Late-onset Pompe disease prevalence among patients with lower girdle muscle weakness in Saudi Arabia: study protocol

Aly Ezzat1,* Marwan ElBagoury1, Sherif Roushdy1, Yahia Aktham1

ABSTRACT

Background: Pompe disease (PD) is a rare genetic lysosomal storage disorder that causes glycogen deposition in different body tissues/organs. Diagnosis of PD is still difficult and often delayed due to several factors as a wide clinical spectrum, overlapping of signs and symptoms with other neuromuscular disorders, and difficulties in completing the diagnostic investigations. Therefore, it was imperative to identify cases of PD amongst the high-risk population. The primary aim of this study is to determine the prevalence of late-onset PD (LOPD) among the high-risk group [patients with limb-girdle muscle weakness (LGMW) with/without HyperCKemia of unknown cause] in the Kingdom of Saudi Arabia (KSA).

Methods: A multicenter, cross-sectional screening study with an interventional diagnostic procedure (dried blood spot enzymatic activity and genetic testing) to primarily assess the prevalence of LOPD in patients with LGMW with/without HyperCKemia in the KSA. All eligible patients were tested after obtaining written informed consent from their parents/guardians.

Results: The analyses of this study were descriptive, and the sample size was chosen to permit the collection of sufficient data in order to determine the prevalence of LOPD in patients with LGMW with/without HyperCKemia. Consequently, the sample size has not been assessed in terms of statistical power but rather precision based on the expected frequency.

Conclusion: Despite multiple previous studies reported the incidence or prevalence of Pompe disease in Saudi Arabia. Still, none of them revealed the incidence of LOPD among the high-risk group (patients with LGMW with/without HyperCKemia of unknown cause). Our screening study was the first to reveal the true numbers of LOPD among the high-risk group in Saudi Arabia, and it set a model for future studies to be conducted in the Middle-East and North Africa region.

Keywords: Pompe disease, late-onset Pompe disease, LOPD, limb-girdle muscle weakness, LGMW, Saudi Arabia.

Introduction

Pompe disease (PD), also referred to as glycogen storage disease type II or acid maltase deficiency, is a rare and often fatal genetic lysosomal storage disorder (LSD). It is caused by a deficiency in acidic alpha-glucosidase (GAA) enzyme, leading to glycogen accumulation in different body organs, especially the heart, skeletal and smooth muscle, and the nervous system [1]. This glyco- gen accumulation disturbs other organ functions leading to myopathy, respiratory weakness, physical disability, and premature death [1-4]. Based on the severity and the age in which symptoms manifested, PD can be categorized into three main categories: classic infantile-onset PD (IOPD), the more aggressive and severe form: non-classic IOPD, and late-onset PD (LOPD) [5]. The classic form of IOPD usually begins within a few months after birth [6]. While the non-classic form usually appears within the first year of life, and the LOPD may appear in late childhood or even in teenage or adult years [6]. The estimated worldwide

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Received: 14 July 2021 | Accepted: 28 October 2021
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incidence of PD is 1 in 40,000 live births [7]. However, many previous studies have reported fluctuating incidence rates, ranging from 1 in 9,000 to 1 in 300,000 live births [3–7]. LOPD is characterized by slowly progressive muscle weakness and often respiratory insufficiency, without clinically significant cardiac involvement [6–8]. LOPD has an estimated worldwide incidence of 1 in 57,000 live births per year [9]. As discussed by Toscano et al. [10], LOPD diagnosis is still difficult and often delayed; this may be due to several factors such as “rarity of the disorder, wide clinical spectrum, overlapping of signs and symptoms with other neuromuscular disorders, variable diagnostic approaches in different countries, insufficient awareness about PD clinical manifestations, and difficulties in completing the diagnostic itinerary”.

