Pompe's Disease in Childhood: A Metabolic Myopathy

Air Cmde U Raju*, Maj SC Shaw⁺, Col KS Rana[#], Col M Sharma^{**}, Maj HR Ramamurthy⁺⁺

Abstract

Background: Myopathy of metabolic origin in childhood occurs due to a variety of conditions. Pompe's Disease also known as Glycogen storage disease Type II, is a rare storage disorder with clinical presentation akin to spinal muscular atrophy.

Methods: A series of patients with suspected metabolic myopathy were reviewed at a tertiary care service hospital over a period of three years. The diagnosis was confirmed by estimation of acid alpha glucosidase activity.

Result: At our centre, these cases presented with generalized hypotonia, organomegaly (hepatomegaly, cardiomegaly) and congestive cardiac failure. Infantile onset, the most severe form of Pompe's disease, was the commonest form accounting for 75% of the cases. Four of the babies with infantile onset Pompe's disease expired, three due to refractory heart failure and one to fulminant respiratory infection before 15 months of age.

Conclusion: Pompe's Disease is now being increasingly diagnosed, due to definitive enzyme estimation facilities. With the recent availability of enzyme replacement therapy with Myozyme, the prognosis is likely to change for the better.

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Key Words : Metabolic myopathy; Pompe's disease; Hypotonia; Cardiomegaly; Hepatomegaly; Acid alpha-glucosidase

Introduction

Metabolic myopathy in childhood is an uncommon entity. Glycogen-storage disease type II (GSDII), also referred to as Pompe's Disease, is a rare storage disorder presenting as metabolic myopathy with multiorgan dysfunction. In our set up it was the commonest metabolic myopathy encountered. It has an incidence of 1/40000 live births with no ethnic predilection [1]. Timely diagnosis is essential for genetic counseling, antenatal diagnosis and definitive treatment with enzyme replacement therapy. We report our experience of encountering metabolic myopathies over three years and discuss babies who presented with generalized hypotonia and congestive cardiac failure in early infancy and were confirmed to be suffering from Pompe's disease by definitive enzyme estimation.

Material and Methods

Over a period of three years, all children admitted in a tertiary care service hospital, who had features suggestive of a metabolic myopathy, were enrolled in the study. In all the cases a detailed history was taken regarding adverse perinatal events, consanguinity, developmental delay and nature of symptomatology. Family history of early deaths was recorded. Detailed general and systemic examination was carried out and abnormalities noted. Multisystemic abnormalities viz cardiomegaly ± congestive heart failure (CHF), hypotonia, seizures, hepatomegaly and other organomegaly gave a clue

to a possible metabolic myopathy which was then more specifically investigated. Investigations included routine blood counts, liver and renal function tests, blood sugar, serum calcium/phosphates, creatinine phosphokinase (CPK), serum electrolytes and arterial blood gas levels. Radiograph of chest, electrocardiogram (ECG) and 2 Dimensional echocardiography (2-D ECHO) was carried out in all cases with cardiomegaly/CHF. Ultrasonography (USG) of abdomen was carried out to delineate organomegaly. Electromyogram (EMG) and nerve conduction studies (NCV) were conducted when indicated. Specific enzyme assays were carried out for suspected metabolic myopathy. In case of Pompe's disease, alpha glucosidase levels were estimated. The patients were provided decongestive therapy in case of CHF. As enzyme replacement therapy is as yet unavailable in our country, only supportive management was provided. These babies were on regular follow up care wherein frequent respiratory infections were treated, decongestive therapy regulated and vitamin supplements provided.

Results

Over a period of three years, we encountered 25 cases diagnosed to be metabolic myopathies. These included Wilson's disease, mitochondrial myopathies, Barter's syndrome and Pompe's disease. The distribution of the cases of metabolic myopathies seen according to the age and frequency of presentation is shown in Fig.1. Pompe's disease was the commonest of the metabolic myopathies encountered accounting for 32% of the cases. Of these children who were diagnosed to have Pompe's disease, six were of the infantile

*AOC, 7 Air Force Hospital, Kanpur Cantt. ⁺Graded Specialist (Paediatrics), 164 Military Hospital, C/O 99 APO. [#]Senior Advisor (Paediatrics & Neurology), ^{**}Senior Advisor (Paediatrics & Cardiology), Army Hospital R & R, Delhi Cantt. ⁺⁺Graded Specialist (Paediatrics), Command Hospital (EC), Kolkata.

variety and only two of the milder juvenile onset category who presented at two and nine years of age respectively. The clinical profile of these cases is as shown in Table 1.

