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Infantile-Onset Pompe Disease: About 5 Cases

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Abstract | **Case Report**

Pompe disease, is a rare severe, autosomal, recessive, and progressive genetic disorder caused by deficiency in alpha-glucosidase. The classic infantile-onset is the most broadly known form of Pompe disease, which presents with severe heart involvement and clear hypotonia, while the non-classic presentation occurs with early motor involvement. Late-onset Pompe disease develops in adults, but it may also occur during childhood or adolescence. We report a retrospective and descriptive study of a series of five Moroccan patients with confirmed diagnosis of IOPD; and we update the available clinical and diagnostic findings because an early management with enzyme replacement therapy may improve patients' survival and quality of life.

Keywords: Cardiomyopathies; Glycogenosis type II; Motor disorders; Muscular hypotonia; Pompe disease.

BACKGROUND

The aim of this case series study is to describe the epidemiological aspects and most common clinical manifestations of a group of Moroccan patients with infantile-onset Pompe disease.

METHODS

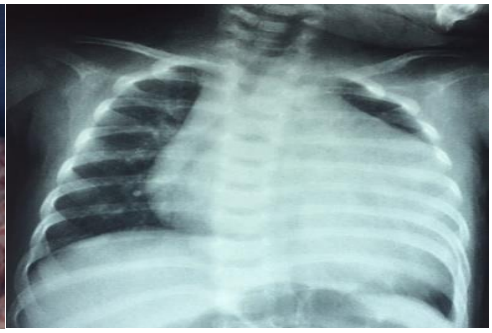
We report a retrospective and descriptive study of a series of five Moroccan patients with confirmed diagnosis of IOPD. Data were obtained from patients in one Moroccan referral center (Department of Pediatric, Mohamed V Military Hospital, Rabat). Pompe disease was suspected based on clinical, chemical and radiological features and confirmed by enzyme activity assay for alpha-glucosidase GAA. Genetic mutation research was realized for three patients. One patient is currently under treatment by enzyme replacement therapy ERT for 6 months.

Table 1: Clinical caracteristics, Enzymatic activity of AAG and gene mutaion of patients with infantile-onset Pompe disease

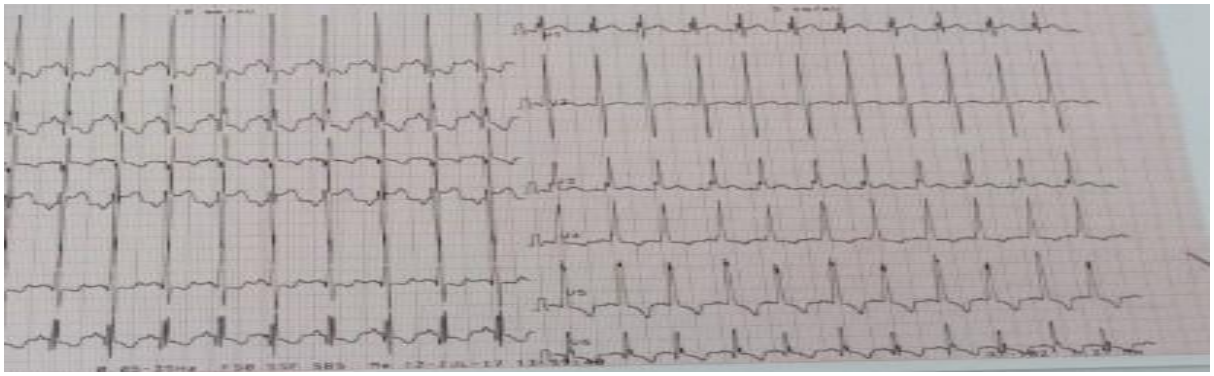
Case	Gender	consanguinity	Initial symptom	Age at diagnosis	ASAT/ALAT/CK	CR	ECG shortened PR & high-voltage QRS	HCMP EF	Enzymatic activity of AAG (Leukocyte)	Genetic analysis
1	M	+	Tachycardia Hypotonia Dyspnea Macroglossia HMG Hypotrohie	8	165/107/690	0,7	+	+ 53%	0,25 (>3,3µmol/l/h)	
2	M	+	Hypotonia Dyspnea Heart failur -	8	189/115/602	0,68	+	+ 45%	0, 3 (>3,3µmol/l/h)	
3	F	-	Tachycardia Hypotonia dyspnea macroglossia HMG	7	209/131/547	0,62	+	+ 57%	0,1 (>3,3µmol/l/h)	C.[2040+3A>C]; [2040+3A>C]
4	F	+	Tachycardia Hypotonia Dyspnea macroglossia HMG	8,5	171/108/580	0,76	+	+ 60%	0,2 (>3,3µmol/l/h)	C. [236_246del11]; C.[655G>A].
5	M	+	Hypotonia	2	216/96/602	0,60	+	+ 61%	00 (>3,3µmol/l/h)	C. [236_246del11]; C.[655G>A].

