Original Article

Pompe Disease (A Rare Metabolic Disease) in Basrah, the South of Iraq

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Abstract

Background: Pompe disease is a progressive, multisystemic, debilitating, often fatal neuromuscular disease caused by a pathogenic variant in the acid α-glucosidase gene leading to GAA enzyme deficiency and lysosomal glycogen accumulation. **Objectives:** This study aimed to determine the prevalence of early onset Pompe disease in Basra, using the dried blood spot (DBS) as a screening tool, also to determine the spectrum of presentation. **Materials and Methods:** In a prospective study conducted in Basrah, Iraq, from October 2021 to September 2023, all infants with a family member diagnosed as a case of Pompe disease, hypotonia, or ventricular hypertrophy referred to the pediatric cardiology unit in Basra Cardiac Hospital were subjected to echocardiographic examination and assessment of GAA enzyme level, and genetic study by dried blood spot. **Results:** Thirty patients with confirmed Pompe disease were evaluated (12 males and 18 females), and the mean age of presentation was 3.7 months. The level of CK raged from 123 to 1471 (mean 614.3 ± 247), and the level of GAA activity ranged from 0.0 to 0.3 (mean 0.123 ± 0.07). All infants were homozygous for mutations in GAA. The most commonly encountered mutation was c.1314C>A. **Conclusion:** Pompe disease is an underestimated disease in Iraq, and the delay in the diagnosis results in established, irreversible myopathic changes even with enzyme replacement therapy and results in high mortality, so a high index of suspicion and early diagnosis will help to provide proper therapy and will help to provide a better quality of life for such patients.

Keywords: Hypertrophic cardiomyopathy, hypotonia, infants, Iraq, Pompe disease

Introduction

Pompe disease is a progressive, multisystemic, debilitating, fatal neuromuscular disease caused by a pathogenic variant in the acid α-glucosidase (GAA) gene leading to GAA enzyme deficiency and lysosomal glycogen accumulation.[1,2]

Pompe disease also known as acid α-glucosidase deficiency, acid maltase deficiency, glycogen storage disease type II, and glycogenosis type 2.[1-3] Originally it was identified in 1932 by Johannes Pompe.[1,3]

Inherited as autosomal recessive disease, with an overall incidence 1:40000 live birth.[4,5]

In the Middle East and North Africa region, consanguinity is common and considered traditional in these communities. In one of the communities in the middle east the overall rate of consanguinity was 57.7% with a high frequency of first-cousin marriages (28.4%).[6]

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Two types of Pompe disease, depending to the age of presentation and the level of enzyme activity: Infantile onset, which presented in the first year of life with generalized hypotonia, cardiomegaly and respiratory insufficiency, while the Late onset, which presented late with dominant proximal muscle weakness, and cardiac involvement is not a feature of late onset Pompe disease.[7]

Infentile-onset Pompe disease (IOPD) may present early in the fetal life (*in utero*), but more often is diagnosed at the first 3–4 months of life as manifested as marked hypotonia, generalized muscle weakness, feeding difficulties, a failure to thrive, hearing loss, hypertrophic

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cardiomyopathy with ventricular dysfunction, and respiratory distress. The patients are likely to die before the first birth day.[8]

The spectrum of *GAA* mutations is very heterogeneous. There are more than 500 variants have been known to be linked to Pompe disease. All types of mutations have been described. Although most gene mutations are restricted to a small number of families, some mutations are frequently reported.[9]

The definitive diagnosis of Pompe disease can be made by assessment the enzyme level, whether through a blood sample or cultured fibroblasts from skin or muscle biopsy. Identification of the type of gene mutations has become of great interest in the last years with the use of gene therapy.[4]

Pompe disease has no curative treatment, and clinical management consists solely of primary supportive therapy. However, recent studies have found that lifelong enzyme replacement therapy can successfully lessen the symptoms or severity of the disease.[8]

This study aimed to estimate the prevalence of early onset Pompe disease in the south of Iraq, using the dried blood spot (DBS) as a main screening tool, and also to determine the spectrum of presentation.

Materials and Methods

Patients and study design

A prospective study conducted in Basrah, Iraq, from October 2021 to September 2023, all infants with a previous family history of Pompe disease, hypotonia, or hypertrophic cardiomyopathy referred to pediatric cardiology unit in Basra Cardiac Hospital were subjected to echocardiography, GAA enzyme level assessment and genetic study by DBS.

To assess the GAA activity of the DBS samples using fluorometry techniques, the metabolic laboratory ARCHIMED Life Science GmbH (Vienna, Austria) was contacted. Thislaboratory specialized in metabolic disorders. Fluorometry was utilized to evaluate GAA activity in the DBS using the methylumbelliferyl-α-D-glucoside substrate.[10] When Alpha-1, 4-glucosidase activity was found to be <0.9 nmol/spot 21 hours, it was considered pathological, according to the filter paper containing acarbose.[11] For each patient with decreased enzyme activity, genetic and molecular analysis was carried out by Centrogene AG (Rostock, Germany) and ARCHIMED Life Science GmbH (Vienna, Austria). The GAA gene was examined genetically using Sanger sequencing.

To begin enzyme replacement therapy, all patients with proven Pompe disease are referred to the clinic of metabolic and rare disorders.

Statistical analysis

The statistical analysis of the data was carried out in SPSS-25.0 (SPSS, IBM Company, Chicago, IL 60606, USA). The results are presented as mean (±SD).

Ethical approval

The research project was approved by College of Medicine, University of Basrah according to the document number 491 on 22 Mar 2022. A verbal consent was obtained from all patient's parents before conducting the study.