Late-onset Pompe early diagnosis (LOPED) study, reported a PD prevalence of 2.9% in patients with persistent HyperCKemia and muscle weakness at upper and/or lower limbs [limb-girdle muscle weakness (LGMW)] [11]. Another study reported a LOPD prevalence of 2.4% in 3,076 patients with HyperCKemia and LGMW [12]. There is no available data about the prevalence of LOPD in Saudi Arabia, and most of the available prevalence rates are originating from screening studies of the western countries [13]. The prevalence of LOPD in Saudi Arabia could differ from Western countries. Moreover, several publications indicate that the rate of consanguineous marriage in Saudi Arabia may reach up to 60%, and this can provide a background in which genetic diseases abound [14]. This study aimed to screen patients with LGMW with/without HyperCKemia of unknown cause with dried blood spot (DBS) testing in outpatient settings as an early screening measure followed by genetic testing for confirmatory diagnosis. In the present study, we are aiming to determine the prevalence of LOPD in the high-risk group patients with LGMW with/without HyperCKemia of unknown cause, to describe the demographic profile and clinical characteristics of all eligible patients and other comorbid conditions in all eligible patients.

Subjects and Methods

This study will be a cross-sectional multicenter screening study, with an interventional diagnostic procedure (DBS enzymatic activity and genetic testing) to be conducted for each patient meeting inclusion criteria in the outpatient setting. Patients will be considered for eligibility in the study if they meet the following inclusion criteria: (1) female or male subject aging 2-60 years (including Saudi and non-Saudi patients), (2) patient/guardian should sign an informed consent form, and (3) presenting with one of the following clinical pictures: (a) undiagnosed limb-girdle or axial muscular weakness, (b) unclassified limb-girdle muscular dystrophy, or (c) asymptomatic or mildly symptomatic, idiopathic, persistent HyperCKemia (sCK >1.5 × ULN measured on at least 2 occasions within previous 6 months). Patients with the following criteria will be excluded: (1) patients with systemic diseases or conditions and/or medications potentially associated with HyperCKemia, (2) patients in whom a GAA enzyme activity assay has previously been performed and for which the result was normal, and (3) previously DBS tested subjects with a normal enzymatic assay. All eligible patients will visit the investigator for one visit and signed the informed consent form. The primary objective of this study is to determine LOPD prevalence in the high-risk group (patients with LGMW with/without HyperCKemia). Therefore, the analyses of this study will be descriptive, and the sample size has been chosen to permit the collection of sufficient data to determine the prevalence of LOPD in patients with LGMW with/without HyperCKemia. Consequently, the sample size has not been assessed in terms of statistical power but rather precision (based on the expected frequency and secondary outcome of descriptive comorbidities).

The LOPD study revealed that the prevalence of LOPD in LGMW patients was 2.9% detected by DBS screening [11]. The recent epidemiological studies suggested that the worldwide prevalence of LGMW is 1 in every 14,500-45,000 live births [15,16]. Considering the total number of the Saudi population is 32,552,336 according to the Saudi General Authority for Statistics [17], we estimated that the total number of patients with LGMW with/without HyperCKemia in Saudi Arabia is 1,628 patients.

The 95% confidence interval (CI) when investigating outcomes of various frequencies depend on sample size and expected prevalence:

with $n$ as the number of the target population per country, $p$ as the estimated proportion (relative precision), and $z = 1.96$ for $\alpha = 5\%$.

Therefore, using the anticipated prevalence of LOPD in the LGMW population of 2.9% resulted in a sample size of 500 patients considering the 95% CI (1.4%:4.4%) with a 5% margin of error.

All of the following data will be collected in a single visit: age, gender, physical examination/vital signs, medical/surgical history, history of LGMW, family history of any genetic disease, creatine kinase (CK) lab result, other comorbidities, and disease symptoms (including musculoskeletal symptoms, CK, elevated aspartate aminotransferase, elevated alanine aminotransferase, respiratory symptoms, and gastrointestinal symptoms). Musculoskeletal symptoms include symptoms of progressive skeletal muscle weakness (as limb-girdle muscles, the difficulty of walking and climbing stairs, difficulty in rising from chair and floor, the difficulty of reaching and throwing, and frequent falls) or symptoms of muscle atrophy (as scoliosis, kyphosis, lordosis, and scapular wining). Respiratory symptoms include respiratory insufficiency/distress, exertional dyspnea, sleep-disordered breathing/nocturnal hypoventilation, or need for mechanical ventilation. While gastrointestinal symptoms include feeding/swallowing difficulties, difficulty chewing, jaw muscle fatigue, gastroesophageal reflux, or poor weight gain.