HCMP: hypertrophyic cardiomiopathy, EF: Ejection fraction, CR: Chest radiography

Patient n°4 at diagnosis (8,5 months)

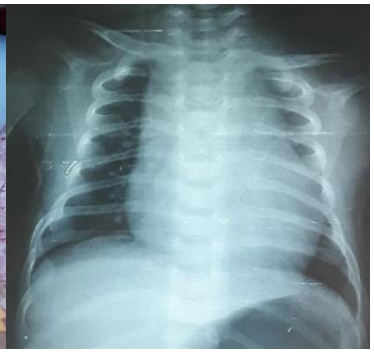


CR a large cardiac silhouette Hypotonia & severe motor delay

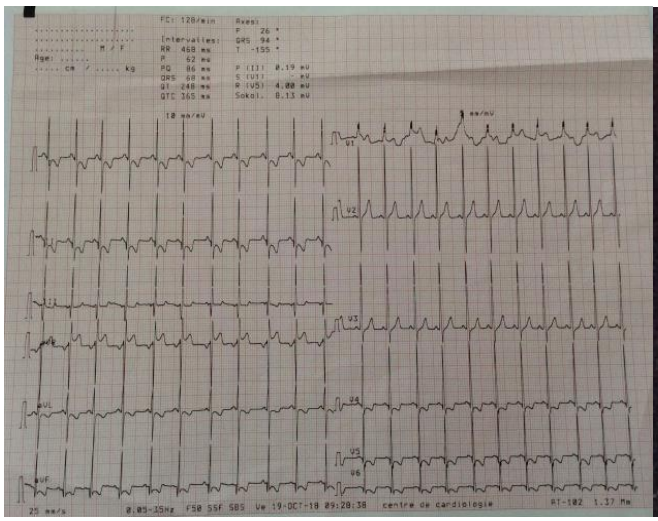


ECG: high-voltage QRS and shortened PR

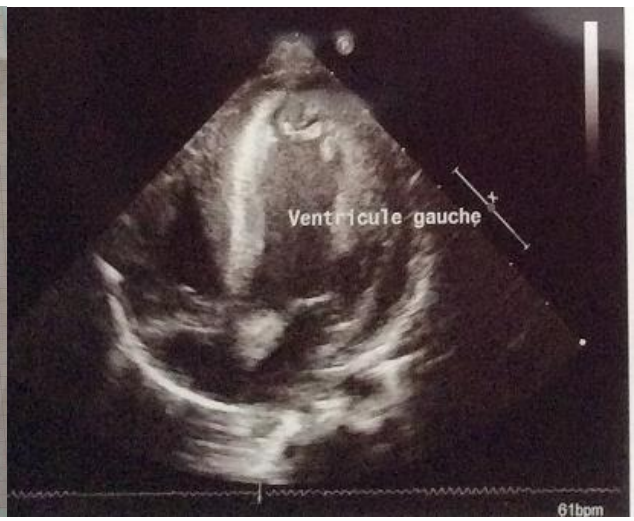
Patient n° 5 at diagnosis (2 months)



CR a large cardiac silhouette ICT: 0,60



ECG: high-voltage QRS and shortened PR



Echocardiography: Concentric left ventricular hypertrophy

RESULTS

Series of five Moroccan patients from four distinct families. Their median age at diagnosis was 6, 7 months (range: 2 months - 8, 5 months), consanguinity was observed in 80 %, Sex ratio is 1, 5 (3Males / 2 Females). The main circumstance of discovery was dyspnea (4 cases); hepatomegaly was noted in 4 cases and generalized hypotonia was noted in all cases. Chemical investigations showed increased serum GOT, GPT, CK. The ECG showed signs of left ventricular hypertrophy and repolarization disorders in all cases. Echocardiography showed hypertrophic cardiomyopathy in all cases. GAA activity was decreased more than normal range for all cases. The genetic study carried out in three cases showed a mutation of the AAG gene in the homozygous state in one case: c. [2040+3A > C]; [2040+3A>C] and heterozygous mutations were detected in two cases: c. [236_246del11]; [655G>A]. The death in a cardiorespiratory failure was noted in four cases. ERT was found to be well tolerated and effective in attenuation symptoms for one patient.

