Clinical Case Report

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Infantile-onset Pompe disease with neonatal debut

A case report and literature review

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Abstract

Rationale: Infantile-onset Pompe disease, also known as glycogen storage disease type II, is a progressive and fatal disorder without treatment. Enzyme replacement therapy with recombinant human acid alpha-glucosidase (GAA) enhances survival; however, the best outcomes have been achieved with early treatment.

Patient concerns: We report a case of a newborn with infantile-onset Pompe disease diagnosed in the first days of life who did not undergo universal neonatal screening. The patient was asymptomatic, with a general physical examination revealing only a murmur. The clinical presentation was dominated by the neonatal detection of hypertrophic cardiomyopathy, without hypotonia or macroglossia.

Diagnoses: Pompe disease was confirmed in the first week of life by GAA activity in dried blood spots, and a GAA genetic study showed the homozygous mutation p.Arg854X.

Interventions: Parents initially refused replacement therapy.

Outcomes: The patient experienced recurrent episodes of ventricular fibrillation during central line placement and could not be resuscitated.

Lessons: Although Pompe disease is rare, and universal screening has not been established, neonatologists should be alerted to the diagnosis of Pompe in the presence of hypertrophic cardiomyopathy. Diagnosis is achieved in a few days with the aid of dried blood spots.

Abbreviations: CRIM = cross-reactive immunological material, EKG = electrocardiogram, ERT = enzyme replacement therapy, GAA = acid alpha-glucosidase, HCM = hypertrophic cardiomyopathy, NBS = newborn screening, PD = Pompe disease.

Keywords: cardiac hypertrophy, case report, echocardiography, glycogen, Pompe

1. Introduction

Pompe disease (PD) (OMIM 232300) is an autosomal recessive glycogen storage disorder caused by deficient activity of the lysosomal enzyme acid alpha-1,4-glucosidase (GAA, EC 3.2.1.20).[1] GAA deficiency leads to glycogen accumulation in lysosomes and the cytoplasm, resulting in tissue destruction. The enzyme is ubiquitous, but the most affected cells are muscle and cardiac tissues.[1] The incidence of PD is 1/40,000 inhabitants but is higher in certain populations, such as African–Americans (1/14,000).[2] Enzyme activity correlates with genotype. The *GAA* gene is located on chromosome 17q25, and more than 450 mutations of this gene have been found (http://www.pompecenter.nl).

In infants with infantile-onset PD, GAA activity levels are typically <1% of the mean activity in healthy control subjects. This form of PD, regarded as a muscular disorder, presents as a spectrum of features in which symptoms typically present during the first few weeks of life. Hypotonia, progressive weakness, macroglossia, and hepatomegaly are common symptoms.[3,4] The heart is also characteristically affected; an electrocardiogram (EKG) showing high voltages, repolarization abnormalities, and/or short PR intervals should alert clinicians to the possibility of PD.[5] Echocardiography is the leading tool for diagnosis and usually reveals marked myocardial thickening, which can affect either ventricle and can obstruct the ventricular outflow tracts, especially the left. Respiratory muscle involvement can cause respiratory failure. Patients with classic infantile-onset PD rarely survive beyond 1 year of age without treatment;[1] the mean age at death in studies with large patient groups is 6.0 to 8.7 months.[1] Enzyme replacement therapy (ERT) with recombinant human GAA is safe and effective for patients with PD and is the

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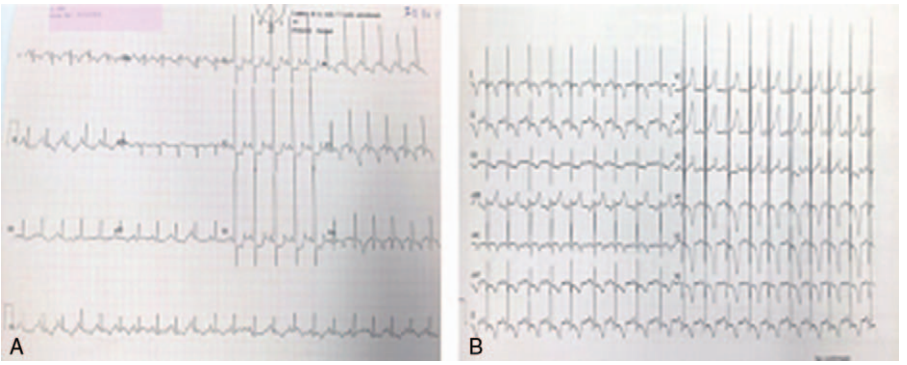