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Data will be collected and managed by electronic case report forms (eCRF) using clinical data management system. An independent contract research organization (CRO) will provide the study centers with the proper access levels, grants, and privileges to eCRFs that the investigator or the authorized designee filled. Data entry, screen development, validation rules programming, and maintenance of the study database will be the responsibility of the independent CRO. The computerized handling of the data by the CRO may generated additional queries automatically identified through pre-programmed and tested validation rules. Validation rules will be detailed in the data validation plan. In addition to automatic validation rules, medical review of data may generate further queries that will be raised on the system as well. Site staff will be responsible for resolving automatic and manual queries by confirming or modifying the data questioned through the electronic data capture system. Data collection and validation procedures will be detailed in an appropriate operational study manual. The general logistic aspects of the study are presented in Figure 1.

The study’s primary endpoint is to investigate LOPD prevalence in the high-risk group (patients with LGMW with/without HyperCKemia of unknown cause). Secondary endpoints include a description of all eligible patients’ demographic profile and clinical characteristics and report the frequency of comorbid conditions in all of the eligible patients. The descriptive analysis will be applied to analyze the collected data, and will be performed using Statistical Package for the Social Sciences (SPSS) version 18 or higher. The analysis will be conducted on two populations: (1) the eligible population: all subjects in the high-risk group (patients with LGMW with/without HyperCKemia of unknown cause) and fulfilling the inclusion and exclusion criteria, who came to the selected centers during the specified study period and signed an informed consent form and (2) the PD positive population: all patients from the eligible population for whom PD was diagnosed positive by DBS Test and genetic testing. The prevalence of LOPD will be reported using counts and percentages (%) with a 95% CI. Other variables will be described using mean ± standard deviation (SD) for continuous variables and counts for categorical variables. Patients’ variables will be compared using Mann-Whitney or Wilcoxon test (as appropriate) for continuous parameters and Chi-square test for categorical parameters. A probability value (p-value) of less than 5% will be considered to be significant.

Results

The analyses of this study will be descriptive, and the sample size will be chosen to permit the collection of sufficient data in order to determine the prevalence of LOPD in patients with LGMW with/without HyperCKemia. Consequently, the sample size has not been assessed in terms of statistical power but rather precision based on the expected frequency. Our protocol was reviewed and approved by the Institutional Review Board (IRB) of the included centers (including King Fahad Medical City, King Faisal hospital and research center, King Saud University Hospital, Security Forces Hospital, and King Fahad University Hospital). The study is supervised and funded by Sanofi Genzyme, Saudi Arabia.

Discussion

Early diagnosis of PD pursued by early treatment can significantly impact the patient’s quality of life. Previous
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We chose to conduct this epidemiological study in Saudi Arabia due to this country’s peculiar characteristics, which is the second-largest country located in the MENA region with a population of more than 33 million. The recent global figure showed fluctuating incidence rates of PD ranging from 1 per 600,000 to 1 per 14,000 live births [24]. Recent reports have noted a trend towards a higher incidence of genetic disorders among Arab countries than other parts of the world, which also apply to the incidence of LOPD [25]. The reports from the United States showed that the incidence of PD is 1/40,000 [26], while this incidence rate was much higher among African Americans, 1/14,000 [24]. This incidence was similar to the reported combined PD forms in the Netherlands as 1/40,000 [27,28]. This overall incidence was then divided into 1/138,000 for LOPD and 1/57,000 for LOPD [27,28]. Martiniuk et al. [26] also reported that the incidence of PD among European descent is 1/100,000 for IOPD and 1/160,000 for the LOPD. Data from China/Taiwan and Australia reported the incidence of PD as 1/50,000 and 1/145,000 live births, respectively [29,30]. While the lowest incidence of PD was reported in Portugal, and it was estimated to be 1 per 600,000 live births [31]. Due to the high consanguineous marriage rates (which may reach up to 60% in some countries), the MENA region is considered as one of the leading regions in the world in terms of congenital and genetic disorders prevalence. Other factors that contribute to this high rate include lack of national genetic screening programs, either high (above 35 years) or low (below 18 years) parental/maternal age, and high prevalence of metabolic disorders [25,32,33]. In a large Saudi retrospective study, authors found that out of 165,530 live births, only 3 infants were diagnosed with PD with an incidence rate of 2/100,000 live births [34]. Another retrospective study that reviewed medical records of the Pediatric Department of King Abdulaziz Medical City of 13 years (2011-2014) revealed almost the same incidence of PD (2/110,601 live births) [35]. Moreover, Al-Sannaa et al. [36] conducted a hospital-based retrospective analysis to estimate the incidence of LSDs in the Eastern Province of Saudi Arabia between 1983 and 2016. PD showed an incidence of 3.31/100,000 live births [36]. If we combine these reported incidence rates of PD presented in the literature, we could get an estimation of the PD incidence rate of about 3-4/100,000 live births in Saudi Arabia.

