Molecular Genetics and Metabolism Reports 15 (2018) 50–54

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

The phenotype, genotype, and outcome of infantile-onset Pompe disease in 18 Saudi patients

Zuhair N. Al-Hassnan[a,e,f,*], Ola A. Khalifa[b], Dalal K. Bubshait[c], Sahar Tulbah[a,f], Maarab Alkorashy[d], Hamad Alzaidan[f], Mohammed Alowain[f], Zuhair Rahbeeni[f], Moeen Al-Sayed[f]

[a] Cardiovascular Genetics Program, King Faisal Specialist Hospital & Research Centre (KFSH&RC), Riyadh, Saudi Arabia
[b] Genetics Unit, Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[c] Department of Pediatrics, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia
[d] Department of Genetics, KFSH&RC, Riyadh, Saudi Arabia
[e] Alfaisal University, Riyadh, Saudi Arabia
[f] Department of Medical Genetics, KFSH&RC, Riyadh, Saudi Arabia

ARTICLE INFO

Keywords:
Pompe disease
Glycogen storage disease type II
Enzyme replacement therapy
GAA

ABSTRACT

Infantile-Onset Pompe Disease (IOPD) is an autosomal recessive disorder of glycogen metabolism resulting from deficiency of the lysosomal hydrolase acid α-glucosidase encoded by *GAA* gene. Affected infants present before the age of 12 months with hypotonia, muscle weakness, and hypertrophic cardiomyopathy. Enzyme replacement therapy (ERT) has been shown to improve survival, cardiac mass, and motor skills. In this work, we aim to illustrate the genotypes of IOPD and the outcome of ERT in our population. The medical records of infants with confirmed diagnosis of IOPD who received ERT were reviewed. Eighteen infants (7 males, 11 females) were included in the study. The median age at presentation was 2 months and the median age at the start of ERT was 4.5 months. Fifteen (83.3%) infants died with a median age at death of 12 months. The 3 alive infants (whose current ages are 6½ years, 6 years, and 10 years), who were initiated on ERT at the age of 3 weeks, 5 months, and 8 months respectively, has had variable response with requirement of assisted ventilation in one child and tracheostomy in another child. All infants were homozygous for *GAA* mutations except one infant who was compound heterozygous. All infants (n = 8) with truncating mutations died. Our work provides insight into the correlation of genotypes and outcome of ERT in IOPD in Saudi Arabia. Our data suggest that early detection of cases, through newborn screening, and immunomodulation before the initiation of ERT may improve the outcome of ERT in Saudi infants with IOPD.

1. Introduction

Pompe disease, also known as glycogen storage disease type II (GSDII), is an autosomal recessive disorder of glycogen metabolism resulting from deficiency of the lysosomal hydrolase acid α-glucosidase [1]. Based on age of presentation and rate of progression, Pompe disease is classified into: (i) Infantile-Onset Pompe Disease (IOPD) which presents before the age of 12 months with hypotonia, muscle weakness, and hypertrophic cardiomyopathy; and (ii) Late-Onset Pompe Disease (LOPD) which manifests with proximal muscle weakness and respiratory insufficiency, typically without clinically significant cardiac involvement [2]. If not treated, the vast majority of patients with IOPD succumb to the disease before the age of one year due to respiratory failure and cardiac compromise [3].

Acid α-glucosidase, deficient in Pompe disease, is encoded by *GAA* which is the only gene known to be mutated in this condition. More than 500 mutations have been reported across the entire coding regions of *GAA* gene [4,5]. Molecular analysis has revealed some degree of genotype-phenotype correlation. Generally, biallelic null variants in *GAA* are expected to produce no enzyme activity leading to IOPD while milder mutations, with some residual enzyme activity, have been associated with LOPD [2,6,7].

