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Significance of early diagnosis and treatment of adult late-onset Pompe disease on the effectiveness of enzyme replacement therapy in improving muscle strength and respiratory function: a case report

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Abstract

Background Pompe disease, a rare autosomal recessive disorder, is caused by mutations in the acid α-glucosidase gene. Pompe disease is a congenital metabolic disorder that affects all organs, particularly the striated muscle and nerve cells. Diagnosis is typically confirmed through enzyme assays that reveal reduced acid α-glucosidase activity. Enzyme replacement therapy utilizing human α-glucosidase is an available treatment option. Timely diagnosis and treatment in the early stages of the disease significantly impact the effectiveness of enzyme replacement therapy in enhancing patient condition. Here, we present a case of a patient with Pompe disease diagnosed 20 years after the onset of clinical symptoms.

Case presentation A 38-year-old Iranian Baloch woman referred to our rheumatology clinic with progressive muscle weakness presents with a complex medical history. On mechanical ventilation for 12 years, she has endured fatigue and limb weakness since the age of 16, exacerbated following an abortion at 19. Despite undergoing corticosteroid and azathioprine therapies, the suspected diagnosis of inflammatory myopathy did not yield improvement. Hospitalization at 23 due to respiratory failure post-pregnancy led to her continued reliance on a ventilator. A dried blood spot test indicated reduced GAA enzyme activity, confirming a diagnosis of Pompe disease through genetic testing. Treatment with myozyme for 2 years demonstrated limited efficacy, as the patient experienced improved breathing but no significant overall improvement in limb-girdle muscular weakness. This case underscores the challenges and complexities involved in diagnosing and managing rare neuromuscular disorders like Pompe disease.

Conclusion Early intervention with enzyme replacement therapy plays a crucial role in halting further muscle loss and disease progression in Pompe disease patients. It is important to note that treatment during advanced stages of the disease may not yield substantial benefits. Nevertheless, enzyme instability and denaturation due

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to temperature and neutral pH levels, along with limited delivery to disease-relevant tissues, can pose challenges in treatment. However, timely diagnosis of Pompe disease is paramount for its effective management and improved outcomes.

Keywords Late-onset Pompe disease, α-Glucosidases, Glycogen storage disease type II, GAA protein, Muscle weakness, Diagnostic Errors

Introduction

Glycogen storage disease II, or Pompe disease (MIM 232300), is an autosomal recessive disorder caused by mutations in the GAA gene (MIM 606800), which encodes acid α-1,4-glucosidase, a lysosomal enzyme involved in the degradation of glycogen that results in glycogen storage, mainly in skeletal muscles but even in several other organs such as the central nervous system (CNS), heart, respiratory system, vessels, and so on. [1]. This degenerative process is sustained by the enlargement and rupture of glycogen-filled lysosomes; however, impaired autophagic flux is also present. The accumulation of glycogen results in cellular dysfunction and cell damage due to hypertrophy and lysosomal ruptures; additional factors such as impaired autophagy, disrupted lysosome signaling pathways, oxidative stress, and abnormal mitochondria also contribute to Pompe disease, causing alterations in muscle structure with the displacement of myofibrils [2–4].

Two major distinctive clinical phenotypes are recognized on the basis of the age at which the symptoms appear and the presence or absence of cardiomyopathy: the most severe classic infantile-onset type (IOPD) includes patients with less than 1% of GAA activity who develop symptoms within the first year of life and, if left untreated, rarely survive beyond 18 months, and the milder late-onset type (LOPD) with higher enzyme activity that may become apparent in childhood, adolescence, or adulthood [5, 6].