Figure 1. (A) and (B) electrocardiogram (A) at diagnosis and (B) at 3 months of age.

only treatment that has shown increased survival. The best motor outcomes have been achieved when ERT was initiated early. Early diagnosis is therefore essential.[6–8]

The response to ERT is, however, heterogeneous. Treatment effectiveness depends on the patient's age when ERT is started, their pre-existing muscle damage and their baseline cross-reactive immunologic material (CRIM) status. Infants are considered CRIM-positive if they have residual GAA enzyme activity. Exposure to the native GAA enzyme results in the development of immune tolerance to the GAA protein. Consequently, CRIM-negative patients do not have immune tolerance to GAA and mount an antibody response to the native enzyme when it is administered as ERT.[9] These patients tend to respond poorly to ERT, but the response can be significantly improved with immunomodulatory therapy. The most commonly used regimen is rituximab, methotrexate and intravenous immunoglobulin.[4,10] Based on a pooling of clinical studies, 28% of PD cases are infantile onset, approximately 85 and 75% of which are classic infantile onset and CRIM-positive, respectively.[10,11]

We present a case of a newborn with an onset of hypertrophic cardiomyopathy (HCM) in the first days of life who was diagnosed with infantile-onset PD with the aid of dried blood spots.

Ethical approval was not applicable due to the case report. Written consent was obtained from the patient's mother for this report.

2. Case report

A male infant, with a gestational age of 37 weeks and 4 days and a birth weight of 3.640 kg, was transferred to our hospital with a diagnosis of HCM at 48 hours of life. The patient was the third child of nonconsanguineous Nigerian parents and had no family history of disease. A heart murmur was detected during the first hours of life, and an echocardiogram showed severe biventricular hypertrophy.

Upon arrival at our unit, the newborn was asymptomatic and had no dysmorphic features or weakness. A cardiac assessment revealed cardiomegaly, and both an EKG (Fig. 1A) and a 2-dimensional (2D) echocardiogram showed severe biventricular hypertrophy. The 2D echocardiogram also showed a ventricular septal thickness of 11 mm and a left ventricular posterior wall thickness of 8 to 9 mm, which was more significant at the apical level (Fig. 2). The systolic function was normal. The severe biventricular hypertrophy as assessed by the EKG and 2D echocardiogram, along with the short PR interval, raised the suspicion of PD.

Laboratory tests showed that the only abnormal values were increased creatine phosphokinase (4168 UI/L) and glutamic oxaloacetic transaminase (250 UI/L). No acidosis or hypoglycemia was detected. The results of the brain and abdominal ultrasounds were normal. Dried blood spots were sent to a reference hospital to assess GAA activity, and results in the diagnostic range of PD were obtained at 7 days of life (0.9 μmol/L/h, reference range 1.35–6.0 μmol/L/h at pH 3.8).

A genetic test confirmed a severe homozygous mutation in *GAA*: exon 18 c. 2560C > T (p.Arg854X). The determination of CRIM status was positive. ERT was indicated; however, after being informed by the multidisciplinary PD team consisting of a neonatologist, expert neurologist, cardiologist and geneticist, the parents refused therapy for the patient. The infant was therefore treated as an outpatient in cardiology and neurology. He was readmitted at 3 months of age with cardiac worsening during an upper respiratory infection 2 months later. At that time, the EKG (Fig. 1B) and 2D echocardiogram showed significantly increased hypertrophy and systolic left ventricular dysfunction. The patient had increasing respiratory failure and was admitted to the prenatal intensive care unit. Treatment with beta-blockers was initiated, consent for ERT was obtained, the medication was administered, and the patient was discharged. A central line placement for the medication was deemed necessary and was

