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

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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)

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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

Table 1
Clinical and molecular data and outcome of ERT in 18 infants with IOPD.

Patient	Gender	Age at presentation	Age at diagnosis	Age at start of ERT (mo)	Duration of ERT (mo)	ERT dosage	Ventilated (age at ventilation in mo)	Gross motor skills		Reversal of HCM	Alive/ died (mo)	Mutation	CRIM status	Reference
								Best	Last/current					
1	M	2 d	2 w	3 w	20	20 mg/kg/2w	yes, 23	Standing with support	none	yes	Died, 24	c.1753_2799del (p.Arg586_Lys933del)	NK	This study
2	F	1 d	1 d	3 w	77	20 mg/kg/2 w	yes (BiPAP), 57	Sitting without support	Sitting without support	yes	Alive, 78	c.1927G > A (p.Gly643Arg)	Pos	[25]
3	F	3 d	1 mo	2 mo	1	20 mg/kg/2 w	no	none	none	NA	Died, 3	c.1657C > T (p.Glu553*)	Neg	[7,26]
4	F	2 mo	2 mo	3.5 mo	8	20 mg/kg/2 w	yes, 11	holding objects	holding objects	no	Died, 12	c.1657C > T (p.Glu553*)	Neg	[7,26]
5	F	2 mo	4 mo	4 mo	1	20 mg/kg/2 w	yes, 3	none	none	NA	Died, 5	c.784G > A(p.Glu262Lys)/ c.1802C > T(p.Ser601Leu)	Pos/Pos	[12,28]
6	F	1 mo	4 mo	4 mo	4	20 mg/kg/2 w	yes, 4	none	none	no	Died, 11	c.1657C > T (p.Glu553*)	Neg	[7,26]
7	M	3 mo	3 mo	4 mo	24	20 mg/kg/2 w	no	none	none	no	Died, 28	c.655G > A (p.Gly219Arg)	Pos	[27,29]
8	F	4 mo	4 mo	4 mo	54	20 mg/kg/2 w	yes, 60	sitting	none	yes	Died, 60	c.1064T > C (p.Leu355Pro)	Pos	[29,30]
9	M	2 mo	4 mo	4.5 mo	4	20 mg/kg/2 w	yes, 7	none	none	no	Died, 10	c.1657C > T (p.Glu553*)	Neg	[7,26]
10	M	3 w	3 mo	5 mo	5	40 mg/kg/w	no	none	none	yes	Died, 12	c.655G > A (p.Gly219Arg)	Pos	[27,29]
11	F	2 mo	4 mo	5 mo	67	40 mg/kg/w	yes, 62	running	running	yes	Alive, 72	c.1064T > C (p.Leu355Pro)	Pos	[29,30]
12	F	4 mo	6 mo	8 mo	0.5	20 mg/kg/2 w	no	none	none	NA	Died, 8.5	c.1657C > T (p.Glu553*)	Neg	[7,26]
13	F	2 mo	6 mo	8 mo	111	20 mg/kg/2 w	no	running	running	yes	Alive, 120	c.1064T > C (p.Leu355Pro)	Pos	[29,30]
14	F	4 mo	8 mo	9 mo	1	20 mg/kg/2 w	yes, 8	crawling	none	no	Died, 10	c.1802C > T (p.Ser601Leu)	Pos	[28]
15	M	4 mo	9 mo	9 mo	12	20 mg/kg/2 w	yes, 10	none	none	yes	Died, 21	c.1082C > T (p.Pro361Leu)	Pos	[28]
16	M	2 d	10 mo	10 mo	6	20 mg/kg/2 w	yes, 11	none	none	no	Died, 16	c.1431delT (p.Ile477fs)	NK	[29]
17	F	3 mo	6 mo	10 mo	18	20 mg/kg/2 w	yes, 26	sitting	sitting	no	Died, 28	c.655G > A;p.Gly219Arg)	Pos	[27,29]
18	M	6 mo	12 mo	12 mo	9	20 mg/kg/2 w	yes, 34	holding objects	holding objects	no	Died, 42	c.1657C > T (p.Glu553*)	Neg	[7,26]

Abbreviations: d:day, F:female, HCM: hypertrophic cardiomyopathy, M:male, mo:month, NA:not available, Neg:negative, NK:not known, Pos:positive, y:year, w: week.

allele which was CRIM-positive. The poor response in these 7 infants could partly be related to the late initiation of ERT (range 4–10 months).