As skeletal and respiratory muscle weakness progress, patients often require ambulatory and ventilation assistance. Respiratory failure is therefore a cause of significant morbidity and the most frequent cause of death. Alglucosidase alfa (Lumizyme®/Myozyme®, Sanofi Genzyme, Cambridge, MA, USA) is an enzyme replacement therapy (ERT) used for the treatment of Pompe disease that provides patients with exogenous recombinant human GAA [7]. Alglucosidase alpha is a 110 kDa precursor protein that contains a mannose-6-phosphate group (M6P), allowing cells to import the enzyme via the M6P receptor (M6PR) and transport the compound to lysosomes [8].

Pompe disease presents as a continuum of disease severity across numerous individual myocytes. Some myocytes already exhibit irreversible changes, such as the accumulation of autophagic debris and extralysosomal glycogen in stage 4 cells, before clinical signs appear. Therefore, early initiation of ERT is important in late-onset Pompe disease [9].

In this report, we describe the case of a 38-year-old Iranian Baloch woman with progressive muscle weakness for over 20 years who had been on a ventilator for approximately 12 years and had been undergoing ERT with a diagnosis of LOPD. Unfortunately, significant improvements in muscle function, especially respiratory muscles, have not been observed due to the late start of treatment.

Case presentation

This was a 48-month observational study of a previously untreated patient with LOPD, followed from 2019 to 2022 in Iran, whose diagnosis and treatment were planned by our team. The initial evaluation was performed for 6 months. Disease screening was performed by measuring the activity of GAA in dried blood spots (DBS) using lysosomal enzyme testing at pH 3.8 with and without specific inhibition that was below their respective reference ranges. The diagnosis of Pompe disease was confirmed by DNA extraction from DBS, PCR amplification, and sequencing of all coding exons and flanking intronic regions in which two mutations were detected. The respiratory system was evaluated using chest computed tomography (CT) between 2019 and 2022 before and after ERT.

The patient was a bedridden, ventilator-dependent 38-year-old Iranian Baloch woman presenting with weakness in the limb-girdle and pelvic muscles and respiratory failure. The patient had eight brothers and two sisters, two of whom had passed away with a history of unknown muscle weakness throughout their lives, with no respiratory problems. The patient's muscle weakness was such that she could only raise her arms against gravity (3/5) and move her feet horizontally with gravity eliminated (2/5) in the limb force test. The patient was unable to perform any additional movements, and we could not conduct a spirometry test due to ventilator dependency. The electromyography (EMG) and nerve conduction velocity (NCV) tests were also performed, but the detailed results are not accessible, although a myopathic pattern was reported. The results of other examinations

were completely normal. The patient tolerated the ventilator and did not show dyspnea or cyanosis of the face, lips, or distal limbs. Her symptoms began with fatigue and limb weakness when she was 16 years of age. She got married at 19 years old and at the same age, conceived a child which led to a spontaneous abortion. After the abortion, she consulted a neurologist for muscle weakness and received prescriptions for EMG and NCV studies, as well as a muscle biopsy, with the results pending. The patient had undergone corticosteroid therapy when she was 20 years old because of a possible diagnosis of inflammatory myopathy for one year, which did not result in any improvements. At 21, the patient undergoes 1 year of pharmacotherapy with corticosteroids and azathioprine, with no change in her condition. At the age of 23 years, the patient conceives another child with no problems during the prenatal period. Afterward, the patient's respiratory status worsened, and she moved into the city in which our health center was located to follow up on her condition. The patient visited the hospital with chief complaints of respiratory symptoms, such as dyspnea and muscle weakness, such that she could no longer get up or walk without assistance. She was admitted to the intensive care unit (ICU) and later on, the wards, for 1.5 years. The patient then spends another 6 months in the ward, during which no definite diagnosis is made. She was ultimately discharged on her ventilator since there were no additional problems. Unfortunately, owing to the deletion of the patient's medical records, no information regarding the clinical course, diagnostic approaches, and treatment regimens is available.