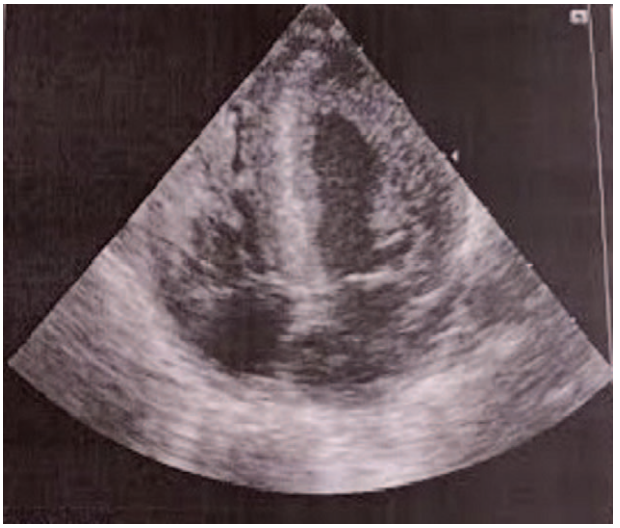

Figure 2. A 2D echocardiogram with an apical 4-chamber view at diagnosis.

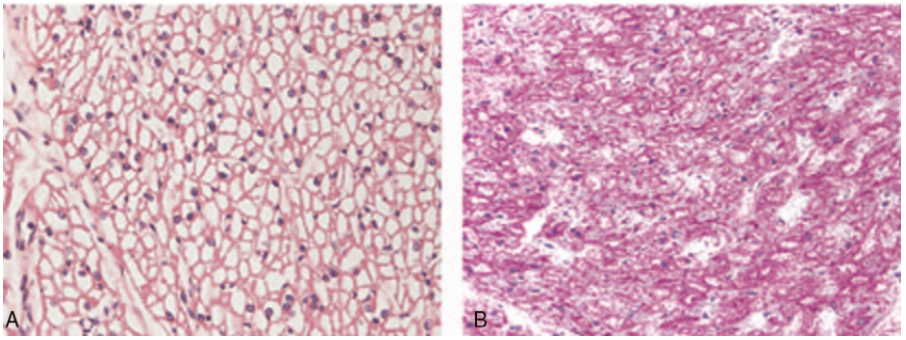

Figure 3. Photomicrography of the myocardium. A (H&E, 400×) and B (PAS, 400×), showing diffuse myocyte vacuolization. H&E = hematoxylin and eosin, PAS = periodic acid–schiff.

scheduled. The patient experienced recurrent episodes of ventricular fibrillation during the procedure and could not be resuscitated.

A postmortem examination showed massive cardiomegaly with severe subsarcolemmal vacuolization of the cardiac muscle, which exhibited prominent glycogen accumulation (Fig. 3). There were also moderate vacuoles due to glycogen accumulation in the skeletal muscle (tongue, proximal esophagus, diaphragm, deltoid, and quadriceps femoris), smooth muscle (urinary bladder and gastrointestinal tract) and in the neurons and glial cells of the nervous system.

3. Discussion

Infantile PD is the most severe form within the spectrum of Pompe phenotypes and is mainly characterized by cardiomyopathy, hypotonia, and respiratory insufficiency. This progressive disorder is fatal after the first year of age without treatment. ERT has been shown to significantly improve survival, quality of life, motor outcomes, and cardiac hypertrophy[12] in most patients. However, the best outcomes have been achieved when treatment was initiated early,[13] before muscle damage occurs.

Table 1

Infantile-onset Pompe disease. Case reports of the literature without newborn screening[15,17–35].