Immunomodulation was shown to induce tolerance in patients with CRIM-negative status especially in the naïve setting. In 4 CRIM-negative infants, the combination of rituximab with methotrexate ± intravenous gammaglobulins lead to immune tolerance to rhGAA and clinical response to ERT [16]. Using another protocol of rituximab and sirolimus or mycophenolate administered before ERT in 6 subjects with IOPD, 4 were CRIM-negative, eliminated immune responses against rhGAA and optimized clinical outcome [17]. Given the very poor response in our population, it would be sensible to adopt an immunomodulation protocol on ERT- naïve setting once the diagnosis of IOPD is confirmed. Immunomodulation was not adopted in any of our cases as they died before the advent of this approach.

In our cohort, 3/18 (16.7%) infants are alive with variable response to ERT. Motor and cognitive delay is observed in one child who also has required invasive ventilation with BiPAP at night since the age of 4 years and 9 months in spite of early initiation of ERT at the age of 3 weeks. The second child needed tracheostomy at the age of 4 years with frequent admissions due to respiratory infections. The third child, whose current age is 10 years and was initiated on ERT at the age of 8 months, has attained good motor skills and has not required invasive ventilation. The cardiac status of all the three children has shown reversal of cardiac hypertrophy. One child (Table 1, patient #2) was diagnosed high myopia which has been reported in 62% of children with IOPD disease [18]. The same child was also affected with alopecia universalis which, to our knowledge, has not been reported in association with Pompe disease. As such, it is hard to discern whether this observation is a mere coincidence or part of the wide array of complications in long-term survivors of IOPD [19]. Compared to infants who died, the 3 alive children are homozygous for different mutations (p.Gly643Arg in patient #2 and p.Leu355Pro in patients #11 and 13); which are known to be CRIM positive. Of note, patient # 8, who had the longest survival among those who died, was also homozygous for p.Leu355Pro. This observation suggests that the better outcome in these three children is related, at least partly, to the genotype.

To overcome the likely poor response in cases with late management, newborn screening (NBS) for Pompe disease has been proposed. In Taiwan, where the first NBS pilot program for Pompe disease started in 2005, it has been shown that early treatment in NBS-positive cases leads to achievement of age-appropriate gains in motor development and better cardiac status [20]. Supporting the importance of early detection through NBS, very early treatment (with a mean age of 11.92 days) was associated with better physical and developmental outcomes and lower anti-rh GAA antibodies [21]. Recently, NBS for Pompe disease has been recommended by the Advisory Committee on Heritable Disorders in Newborns and Children in the United States [22]. Initiatives of NBS for Pompe have also been proposed and carried out in other countries as well [23,24]. In Saudi Arabia, given the severe phenotype of IOPD and the overall poor response associated with late management, it would be prudent to conduct a pilot NBS study before recommending the inclusion of this condition to the current national panel. The pilot study could provide insight on the incidence, phenotype, and genotype, and on the cost-benefit analysis of early detection and treatment.

From preventative standpoint, establishing the diagnosis in affected families would serve several clinical purposes. It helps in providing proper genetic counseling to parents. Recurrence of the disease in next pregnancy can be prevented either by prenatal diagnosis or preimplantation genetic diagnosis. In addition, testing at-risk family members for carrier status and targeted premarital screening would also be possible to prevent the recurrence of the disease. In our study, the 18 infants were from 18 families who were offered preventive interventions. Consequently, none of these families had another affected child with Pompe disease after establishing the diagnosis in the index case.

Due to logistics reasons, antibody titres could not be obtained in our cohort of patients. Consequently, it was not possible to ascertain if the poor outcome was solely due to the development of neutralizing antibodies or not. This limitation in our study obscures a clear conclusion on genotype-outcome correlation. However, negative CRIM status and late initiation of ERT were probably important factors in determining the poor outcome.

5. Conclusions

Our work demonstrates the spectrum of mutations and poor outcome of ERT in IOPD in Saudi Arabia. Our data suggest that further studies are needed to address the impact of early detection of cases and the role of immunomodulation in assessing the outcome of ERT in IOPD in our population.

Conflict of interest

The authors declare that they have no conflict of interest.

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