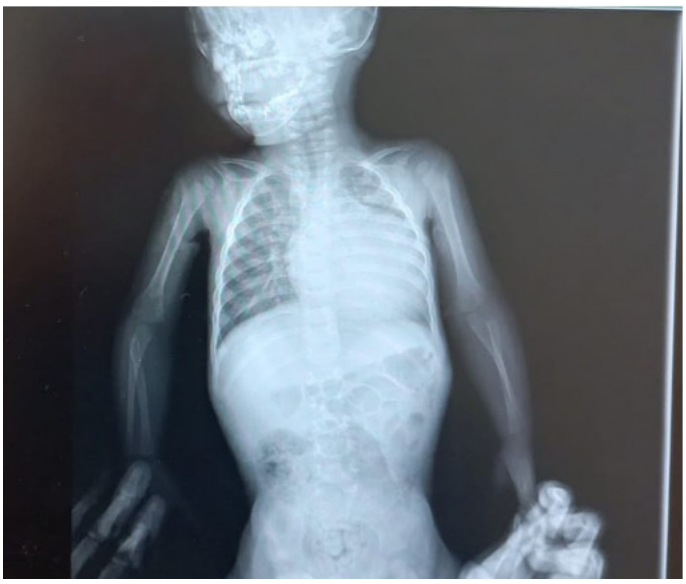


Figure 2. Shows a chest X-ray for case two at time of admission, which revealed cardiomegaly.



A deficiency of GAA results in the accumulation of glycogen in Pompe disease, also known as GSD type II, which destroys muscle tissue [9]. In addition, there are two types of Pompe disease: infantile-onset and late-onset. The consequences of glycogen accumulation in the heart are clear in infantile-onset Pompe disease [10]. Heart hypertrophy caused by lysosomal glycogen accumulation is significant, may begin in utero, and is commonly identified as early as four to eight weeks of age. Therefore, based on the preceding categorization, case two had an illness of an infantile nature. Meanwhile, it is now recognized that this illness has a variable clinical presentations and a multisystemic nature, a late-onset variant often shows a gradually deteriorating weakness of the respiratory, trunk, and proximal muscles. This variant was discovered in case one.

The gene that produces the GAA is mutated in Pompe disease [11]. Age of onset (below or over one year) and course of the disorder are determined by the degree of GAA enzyme activity [8]. The prevalence of Pompe disease is normally one per 40,000 persons, however, it is greater in some populations, such as Southeast Asians, African Americans, and Northern Europeans of Dutch heritage [4].

It is essential for the diagnosis of Pompe disease to measure the activity of the lysosomal GAA, usually in leukocytes and dried blood spot samples. It is complicated by interference from non-lysosomal maltase glucoamylase, which mandates the use of inhibitors such as acarbose along with testing at neutral and acidic pH to derive the required test sensitivity and specificity. If the results were abnormal, they should be confirmed using one of the following: enzymology in another sample type, supportive assays like periodic acid-Schiff stain (PAS)-positive vacuolated lymphocytes in a blood sample and elevated urine glucose tetrasaccharide levels, or molecular genetic testing of mutations in GAA gene, which is the gold-standard for diagnosis. There are more than 500 described mutations, with the intervening sequence (IVS) splice site mutation c.-32-13T>G associated with late-onset disease. Other common mutations include the Taiwanese mutation (resulting in p. Asp645Glu) and p. Arg854X mutation which is frequent in African/African American populations [12]. In case one, investigations revealed a diagnosis of Pompe disease based on low GAA activity of 0.1 nmol/ml/hr (normal 2.2-21.5 nmol/ml/hr) confirmed by sequence analysis of GAA gene which revealed the presence of one GAA missense mutation [c.2015G>A P.(Arg672Gln)]. In case two, the patient was also diagnosed based on low GAA activity of 0.00 nmol/ml/hr (normal 2.2-21.5 nmol/ml/hr) and the presence of two homozygous GAA nonsense mutations c.[2560C>T];[2560C>T] and p.[Arg 854Ter];[Arg854Ter].

Patients with severe infantile-onset Pompe disease can be classified into two groups based on the presence of GAA enzyme, either Cross Reactive Immunologic Material Positive (CRIM+) if the enzyme is detectable or Cross-Reactive Immunologic Material Negative (CRIM−) if not. This can be determined from the genotype or the rapid-turnaround blood-based assay in leukocytes. The generation of high titer anti-drug antibodies by patient's immune system in the CRIM− cohort is associated with worse prognosis and poor response to treatment with ERT [13]. This warrants modifications to the treatment regimen.

The management of patients with Pompe disease requires multidisciplinary teams in addition to ERT to address the multisystem manifestations. The team should include cardiology, respiratory, speech and language, physiotherapy/neurology, genetics, and metabolic physicians. Many patients need mobility support and non-invasive respiratory support. Because Pompe disease is a progressive disease, it requires improvement in disease-modifying treatment and innovative approaches to address its associated complications.

ERT for lysosomal storage disorders depends on the cross-correction principle, with the uptake of circulating enzyme protein into the cells and trafficking to the lysosome via the mannose-6-phosphate signaling system [12]. Studies have confirmed the effect of this treatment in improving the natural history of infantile-onset and late-onset Pompe disease, but there are multiple factors that affect the efficacy of enzyme replacement therapy. These include the CRIM status of infantile-onset patients, the generation of anti-drug antibodies, the degree of (irreversible) muscle damage when treatment is started, and concordantly the age and clinical status at time of starting the treatment [14]. Several approaches are used to improve the efficacy of treatment, they include increasing the dose and frequency of ERT, using immunomodulation at the time of ERT initiation for CRIM− infantile-onset Pompe disease patients (which decreases the generation of high-titer anti-drug antibodies and improve the clinical outcomes) and exercise regimens during infusions with the use of beta-agonists to increase muscle uptake of the recombinant enzyme [12]. The patient in case one was started on rhGAA 20 mg/kg at age

of three and caused a significant improvement in her symptoms.

CONCLUSION

Pompe disease is a rare genetic disorder. It is diagnosed by GAA enzyme activity level and sequence analysis of GAA gene. Although there is advancement in ERT, this disease is progressive and accounts for significant morbidity and mortality in these patients.

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