Reference	Pt	Sex	Familial history of PD/ (CP)	Age at debut	Presentation	Age at diagnosis
Lacombe et al[17]	1	F	First cousin: infantile-onset PD (case 2)	12 m	Flaccid tetraparesis, heart and respiratory failure	12 m
Lacombe et al[17]	2	M	First cousin: infantile-onset PD (case 1)	1 m	Hypotonia, HCM, hepatomegaly	1 m
Tripathi et al[18]	3	M	CP	4 m	Respiratory distress	5 m
Morales et al[19]	4	M	N	3 m	Respiratory distress	6 m
Moreno Medinilla et al[20]	5	M	N	First days of life	Bradycardia,	10 d
Moreno Medinilla et al [20]	6	M	N	First months of life	Motor delay, areflexic hypotonia	14 m
Aykut et al[21]	7	F	CP Brother: IOPD	9 m	Hypotonia, frequent pulmonary infections, hepatomegaly, HCM	9 m
Aykut et al[21]	8	F	N	6 m	Hypotonia, weakness, hepatomegaly	6 m
Aryani et al[22]	9	M	CP Brother: IOPD	5 m	Hypotonia, motor delay, failure to thrive	5 m
Nilsson et al[23]	10	M	Paternal grandmother: LOPD	5 m	Respiratory distress, feeding difficulties, hypotonia	5 m
Markic et al[24]	11	F	N	4 m	Feeding difficulties, failure to thrive, muscle weakness	5 m
Tan et al[25]	12	F	NR	3 m	HCM, macroglossia, hypotonia	3 m
Tan et al[25]	13	F	N	2 m	Hypotonia, supraventricular tachycardia, HCM	5 m
Tan et al[25]	14	F	N	2 m	Hypotonia, feeding difficulties	5 m
Amartino and Cavagnari[26]	15	M	N	5 d	Hypotonia, HCM	1 m
Del Rizzo et al[27]	16	F	N	2 d	Bradycardia, HCM	3 d
Burrow et al[28]	17	F	N	5 m	Hypotonia	5 m
Dixon et al[29]	18	F	N	5 m	Motor delay, respiratory distress	6 m
But et al[30]	19	M	CP Brother: IOPD	1 m	Heart failure, hepatomegaly	1 m
Willems et al[31]	20	M	NR	2 m	HCM, cardiorespiratory failure	3 m
Willems et al[31]	21	F	NR	NR	HCM	NR
Teng et al[32]	22	M	N	5 m	Respiratory distress	5 m
Hoefsloot et al[33]	23	F	Paternal grandfather: LOPD	3 m	NR	3 m
García Mendoza et al[34]	24	F	NR	8 m	Muscular weakness, cardiac failure	8 m
Meola et al[35]	25	M	NR	7 m	Weakness, macroglossia cardiomegaly, hepatomegaly	7 m
Liu et al[15]	26	F	N	3 d	Hepatomegaly, HCM	1 m

CP = consanguineous parents, d = days, F = female, HCM = hypertrophic cardiomyopathy, IOPD = infantile-onset Pompe disease, LOPD = late-onset Pompe disease, M = male, m = months, N = no, NR = not reported, PD = Pompe disease.

The newborn presented in this case appeared healthy, presenting only a murmur during the physical examination, and the echocardiogram demonstrated significant HCM. The differential diagnosis of HCM in the newborn was performed considering[14] inborn errors of metabolism (storage diseases, fatty acid oxidation disorders and mitochondrial and respiratory chain disorders), congenital syndromes (Noonan syndrome and Beckwith-Wiedemann syndrome), neuromuscular disorders, iatrogenic disorders and gestational diabetes. Our patient presented no abnormal features, hypoglycemia or acidosis. The main diagnostic suspicion was therefore PD, which was confirmed during the first week of life due to the presence of clinical symptoms such as respiratory distress and muscle weakness. Neonatal diagnoses without newborn screening (NBS) have infrequently been achieved.[15] Almost no infants diagnosed before 30 days of age have undergone NBS through the measurement of GAA activity in dried blood spots.[16] However, NBS for PD has not been conducted in most countries due to the high rate of false positives and the lack of clarity on how to follow and manage asymptomatic cases. We reviewed the 26 reported cases of infantile-onset PD without NBS (Table 1),[15,17–35] which had a median age at diagnosis of 5 months. Only 6 cases were confirmed in the first month of life. To the best of our knowledge, this is the second case of a diagnosis in the first days of life without NBS. Abbot et al[36] reported a patient who was prenatally diagnosed (not included in Table 1), based on a positive family history.

Our patient was homozygous for the p.Arg854X mutation, which has been reported as the most frequent GAA sequence variation among patients of African descent African–American with PD,[37] and homozygotes for this mutation have infantile-onset PD.[38,39] The patient was CRIM-positive, a type that tends to respond better to ERT. Despite the improved survival, patients are at high risk of adverse events. Wang et al[40] reported 9 severe anesthetic adverse events in a series of 139 patients undergoing ERT.

The main limitation of our case was the rapid disease progression, despite an early diagnosis, due to the family's initial rejection of ERT. We cannot state that the disease would have been subsequently controlled because the patient had a fatal complication soon after treatment began. Follow-up of these early diagnosed and treated cases will confirm the pertinence of ERT. A multidisciplinary approach is essential due to the special needs of these infants.

In conclusion, it is of paramount importance that frontline neonatologists suspect this rare but life-threatening disease. It is extremely important to consider the diagnosis in regular assessments of newborns and infants with HCM, especially if severe hypertrophy is present.

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