Of the infantile onset Pompe's disease, two presented antenatally with cardiomegaly and reduced foetal movements detected on routine USG, who developed CHF soon after birth. Four children presented in late infancy with hypotonia, CHF, cardiomegaly and frequent respiratory infections and one child presented at two years of age with hypotonia and motor delay of six months duration. In addition, one girl with manifest features of juvenile onset disease presented with reduced mobility and hypotonia since 8 years of age. In our series of Pompe's disease, there were two girls and six boys. History of consanguinity was present in all but two of juvenile Pompe's disease. In two of the babies who presented at birth, antenatal USG in final trimester revealed cardiomegaly and decreased foetal movements. Motor delay was evident in all except in one juvenile onset case. Generalized hypotonia was a universal feature and the babies exhibited the pathognomonic frog like position (Fig. 2). Organomegaly was the hallmark of all our cases of infantile onset Pompe's disease. Hepatomegaly was a marked and universal feature in all the infantile onset cases though LFT was normal in all them. Cardiomegaly was a prominent feature in all of the babies with infantile onset disease (Fig. 3). It was associated with CHF. ECG pathognomically revealed short PR interval,

Fig. 1 : Etiological distribution of metabolic myopathies vs age of presentation

Table 1

Clinical vs Investigative profile of Pompe's disease cases

S. No.	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case7	Case 8
Age at presentation	7 months	2 years	8 months	At birth	At birth	8 months	9 months	9 years
Symptomatic since	Birth	6 months	Birth	Birth	Birth	15 days	7 months	1 year
Sex	Male	Male	Male	Male	Male	Female	Male	Female
Consanguinity	Present	Absent	Present	Present	Present	Present	Present	Absent
Reduced fetal movements	Absent	Absent	Absent	Present	Present	Absent	Absent	Absent
Motor delay	Present	Present	Present	NA	NA	Present	Present	Absent
Generalised hypotonia	Present	Present	Present	Absent	Absent	Present	Present	Present
Hepatomegaly	Present	Absent	Present	Present	Present	Present	Present	Absent
Cardiomegaly	Present	Absent	Present	Present	Present	Present	present	Absent
Congestive heart failure	Present	Absent	Present	Present	Present	Present	Present	Absent
ECG	Giant QRS	Normal	Giant QRS	Normal	Normal	Giant QRS	Giant QRS	Normal
Echocardiography	HCM	Normal	HCM	HCM	HCM	HCM	HCM	Normal
Enzyme level nmol/hr/mgm	11	13	9	4	6	9	12	16

tall biphasic QRS complexes and deep T wave inversions in precordial leads (Fig. 4). 2D Echo revealed non obstructive hypertrophic cardiomyopathy in all of the cases of infantile Pompe's disease. Of the clinical presentation, features observed in order of increasing frequency were hepatomegaly (71%), cardiomegaly (71%), hypertrophic cardiomyopathy (71%), CHF (71%), motor delay (85%) and hypotonia (100%).

Definitive diagnosis of Pompe's disease was based on estimation of the effected enzyme viz acid alpha glucosidase activity. It ranged from 4 to 16 nmol/hr/mg which was grossly deficient as opposed to a normal level of > 60 nmol/hr/mg. It was further observed that the deficiency was more profound in the babies who manifested the disease early with the levels rising with the age of presentation.

In our series, four out of the six cases of infantile onset Pompe's Disease babies expired. The cause of death was pulmonary haemorrhage related to CHF in the neonate. Of the remaining three cases, refractory heart failure in two cases and fulminant respiratory infection in one lead to death. Death occurred between 15 to 18 months of age in these babies. The remainder are on regular follow up.