After discharge, the patient spent 12 years at home, was bedridden, and ventilator-dependent, during which she had only had a few visits to the hospital due to issues related to her ventilator, and the condition of the patient remained unchanged. Later, the patient was referred to us, and after primary investigations, with suspicion of Pompe disease, we performed a dried blood spot test for Pompe disease, in which reduced activity of α-glucosidase enzyme was reported. Finally, to confirm our diagnosis, genetic testing was conducted where two homozygous mutations, namely c.[1555A > G];[1555A > G] and p.[Met519Val];[Met519Val] were reported, which confirmed the diagnosis of Pompe disease at the age of 36.

Treatment with myozyme (20 mg/kg every 2 weeks) was initiated and continued for 2 years. After 2 years, no progressive clinical course was observed, nor was there any improvement, except for the patient's reported easier breathing. The patient was bedridden and ventilator-dependent and the muscular force of the upper limbs was (4/5) and is (3/5) of the lower limbs.

Figure 1 shows the patient's chest CT scan in two stages: (1) before and (2) 2 years after ERT initiation, which showed consolidation and mild pleural effusion

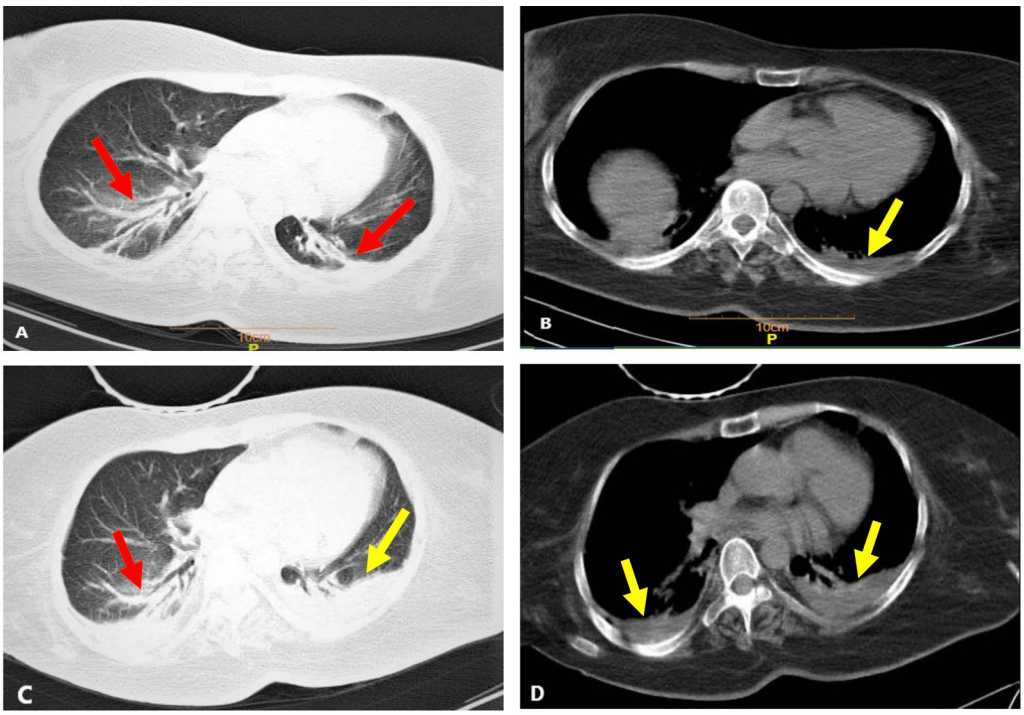

Fig. 1 The patient's chest CT scan is shown in two stages. **A** and **B** before and (**C** and **D**) 2 years after enzyme replacement therapy (ERT), which shows consolidation (red arrows) and mild pleural effusion (yellow arrows) at the bases of both lungs

at the bases of both lungs. Due to the lack of respiratory symptoms such as cough, dyspnea, phlegm discharge, and fever, and the fact that the patient has been bedridden for a long time, it can be said that this chest CT pattern is due to repeated aspirations. CT scans were performed during the coronavirus disease 2019 (COVID-19) pandemic.