Results

Thirty Iraqi infants with IOPD were involved in the study. These patients attended for cardiology clinic for one of the following reasons: recurrent chest infection, hypotonia, cardiomegaly by CXR, or history of previously affected infant.

There were twelve boys and eighteen girls. The consanguinity present in 27 of the involved families, non-consanguineous marriages were only noted in three families. The mean age at presentation was 3.7 months (range: 7 day–9 months), [Table 1]. The median age at diagnosis was 4 months. [Table 2]

All patients were from south of Iraq, 21 from Basrah, 7 Maysan, and 2 from Nasseria, 14 patients lived in the city center (46.7%), while 16 patient (53.3%) lived in the periphery where the incidence of consanguinity is high. Family history with previously affected infant with Pompe seen in 23 (76.7%) patient. [Table 1]

Eighty percent of patient presented with hypotonia, 50% had hepatomegaly and 73% had cardiomegaly on chest X ray. [Table 1]

Table 1: Description of the clinical data

Variants		No. (%)	
Sex	Male	12 (40)	
	Female	18 (60)	
Consanguinity	27 (90)	First	26 (86.7)
		Second	1 (3.3)
Family history of previous Pompe disease	23 (76.7)	1	9 (30)
		2	11 (36.7)
		>3	3 (10)
Hypotonia		24 (80)	
Hepatomegaly		15 (50)	
Cardiomegaly		22 (73.3)	
Outcome	Died	22 (73.3)	
	Alive	8 (26.7)	

Table 2: Enzymatic and echocardiographic characteristics

Variant	Minimum	Maximum	Mean	Std. Deviation
Age (month)	0.2	9	3.79	2.25
Weight (kg)	2.7	6.80	4.71	1.13
Length (cm)	48	72	56.13	5.82
CK (U/L)	123	1471	614.33	247.04
GAA enzyme level (Mmol/L/h)	0.00	0.30	0.12	0.07
IVS (mm)	9	19	14.03	2.61
LVPWT (mm)	8	20	11.56	2.71
LVMASS (g)	89	287	147.70	48.42
EF (%)	23	75	53.73	13.72
SF (%)	10	42	26.40	8.62

Table 3: Molecular characteristics of Iraqi patients

Frequency	No.	Percent
c.1076-2A	1	3.3
c.1314C>A	18	60.0
c.1327_2A	1	3.3
c.1802C>T	1	3.3
c.2078dup	1	3.3
c.2078dupA	2	6.7
c.863delG	5	16.7
c1327-2A>G	1	3.3
Total	30	100.0

The level of CK raged from 123 to 1471 (mean 614.3 ± 247), and the level of GAA activity ranged from 0.0 to 0.3 (mean 0.123 ± 0.07), [Table 2]. All infants were homozygous for mutations in GAA. The most commonly encountered mutation was c.1314C>A (n = 18), followed by c.863delG (n = 5), c.2078dupA (n = 2). Infrequent mutations detected in single families: c.1076-2A, c.1327-2A, c.1802C>T, c.2078dup, c1327-2A>G. [Table 3].

Table 2 shows the echocardiographic parameters of infants with Pompe disease with IVS 9-19 mm (14 mm ± 2.6), with LV mass 89-287 (147 ± 48 g), among these patients 15 (50%) patients complained from LV dysfunction.

The mortality among patients diagnosed with Pompe disease with or without treatment was 73.3%. [Table 1].

Discussion

Pompe disease is a rare disease, with an overall incidence 1:40000 live birth,[1,5] its incidence in Iraq appears to be underestimated. Nevertheless, no previous statewide investigation was done to offer trustworthy data on the frequency of Iraqi patients with Pompe disease.

We documented the genotypes of thirty newborns with IOPD in this paper, which to our knowledge constitutes the first and biggest series of individuals identified with Pompe disease published in the Middle East. All of the infants in our sample who had positive gene mutations and an inadequate enzyme level were diagnosed with IOPD.

The age at presentation ranged from 7 days to 9 months (3.7 ± 2.2 months) which similar to that mentioned in Fatehi *et al.*[12]

The most common presentation for Pompe disease in our cohort was hypotonia (24 (80%)) and cardiomegaly (22(73.3%)) which similar to that described by Manganelli F *et al.*[13]

Familial recurrence of Pompe disease was reported in 23 (76.7%) patients, the consanguinity reported in 27 (90%) patients, because the high rate of relative marriages in the middle east and the mode of inheritance of the disease as autosomal recessive,[6,14] both were explain the high rate of recurrence of Pompe disease.

The most commonly encountered mutation was c.1314C>A, which was reported in 18 (60%) patients, which differs from the gene mutation that is most commonly reported in Pompe disease c.-32-13T>G as mentioned by Peruzzo *et al.*[15]

The high mortality in our cohort (22, 73.3%) of the patients attributed to the low level of awareness of Pompe disease among families and pediatricians result in delayed diagnosis and established hypotonia, which results in irreversible myopathic changes even with enzyme replacement therapy.

Conclusion

We concluded that Pompe disease is underestimated in Iraq, and the delay in the diagnosis results in established, irreversible myopathic changes even with enzyme replacement therapy and results in high mortality. So increase the awareness about Pompe disease among families with the previous similar diagnosis, and among medical personal will help early detection and diagnosis and establishment of enzyme replacement therapy.

As a preventive approach, the diagnosis of Pompe disease would very helpful in different ways: Providing appropriate genetic counselling, prevention of the recurrence in the

next pregnancy by preconceptional and prenatal diagnosis, finally the detection of carrier state targeted families during the premarital assessment for inheritable diseases also can help in prevention of the recurrence of the disease.

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Conflicts of interest

There are no conflicts of interest.

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