Fig. 2 : Infant of Pompe's disease with generalized hypotonia

Fig. 3 : Chest radiograph (PA view) showing cardiomegaly with normal pulmonary vasculature

Discussion

Glycogen storage disorder type II or Pompe's disease named after the physician who first described this clinical entity in 1932, is a rare autosomal recessive disorder characterized by glycogen accumulation in the lysosomes of skeletal muscles, heart, liver, nervous system, leucocytes and kidneys [2]. Pompe's disease is one of a family of 49 rare genetic disorders known as Lysosomal Storage Diseases. It is also known as Acid Maltase Deficiency. It affects an estimated 5,000 to 10,000 people in the developed world. Statistics in our country of this entity are as yet unavailable. However, more and more of these cases are now coming to light because of the availability of enzyme estimation facility, which enables definitive diagnosis. Pompe's disease is caused by a complete or partial deficiency of the lysosomal enzyme, alpha-glucosidase. This enzyme is necessary to break down glycogen and to convert it into glucose. Without this enzyme, glycogen, a thick sticky substance, accumulates in the lysosomes and leads to severe muscle degradation. It predominately affects the heart, skeletal, and respiratory muscles of the patient.

There are three major forms of this disorder described based on the age of presentation viz infantile, juvenile, and adult type. Complete or profound deficiency of alpha glucosidase causes a progressive lethal cardiac and skeletal muscle disorder known as infantile Pompe's Disease [3]. The history of consanguinity and clinical profile of most of the cases in our series resemble the infantile form of the disease. Onset of this rare disorder may be apparent in the first few days of life, although clinical phenomena are not obvious for several weeks or more [4]. The infantile form is marked by a rapidly progressive and fatal course. As noted in our series, these children present with delayed motor milestones, generalized hypotonia, recurrent respiratory infections,

Fig. 4 : ECG shows short PR interval, huge biphasic QRS complexes and deep T wave inversions in precordial leads.

respiratory and cardiac failure. Other common features include alert look, hepatomegaly and macroglossia which were seen in most of our cases. The history of scanty fetal movements is occasionally elicitable as evident in two of our cases. Patients with the infantile form of the disease are the most severely affected. Progression of the disease is rapid and these patients are so severely affected that they become "limp" and are unable to feed or move. Severe cardiomegaly ensues and they typically die of cardio-respiratory failure between one to two years of age. Six out of the eight cases in our series belonged to this category.

In the delayed onset form, progression of the disease is less rapid. Symptoms can manifest at any age and can greatly affect the quality of life as well as life span of the afflicted child. Delayed onset patients that develop symptoms in childhood are more severely affected and typically die by the second or third decade of life. This form of disease is characterized by less severe or absent cardiac involvement. It usually presents as a slowly progressive muscular weakness of proximal muscles in the lower limbs with subsequent progression to involve the rest of the body and respiratory muscles [5]. Rarely, respiratory muscle involvement with respiratory failure as the first and presenting symptom occurs [6]. As the disease progresses, patients lose mobility, become wheelchair bound or bedridden. Respiratory functions greatly diminish and mechanical ventilation becomes necessary. Death results from cardio-respiratory complications. Only two of our series manifest this kind of disease. It could be related to the fact that the symptoms are mild in childhood and the disease therefore remains unnoticed till the second decade when the patient reports to the adult physician.

In our series, two of the babies presented in the antenatal period with reduced foetal movements and cardiomegaly, while four sought attention in late infancy

with features of CHF and one presented at two years of age with hypotonia and macroglossia. In addition one girl presented at nine years of age with problems of hypotonia and reduced mobility of one year's duration. History of consanguinity was present in all but two cases and only two of our babies were girls.

In a retrospective, multinational, multicentre study on the natural course of infantile Pompe's disease, it was observed that the clinical features reported were cardiomegaly (92%), hypotonia (88%), muscle weakness (63%), feeding difficulties (57%) and failure to thrive (53%) [7]. This pattern was akin to our observation.

The nearest differential diagnosis of Pompe's disease is another inheritable entity viz spinal muscular atrophy (SMA). The involvement of heart, liver, tongue, face and diaphragm in Pompe's disease and normal nerve conduction studies differentiate it from SMA. The other metabolic myopathies with hepatic and cardiac involvement are lipid and mitochondrial cytopathies. Absence of hypoglycaemia, ketonuria and normal arterial blood lactate differentiated our cases from these myopathies.