A timeline summarizing the history of disease and therapeutic interventions related to patients with LOPD is presented in Fig. 2.

Discussion

In our study, the detection of two homozygous mutations c.[1555A > G] and p.[Met519Val] confirmed Pompe disease. Interestingly, other family members of the presented case were later diagnosed with Pompe disease, as confirmed by enzyme testing of alpha-1,4 Glucosidase and the following heterozygous variants: c.[631G > A];[1594G > A], (p.[Val211Met];[Gly532Ser]) and c.631G > A (p.Val211Met), c.1555A > G (p.Met519Val). Identification of heterozygous variants among family members highlights the autosomal recessive inheritance pattern of the disease; both parents must

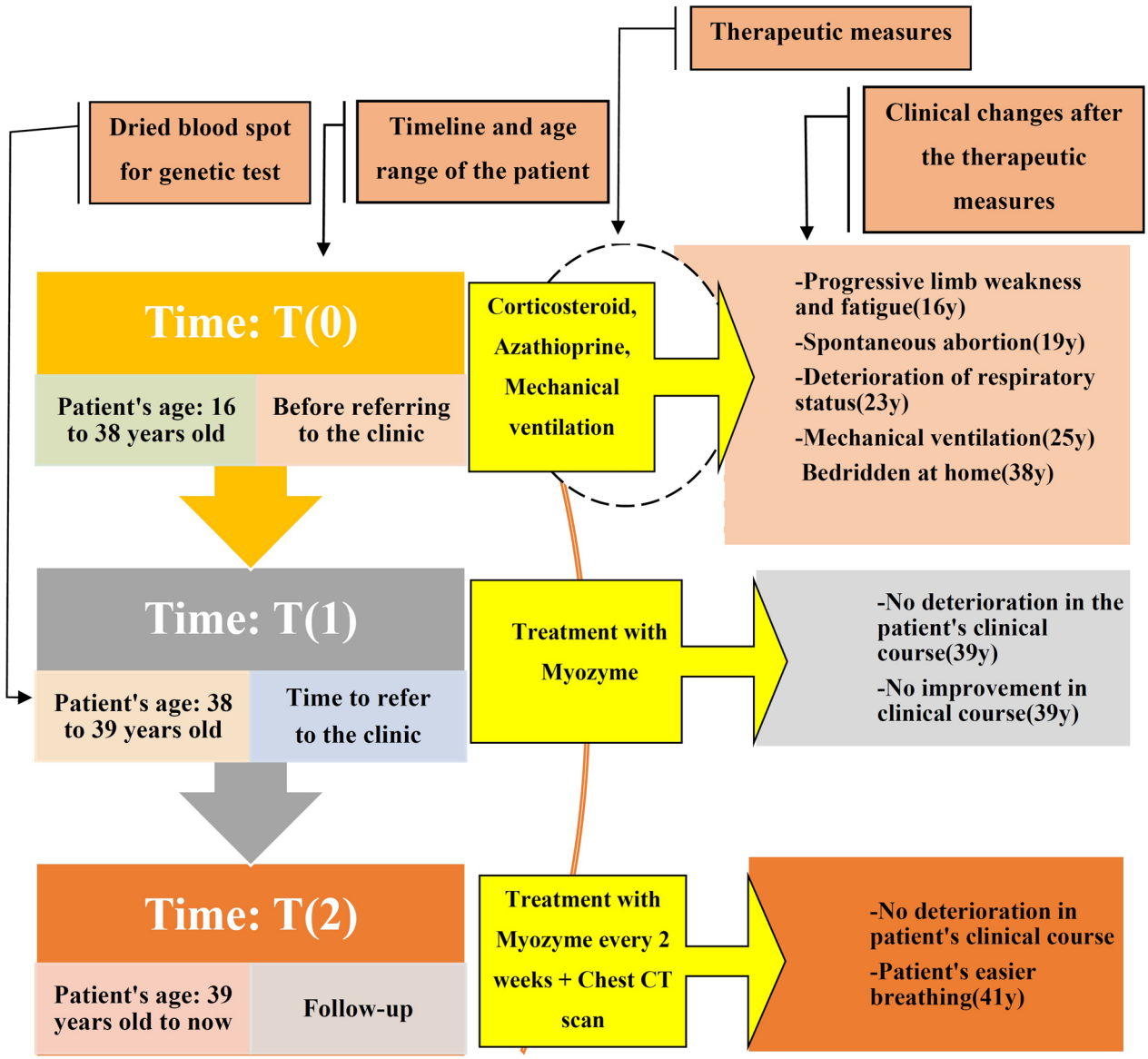

Fig. 2 A timeline of historical events and therapeutic interventions for the patient with LOPD

contribute a mutated allele for offspring to manifest the disorder.

Progressive proximal weakness exhibited a limb-girdling distribution, particularly in hip flexors. The respiratory muscles and diaphragm are involved early, but late-onset GAA deficiency may be present in those aged up to 60 years (even within the same family). Late-onset Pompe disease (LOPD) may be diagnosed in individuals > 12 months of age or in younger patients (who, however, do not exhibit clinically apparent cardiac involvement). Chronic respiratory insufficiency is a major clinical problem in patients with LOPD. The definitive etiology remains unclear; however, the intercostal muscle, diaphragm, and motor neuron pathology play a role. Patients with LOPD often require respiratory support, either inspiratory/expiratory training or noninvasive ventilation, continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP) to treat hypoxemia at night and hypercapnia during the day. Some patients require tracheostomies and mechanical ventilation. Respiratory insufficiency may occur early in the course of LOPD in patients with progressive myopathy and muscle weakness accompanied by diaphragmatic involvement. It is difficult to predict the dynamics of respiratory decline. Male sex, the extent of skeletal muscle involvement, and disease duration are known risk factors for the development of severe respiratory insufficiency. A significant link between disease severity and disease duration (rather than age per se) was evident: the risk of progression to respiratory support increased by 8% every year since diagnosis. Importantly, no genotype–phenotype correlations have been described. The available data are few, but encouraging. Patients with LOPD commonly benefit from ERT, exhibiting improvements in muscular and/or respiratory function (66% of patients treated with alglucosidase alfa) [10].