DISCUSSION

Pompe disease (PD), known as acid maltase deficiency or glycogenosis type II, is a rare severe, autosomal, recessive, and progressive genetic disorder caused by deficiency in acid alpha-glucosidase (AAG) [1]. This condition is recognized as the first lysosomal storage disease that was described for the first time by Dutch pathologist Johannes Pompe in 1932, in a female child who died after presenting severe muscle weakness and hypertrophic cardiomyopathy, glycogen storage in the heart, liver, kidneys, and skeletal muscle [2, 3].

In 1979, Hers demonstrated that glycogen accumulation was caused by lysosomal acid maltase deficiency. The gene related to this enzyme (GAA) was identified in the long arm of chromosome 17, and more than 450 mutations have been described [4, 5].

There are different presentations: infantile-onset PD (IOPD), late-onset.

PD (LOPD), and intermediate forms [6, 7].

Diagnosis of Late-Onset Pompe Disease. The diagnosis of Pompe disease, particularly the late-onset form, is often difficult because it can clinically resemble a myriad of other neuromuscular disorders. A high level of clinical suspicion is necessary for a timely and accurate diagnosis [8]. A complete discussion of the clinical presentation and diagnostic guidelines for late-onset Pompe disease was published in 2009 [9]. Briefly, physical examination usually reveals more proximal than distal weakness. The pelvic girdle is affected to a greater degree than the shoulder girdle, and weakness of the abdominal muscles and diaphragm may be present early on. Scapular winging, paraspinal muscle atrophy, scapuloperoneal weakness [10], and facial involvement with weakness or ptosis (unilateral or bilateral) have also also been observed [11, 12].

Clinical myotonia is absent, but electrophysiological myotonia, especially in the paraspinal muscles, is detected frequently [9].

Fatigue of the jaw muscles and difficulties with chewing and swallowing often result in inadequate intake of protein, calories, vitamins, and minerals, which leads to endogenous muscle protein breakdown [8].

Swallowing dysfunction can be diagnosed in patients with late-onset Pompe disease by a videofluoroscopic swallowing assessment [8].

Sensory, cerebellar, and cognitive involvement have not been reported [10].

Laboratory testing usually reveals nonspecific elevation of serum creatine kinase [13].

Needle electromyography (EMG) studies often indicate myopathic potentials with increased muscle membrane irritability and myotonia [9].

Of note, even when needle EMG findings in limb muscles are normal, abnormalities may still be found in the paraspinal muscles alone [10].

Pulmonary function testing may reveal decreased forced vital capacity (FVC); a detailed discussion of pulmonary involvement is provided in what follows. Although the clinical phenotype of late-onset Pompe disease varies, genetic analysis of the GAA gene [8], or a determination of the level of GAA enzyme activity in blood, fibroblasts, or muscle tissue, can provide a definitive diagnosis [3, 2]. Although muscle biopsy often reveals a vacuolar myopathy with increased amounts of glycogen [12, 13] a normal muscle biopsy does not exclude late-onset Pompe disease.

It is very important to diagnose Pompe disease early to begin treatment. Early treatment is critical to delay some of the permanent damage caused by the disease.

It is possible to have tests before or during a pregnancy to find out if the baby is affected [16].

Testing for Pompe can be done before pregnancy by a process called preimplantation genetic testing.

The specific treatment available for PD at all ages is enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase (rhAAG),

alglucosidasealfa (Myozyme®, Genzyme Corporation), approved for the United States by the Food and Drug Administration (FDA) in 2006 [16, 17].

CONCLUSION

Early diagnosis and initiation of ERT are critical for improvements in patient-important outcomes and quality of life.

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