Pompe Disease (A Rare Metabolic Disease) In Basra, the South of Iraq

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, 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 mutations in GAA. The most common 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 high index of suspicion and early diagnosis will help to provide proper therapy and will help to provide better quality of life for such patients.

Keywords: Pompe disease, Infants, hypotonia, hypertrophic cardiomyopathy, Iraq.

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]

Its also known as acid α-glucosidase deficiency, acid maltase deficiency (AMD), glycogen storage disease type II, and glycogenosis type 2.[1,2,3] 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 othe communities in the middle east the overall rate of consanguinity may reach up to 57% with a frequency of first-cousin marriages reached 28%. [6]

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].

Infantile-onset Pompe disease may presented early in the fetal life, but often the disease is diagnosed at the first 3-4 months of life as manifested as marked hypotonia, generalized muscle weakness, feeding difficulties, hearing loss, a failure to thrive, hypertrophic cardiomyopathy with ventricular dysfunction, and respiratory distress. Most of them 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 the 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 by using a blood sample or cultured fibroblasts from skin or muscle biopsy. Identification of the type of gene mutation 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 screening tool, also to determine the spectrum of presentation.

Materials and Method:

Patients and study design

In 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 ventricular hypertrophy who were referred to the pediatric cardiology unit at the 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 carried out in SPSS-25.0 (SPSS, IBM Company, Chicago, IL 60606, USA). The results 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 days to 9 months) (Table 1). The median age at diagnosis was four months.. (Table 2)

All patients were from south of Iraq, 21 from Basrah, 7 Maysan, and 2 from Nasseria, 14 patient lived in the city center (46.7%), while 16 patient (53.3%) lived in the periphery were 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)

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 common 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).

The 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 patient diagnosed with Pompe disease with or without treatment was 73.3%. (Table 1).

Table 1: Description of the clinical data

Variants		No. (%)	
Sex	Male	12 (40)	
	Female	18 (60)	
Consanguinity	27 (90)	1st	26 (86.7)
		2nd	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

Discussion:

Pompe disease is a rare disease with an overall incidence of one in every 40000 live births (1,5), and its incidence in Iraq appears to be underestimated. Nonetheless, no previous statewide investigation was done to offer trustworthy data on the frequency and features of Iraqi individuals 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 F. etal. [(12)]

The most common presentation for Pompe disease in our cohort were hypotonia (24 (80%)) and cardiomegaly (22(73.3%)) which similar to that described by Manganelli F etal. [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 reported in 18 (60%) patients, which differ from the gene mutation that most commonly reported in Pompe disease c.-32-13T>G as mentioned by Peruzzo P. 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 that result in delayed diagnosis and established hypotonia, which result 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 result in established, irreversible myopathic changes even with enzyme replacement therapy and result in high mortality. So increase the awareness about Pompe disease among families with 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.

Acknowledgments:

We thank Genzyme, Sanofi and ARCHIMEDlife GmbH Leberstraße, for their valuable role in completion of this study. They had no involvement in the design of the study; data collection, analysis; or manuscript writing, reviewing, or approval.

Conflict of Interest:

There is no conflict of interest to be declared.

References

1 van der Ploeg AT, Reuser AJ. Pompe's disease. Lancet. 2008;372(9646):1342-53. doi: 10.1016/S0140-6736(08)61555-X. PMID: 18929906.

2 Ausems MG, Verbiest J, Hermans MP, Kroos MA, Beemer FA, Wokke JH, Sandkuijl LA, Reuser AJ, van der Ploeg AT. Frequency of glycogen storage disease type II in The Netherlands: implications for diagnosis and genetic counselling. Eur J Hum Genet. 1999;7(6):713-6. doi: 10.1038/sj.ejhg.5200367. PMID: 10482961.

3 Kishnani PS, Howell RR. Pompe disease in infants and children. J Pediatr. 2004;144(5 Suppl):S35-43. doi: 10.1016/j.jpeds.2004.01.053. PMID: 15126982.

4 Mahnashi M, Alshehri A, Cupler E, Faden M, Malibari O, Hakami A, et al. Diagnosis and management of Pompe disease in Saudi Arabia. Am J Med Med Sci. 2021;11:373–81.

5 Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, Hirschhorn R, et al. The metabolic and molecular bases of inherited disease. In: Glycogen storage disease type II. Acid alpha-glucosidase (acid maltase) deficiency. USA: McGraw-Hill, 2001:3389-420))

6 Al Shehri A, Al-Asmi A, Al Salti AM, Almadani A, Hassan A, Bamaga AK, Cupler EJ, Al-Hashel J, Alabdali MM, Alanazy MH, Noori S. A Multidisciplinary Perspective Addressing the Diagnostic Challenges of Late-Onset Pompe Disease in the Arabian Peninsula Region Developed From an Expert Group Meeting. J Neuromuscul Dis. 2022;9(5):661-673. doi: 10.3233/JND-220819. PMID: 35754286; PMCID: PMC9535603.

7 Al-Hassnan ZN, Khalifa OA, Bubshait DK, Tulbah S, Alkorashy M, Alzaidan H, Alowain M, Rahbeeni Z, Al-Sayed M. The phenotype, genotype, and outcome of infantile-onset Pompe disease in 18 Saudi patients. Mol Genet Metab Rep. 2018;15:50-54. doi: 10.1016/j.ymgmr.2018.02.001. PMID: 30023291; PMCID: PMC6047460.

8 Nabiollah Asadpour, Najmeh Bagheri-Kakolaki, Infantile Pompe disease treatment haharmahal and Bakhtiari: A case report, Journal of Shahrekord University of Medical Sciences, 2019; 21(3):149-152, doi:10.34172/jsums.2019.26

9 Essawi, M., ElBagoury, N., Ashaat, E. et al. Molecular study of Pompe disease in Egyptian infants. Egypt J Med Hum Genet 2021; 22: 87. https://doi.org/10.1186/s43042-021-00203-7)

10 Van der Ploeg AT, Kroos MA, Willemsen R, Brons NH, Reuser AJ. Intravenous administration of phosphorylated acid alpha-glucosidase leads to uptake of enzyme in heart and skeletal muscle of mice. J Clin Invest. 1991;87:513–8.

11. Amalfitano A, Bengur AR, Morse RP, Majure JM, Case LE, Veerling DL, et al. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. Genet Med. 2001;3:132–8.

12 (Fatehi F, Ashrafi MR, Babaee M, Ansari B, Beiraghi Toosi M, Boostani R, Eshraghi P, Fakharian A, Hadipour Z, Haghi Ashtiani B, Moravej H, Nilipour Y, Sarraf P, Sayadpour Zanjani K, Nafissi S. Recommendations for Infantile-Onset and Late-Onset Pompe Disease: An Iranian Consensus. Front Neurol. 2021;12:739931. doi: 10.3389/fneur.2021.739931. PMID: 34621239; PMCID: PMC8490649.)

13 Manganelli F, Ruggiero L. Clinical features of Pompe disease. Acta Myol. 2013;32(2):82-4. PMID: 24399863; PMCID: PMC3866902.

14 Lacombe D, Thambo JB, Fayon M, Goizet C, Guffon N. RECURRENCE OF POMPE DISEASE IN FIRST COUSINS. Genet Couns. 2015;26(2):227-31. PMID: 26349193.

15 Peruzzo P, Pavan E, Dardis A. Molecular genetics of Pompe disease: a comprehensive overview. Ann Transl Med 2019;7(13):278. doi: 10.21037/atm.2019.04.13