In the setting of the pathognomonic clinical features comprising hypertrophic cardiomyopathy with CHF, characteristic ECG, muscle weakness and hypotonia, the investigations were carried out to substantiate the diagnosis. Creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT) and muscle glycogen levels are frequently but not always elevated. In our series, we did not find any aberration of liver function tests. In most cases, a muscle biopsy reveals lysosomal pathology, but normal muscle biopsy does not exclude Pompe's disease. Data on skeletal muscle function, pulmonary function, disability, handicap and quality of life have been insufficiently reported in the literature. Definitive diagnosis depends on the demonstration of absent or markedly reduced acid alpha-glucosidase (GAA) activity in muscle, cultured fibroblast or white blood cells. Newer methods using blood samples for measuring GAA activity are the most popular because of speed and convenience [8]. In 10% of cases in which the enzyme assay on leukocytes has been used in the non classic variety of Pompe's disease, a normal alpha glucosidase activity have been reported [9]. Activity of the enzyme was markedly reduced in all our cases. Symptomatic treatment of cardiac and respiratory failure does not significantly alter the clinical course.

In 2006, the Food and Drug Administration approved an enzyme replacement therapy (ERT), alglucosidase alfa (Myozyme), for the treatment of Pompe's disease [10]. The recommended dosage regime of Myozyme ranges from 10 mgm/kg/week to 20-40 mgm/kg every

two weeks, administered as an intravenous infusion. Initial reports of its usage suggest that the ERT has been well tolerated and an improvement in cardiac size and function, as measured by left ventricular mass index (LVMI) and fractional shortening, with a continued improvement in motor function has been recorded [11]. Furthermore it has been observed that on ECG, the PR interval lengthened, decrease in QTc and left ventricular voltage occurred which correlated with a decrease in LVMI on 2D ECHO [12,13]. Long term effectiveness of this modality has not been established. Therefore what is reversible by ERT and what is preventable is unclear [14]. The main known adverse effect of ERT is the potentially severe infusion reaction due to anti GAA antibodies [15]. Animal studies suggest that methotrexate priming induces immune tolerance to ERT in Pompe's disease and reduces the incidence of severe reactions [16]. Glucose tetrasacchride has been used as a biomarker for monitoring the therapeutic response to ERT in Pompe's disease [17]. The enzyme is present in fibroblasts grown from amniotic fluid cells and can be utilized for prenatal diagnosis as well [18, 19]. Gene encoding of acid alpha-glucosidase has been localized to band 17q23 and gene therapy is in the early stages of preclinical investigation. A fully deleted adenovirus vector expressing hGAA via non viral regulatory elements introduced intravenously into mice resulted in long term hepatic secretion of hGAA [20-21]. Fetal gene therapies in animal models have shown long term postnatal therapeutic effects and tolerance of the transgenic protein after in utero gene delivery. However more investigations into the safety and ethical aspects of this form of gene therapy based on risk/benefit ratio need to be undertaken before application in humans can be contemplated [22]. Gene replacement therapy will eventually be the cure for Pompe's disease and other such rare disorders. But until then, enzyme replacement therapy offers hope in the near future for those affected by Pompe's disease.

Given the increasing incidence of these cases due to improved diagnostics, there is a role of early detection of Pompe's disease through newborn screening. However it would not be able to distinguish between infantile and late onset disease. Therefore pilot studies are required to identify the most efficacious strategy for screening before it is widely adopted by newborn screening programmes [23].

The prognosis for the infantile form till now had been uniformly poor. Most of them died within first two years of life and the cause for early mortality is respiratory and cardiac failure. In our series three died due to heart failure and one to fulminant respiratory infection.

With the recent availability of enzyme replacement

therapy, the prognosis of this condition which was uniformly gloomy is likely to change for the better. Hence it has become necessary for us to entertain a high index of suspicion and pick up these cases early, as definitive treatment has now become a reality. Gene replacement therapy will eventually be the cure for Pompe's disease and other rare metabolic disorders.

Conflicts of Interest

None identified

Intellectual Contribution of Authors

Study Concept : Air Cmde U Raju

Drafting & Manuscript Revision : Air Cmde U Raju, Col KS Rana, Maj SC Shaw, Maj HR Ramamurthy

Study Supervision : Air Cmde U Raju, Col KS Rana, Col M Sharma

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