Diagnosis of LOPD is still challenging and often delayed for several reasons, such as rarity, wide clinical spectrum, overlap of signs and symptoms with other neuromuscular disorders, or variable diagnostic approaches in different countries. Since 2006, specific treatment with ERT has become available, making early diagnosis crucial for limiting disease progression [11, 12].

Two main options to support breathing in these patients are noninvasive mechanical ventilation (NIV) and assisted cough. Replacement therapy with alglucosidase alfa (Myozyme®, Genzyme), a recombinant lysosomal glycogen-cleaving enzyme, is currently the only specific pharmacological approach for LOPD. Treatment with alglucosidase alfa resulted in a mortality rate nearly five-fold lower than that of the untreated patients. Replacement therapy was associated with a reduction in forced vital capacity (FVC) decline, improvement in the 6-minute walk test, and ambulation within the first few months. These data confirm that the early initiation of ERT yields the best outcomes [13].

Pompe disease primarily affects muscle tissue. As the disease advances, the muscle tissue becomes atrophic and is gradually replaced by fatty tissue [14]. Individual variation in the effects of treatment has been well-documented in numerous studies [15]. It has been suggested that early initiation of treatment can be beneficial, particularly for more severely affected patients who may have experienced a higher degree of muscle damage and loss of functional abilities [16].

In 2020, Stockton *et al.* conducted a study aimed at investigating the effects of the time from diagnosis to treatment on 369 patients with LOPD. Their findings revealed that early initiation of ERT with alglucosidase alfa post-diagnosis positively impacted maintaining forced vital capacity (FVC) at a higher level. Conversely, the study suggested that delaying the commencement of ERT in symptomatic patients might lead to less effective preservation of respiratory function over time [17].