Treatment of Pompe disease with enzyme replacement therapy (ERT) using recombinant acid α-glucosidase (Myozyme®) was approved in 2006. Compared to untreated cohort, ERT with Myozyme® has shown a clear improvement on survival, cardiac mass, and acquisition of motor skills especially if ERT is initiated before 6 months of age [8,9]. However, despite treatment, some infants affected with IOPD die during childhood with a mortality rate of 25–43% [8–10]. It has been shown that the status of cross-reactive immunological material (CRIM)

* Corresponding author at: Department of Medical Genetics, MBC-75, King Faisal Specialist Hospital & Research Centre, Takhassusi Street, PO Box 3354, Riyadh 11211, Saudi Arabia.
E-mail address: zhassnan@kfshrc.edu.sa (Z.N. Al-Hassnan).

https://doi.org/10.1016/j.ymgmr.2018.02.001
Received 29 November 2017; Received in revised form 1 February 2018; Accepted 2 February 2018

affects the outcome of ERT in IOPD. Infants with deleterious *GAA* mutations are unable to form GAA protein and are CRIM-negative while infants with some residual protein are CRIM-positive. CRIM-negative status leads to higher antibody titer to recombinant human GAA (rhGAA) and is associated with reduced overall survival and invasive ventilator-free survival and poorer clinical outcomes [11]. In addition to CRIM status, male gender, severe muscle weakness, and advanced disease duration have been observed as predictive factors of poorer outcome [12].

In this work, we retrospectively reviewed the clinical presentation, genotypes, and outcome of ERT on 18 Saudi infants with IOPD. We aimed to illustrate the correlation between the genotypes of IOPD in our population and the outcome of ERT and to shed light on the impact of early diagnosis and management. To our knowledge, our work represents the largest series pf patients with Pompe disease reported from the Arab populations.

2. Patients and methods

This study was approved by the Research Advisory Council at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. Criteria for inclusion were a definite diagnosis of classic IOPD and treatment with Myozyme®. Definite diagnosis of classic IOPD was accepted when affected patients had significantly reduced GAA activity in lymphocytes confirmed by determination in fibroblasts and/or by mutational analysis of the *GAA* gene. A retrospective chart review for all patients was conducted and the following data were extracted: age at presentation, age at diagnosis, age at start of ERT, duration of ERT, age at ventilator dependency, the best motor milestone, the current or last status of motor skills, *GAA* mutation, and age at death, or current age (Table 1). Cardiac function was analyzed in patients for whom reliable data were available at least at start, after 6 months, and after 12 months of ERT.

3. Results

Eighteen Saudi infants with IOPD were included in the study. There were 7 males and 11 females. The parents were consanguineous in all the recruited families except one (Table 1: patient #5). The cases were referred from several regional hospitals in Saudi Arabia. The median age at presentation was 2 months (range: 1 day–6 months). The median age at diagnosis was 4 months (range: 1 day–12 months) and the median age at the start of ERT was 4.5 months (2 weeks–12 months). All patients received Myozyme® at a dose of 20 mg/kg every 2 weeks except 2 infants (Table 1: patients #10 and 11) who received a dose of 40 mg/kg weekly. In spite of management with ERT, 15 (83.3%) infants died with a median age at death of 12 months (range: 3–60 months) and median age of requirement of invasive ventilation of 11 months (range: 3–60 months). Nine (60%) of them had ERT initiated before 6 months of age including one infant (patient #1) who was started on ERT at 3 weeks of age. Out of the 15 infants who died, the best motor skills achieved were: holding objects in 2 infants, sitting in 2, crawling in 1, and standing with support in 1. The majority of infants who died (11/15, 64.7%) could not achieve any appreciable gross motor skills. Reassessment of the cardiological status was obtained on 12 out of 15 infants who died, 4 had reversal of HCM.