<table>
<thead>
<tr>
<th>Number of patients with LGMW (expected sample size)</th>
<th>Expected 95% CI of LOPED prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>(0.2:5.6) (1.7:8.9) (2.6:10.5)</td>
</tr>
<tr>
<td>200</td>
<td>(0.2:5.6) (2.2:8.4) (3.1:9.9)</td>
</tr>
<tr>
<td>250</td>
<td>(1.0:4.9) (2.05:8.1) (3.4:9.6)</td>
</tr>
<tr>
<td>300</td>
<td>(1.0:4.8) (2.8:7.8) (3.7:9.3)</td>
</tr>
<tr>
<td>500</td>
<td>(1.4:4.4) (3.3:7.3) (4.3:8.7)</td>
</tr>
</tbody>
</table>

Table 1. Expected sample size calculation.
This rate denotes the high prevalence of PD and other metabolic disorders in Saudi Arabia, compared to other world regions.

Conclusion

Despite plenty of previous studies that reported the incidence or prevalence of PD in Saudi Arabia, yet none of them revealed the incidence of LOPD among the high-risk group (patients with LGMW with/without HyperCKemia of unknown cause). Our screening study will be the first to reveal the true numbers of LOPD among the high-risk group in Saudi Arabia, and it will set a model for future studies to be conducted in the MENA region.

Acknowledgment

Medical writing support in the development of this manuscript was provided by Dr. Ahmed Salah Hussein MBBC and Dr. Omar M Hussein MD of Ray-CRO, and funded by Sanofi Genzyme, Saudi Arabia (Nojoud Center, Tahlia Street, Gate C, Jeddah, Saudi Arabia). Sanofi Genzyme will provide support for all of the study steps, including protocol formation, data collection, medical writing, and manuscript submission. In accordance with local and international regulations, Sanofi Genzyme Saudi Arabia will provide all of the required resources needed for the study to be conducted and published. Additionally, we confirm that the study protocol was peer-reviewed by the representative of Sanofi Genzyme before submission.

List of Abbreviations

- **GAA**: Acidic alpha glucosidase
- **CI**: Confidence interval
- **CRO**: Contract research organization
- **DBS**: Dried blood spot
- **eCREF**: Electronic case report form
- **ERT**: Enzyme replacement therapy
- **GP**: General practitioner
- **IOPD**: Infantile-onset Pompe disease
- **LGMW**: Limb-girdle muscle weakness
- **LOPD**: Late-onset Pompe disease
- **LSDs**: Lysosomal storage disorders
- **MENA**: Middle-East and North Africa
- **PD**: Pompe disease

Conflict of interest

- Aly Ezzat, Marwan ElBagouy, Sherif Roushdy, and Yahia Aktham are employees of Sanofi Genzyme. The study has been funded and managed by Sanofi Genzyme, Saudi Arabia.

Consent to participate

- Informed consent was obtained from all the participants.

Ethical approval

- The study's protocol was approved by the ethics committee and registered by the IRB of the related centers (including King Fahad Medical City, King Faisal hospital and Research Center, King Saud University Hospital, Security Forces Hospital, and King Fahad University Hospital

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References

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