In 2020, Semplicini *et al.* conducted a prospective analytical study to assess the long-term benefits of ERT with alglucosidase alfa in adults with Pompe disease. The study found that there was no observed stabilization or improvement in forced vital capacity (FVC) during the initial years of treatment, aligning with findings from a Dutch 5-year prospective study [18]. Additionally, in 2016, Boentert *et al.* conducted a systematic review to provide practical recommendations for diagnosing and managing respiratory muscle weakness in LOPD. These findings highlight the importance of early initiation of appropriate treatment and strongly recommend linking patients to specialized centers [19].

In a recent study, the effectiveness of ERT in treating advanced LOPD was examined in a 57-year-old woman who had been experiencing symptoms for 30 years and had initially been misdiagnosed. This patient, who was reliant on NIV and confined to a wheelchair, was admitted for acute respiratory failure. Following 5 years of ERT treatment, she experienced significant improvements, being able to walk longer distances with the assistance of a cane or walker and only requiring NIV at night. The findings of this study suggest that ERT should be considered as a feasible treatment option for individuals with advanced LOPD [20].

It is important to recognize that even patients who may initially appear unresponsive to therapy can show improvement with ERT. This improvement can be particularly significant when considering the limitations of ERT, especially in advanced stages of disease. One limitation of ERT in advanced stages is the short duration of action, which can compromise its efficacy. Patients often

require frequent hospital infusions every other week to maintain therapeutic enzyme levels. Additionally, as the disease progresses, it becomes harder to deliver enough enzymes to muscle tissues, reducing the desired therapeutic effect. Another challenge is the precise targeting of enzymes to lysosomes, as this can impact treatment outcomes. Moreover, ERT may not address all associated biochemical disruptions, such as autophagic buildup, which can persist despite treatment. Some patients may also develop an immune response to the administered enzyme, leading to a loss of efficacy or even anaphylactic reactions [16, 20].

Understanding these limitations is crucial for making informed clinical decisions and underscores the need for complementary therapeutic approaches in managing advanced disease stages. By acknowledging these challenges, healthcare providers can better tailor treatment plans to optimize patient outcomes.

Conclusion

The absence of symptoms such as dyspnea, cyanosis, or sleep disturbance in our ventilated patient suggests that only the muscular aspect of the respiratory system was impacted. Due to the substantial time lapse between symptom onset and the initiation of ERT, coupled with the lack of respiratory improvement over 2 years, except for marginal breathing ease, it is evident that irreversible histopathologic changes had affected the patient's respiratory muscles. Consequently, ERT did not alleviate their respiratory failure. This highlights the crucial significance of early LOPD diagnosis and prompt treatment to prevent significant muscle damage and improve the effectiveness of ERT on respiratory muscle functions. As new treatment alternatives surface, it is essential to carry out further research in extensive studies to discover more efficient management and treatment choices for Pompe disease.

Limitations

The current study was limited by the inability to determine the best timing for starting ERT when symptoms first appear to achieve maximum effectiveness. The pulmonary function tests could not be conducted due to the patient's ventilator dependency. Further research with a larger sample size is needed. Moreover, the lack of a clear consensus in the literature on the ideal stage of LOPD progression for diagnosis and the most efficient time to start treatment, as well as the definition of a delayed diagnosis, complicates the categorization of other relevant studies. As a result, a more thorough understanding of the optimal timing for initiating ERT remains elusive.

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Author contributions
MM was the principal investigator of the study; KR and MH drafted the manuscript; MA contributed to the design of the study; MRD and Kiana R collected the data; SY approved the final version of the manuscript.

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Data availability
Data will be made available on request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Golestan University of Medical Sciences with under the ethical code IR.GOUMS.REC.1401.387.

Declaration of generative AI and AI-assisted technologies in the writing process
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interest
None.

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