The 3 alive infants were initiated on ERT at the age of 3 weeks, 5 months, and 8 months respectively (Table 1: patients #2, 11 and 13). The first alive patient (patient # 2, current age: 6½ years) was initiated on ERT at 3 weeks of life. Since then, she has been receiving Myozyme® at a dose of 20 mg/kg every 2 weeks. Her best gross motor skill that she has achieved was sitting without support. She has been noticed to have mild cognitive delay and language impairment with no evidence of sensorineural hearing loss. At the age of 4 years and 9 months she was diagnosed with obstructive sleep apnea and since then she has been on BiPAP ventilation at night. She also has high myopia, and has been recently diagnosed with alopecia universalis. The second alive patient (patient #11, current age: 6 years) was diagnosed with IOPD at the age of 4 months and has been on ERT since the age of 5 months. She has attained good motor skills with ability to run with no signs of motor regression. However, she has had frequent admissions with aspiration pneumonia leading to respiratory failure and mechanical ventilation. At the age of 3 years, she was diagnosed with right diaphragmatic paralysis which required plication. She was also diagnosed with swallowing dysfunction for which she was managed with laparoscopic Nissen fundoplication and gastrostomy tube insertion. A year later, she presented with severe respiratory distress due to rhinovirus infection requiring mechanical ventilation. ERT was maximized to 40 mg/kg weekly, tracheostomy had to be performed, and diaphragmatic plication was released. She improved and went home on oxygen using a tracheostomy mask. The third alive patient (patient #13, current age: 10 years) was diagnosed with IOPD at the age of 6 months. She has been on Myozyme® 20 mg/kg every 2 weeks since the age of 8 months. She has attained good motor skills with ability to run and climb upstairs. She can speak and converse well. She has been remarkably well on room air at home and has rarely been admitted with pneumonia. In all the 3 children, periodic echocardiographic assessment has shown reversal of the cardiac hypertrophy.

All infants were homozygous for mutations in *GAA* except one infant who was compound heterozygous (Table 1, patient #5). The most commonly encountered mutation was p.Glu553* (n = 6), followed by p.Gly219Arg (n = 3), p.Leu355Pro (n = 2), and p.Ser601Leu (n = 2). The following mutations were detected in single families: p.Gly643Arg, p.Ile477fs, and p.Arg586_Lys933del. The latter was the only novel mutation detected in this cohort of patients. The 3 alive children were found to have p.Gly643Arg (patient #2) and p.Leu355Pro (patients #11 and 13). Of note, patient # 8, who had the longest survival among those who died, was also homozygous for p.Leu355Pro.

Of the 18 infants, 6 were CRIM-negative and 10 were CRIM positive (Table 1). Two infants had truncating mutations (p.Ile477fs, and p.Arg586_Lys933del) which are predicted to be CRIM-negative [7]. Due to logistics reasons, CRIM analysis on these two mutations and periodic measurements of antibody titers to rhGAA could not be obtained.

4. Discussion

In this work, which to our knowledge represents the largest series of patients with Pompe disease reported from Arabs, we describe the genotypes and outcome of ERT on 18 infants with IOPD. In our cohort, all infants had a confirmed diagnosis of IOPD with the demonstration of deficient acid hydrolase level and positive biallelic GAA mutations. Treatment with ERT was initiated in all affected infants (n = 18) with a median age of 4.5 months; 11 of them (61%) were started on treatment before the age of 6 months. Yet, the mortality rate was very high (n = 15, 83.3%) with a median age of death of 12 months. The very poor response in our patients is much worse than what has been reported in other studies. In the first multinational, multicenter open-label clinical trial of Myozyme®, a follow up of 12 months for 8 infants revealed a mortality rate of 25% with a median age of death of 21.7 months [15]. The mortality rate (28%) was similar in another study that initiated ERT before the age of 6 months [9]. The outcome of treating 20 cases with IOPD in United Kingdom showed a mortality rate of 35% with a median age of death of 10 months [10]. Recently, retrospective analysis of data on two cohorts of cases with IOPD; 23 infants in Germany and 33 infants in UK, revealed a mortality rate of 43% and 40% respectively [13,14].

In IOPD, it has been shown that CRIM-negative status is associated with reduced overall survival and poor outcome [11]. In our cases, among those infants who died (n = 15), eight (53%) were homozygous for truncating mutations (p.Glu553*, p.Arg586_Lys933del, p.Ile477fs) which are known or predicted to be CRIM-negative [7]. The other 7 infants who died had missense mutations, including the p.Gly219Arg