

## Infantile Pompe disease in a female neonate with significant family history: A case report

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**Abstract:** Pompe disease is a rare metabolic myopathy of autosomal recessive inheritance. It is caused by the deficiency of lysosomal enzyme acid alpha-glucosidase, which results in lysosomal and cytoplasmic glycogen accumulation. A wide spectrum of disease exists, varying from hypotonia and severe hypertrophic cardiomyopathy in infancy, to a milder form which manifests in adulthood. In either condition, the involvement of several systems leads to progressive weakness and disability. We report a six month old female infant who presented with hypotonia, developmental delay and hypertrophic cardiomyopathy. Significantly elevated CPK and LDH levels coupled with reduced acid  $\alpha$  glucosidase activity, confirmed the diagnosis of Infantile Pompe disease. This infant had recurrent respiratory infections, failure to thrive and succumbed to death, due to hypertrophic cardiomyopathy at one year of age. The younger sibling was a carrier for pompe disease and there was a family history of hypertrophic cardiomyopathy.

**Keywords:** Acid  $\alpha$ - glucosidase, cardiomyopathy, carrier, myopathy, Pompe

### INTRODUCTION

Pompe disease is a rare autosomal-recessive metabolic myopathy resulting from deficiency of lysosomal acid alpha-glucosidase (GAA) also known as acid maltase[1]. This enzyme is required for glycogen degradation in lysosomes[2]. Hence its deficiency leads to lysosomal and cytoplasmic glycogen accumulation, which results in progressive muscle weakness. Phenotypes range from an infantile form with severe hypertrophic cardiomyopathy to a milder adult onset form, which is characterized by skeletal and respiratory muscle weakness[3]. In either condition, the involvement of several systems leads to progressive weakness and disability[4].

### CASE REPORT

A 36 weeks female neonate, weighing 2600 grams was delivered to primigravida by emergency caesarean section, done for obstetric indication. There was second degree consanguinity and the neonatal period was uneventful. The neonate had gross motor delay with hypotonia from sixth month of life, which was associated with repeated respiratory tract infection and failure to thrive. Chest X ray showed cardiomegaly and Echocardiogram revealed infiltrative cardiomyopathy with severe left ventricular dysfunction. In view of hypotonia and infiltrative cardiomyopathy infantile variant of pompe disease was considered and the infant was investigated further. The

Creatine phosphokinase (CPK) levels were 554  $\mu$ /l (ref: 25-200  $\mu$ /l), and lactate dehydrogenase (LDH) levels were 2550  $\mu$ /l (ref: 235-470  $\mu$ /l). In view of highly elevated CPK and LDH levels, infantile Pompe disease was diagnosed and acid  $\alpha$  glucosidase activity was estimated. There was a markedly decreased  $\alpha$  glucosidase activity (0.6 nmoles/hr/mg, normal range 56- 296 nmoles/hr/mg), which confirmed the diagnosis of infantile pompe disease. The infant eventually died of hypertrophic *cardiomyopathy* and associated complications at one year of age.

The younger male sibling was born at 36 weeks of gestation and was admitted with respiratory distress to the neonatal unit. This was diagnosed to be transient tachypnea of newborn, which resolved by 24 hours of life. Sepsis screen was negative and the Chest x-ray showed evidence of transient tachypnea of newborn. In view of family history of infantile pompe disease, the neonate was investigated for the same. Echocardiogram revealed normal four chamber view with a small patent foramen ovale, a normal septal wall and good myocardial function. CPK and LDH levels were normal. However, acid  $\alpha$  glucosidase activity was marginally reduced (23 nmoles/hr/mg: normal range 56- 296 nmoles/hr/mg) during second week of life, which was suggestive of carrier status for pompe disease. Hence, this infant underwent periodic cardiac and neuro developmental follow up. At seven months age, the

child had attained appropriate milestones and had good muscle tone. There was adequate weight gain. Cardiac examination and echocardiogram were normal. GAA mutation analysis confirmed *carrier* status.

Incidentally there was a family history of second degree consanguinity in grandparents. Also, there was history of early onset hypertrophic cardiomyopathy leading to death in mid thirties in the maternal grandmother, her sibling and her niece, which could have been caused by adult onset pompes disease. However no enzyme levels or genetic analysis was done to confirm pompes disease.



**Fig-1: Chest radiograph, AP view showing marked cardiomegaly.**

## DISCUSSION

Pompes is a rare muscular disorder with multi systemic involvement. It has a wide clinical spectrum with varying age of onset and variable rates of progression. Pompes disease is thought to affect all races. Incidence varies from 1 in 14000 to 138000 in different countries[5]. It is one of the leading causes of familial (idiopathic) hypertrophic cardiomyopathy in neonatal and paediatric age group[6]. The most commonly affected muscles in infantile Pompes disease are cardiac and respiratory muscles along with proximal skeletal muscles of the limbs[7]. Similarly, the index infant manifested with hypertrophic cardiomyopathy, frequent respiratory infections along with hypotonia and developmental delay. Death typically occurs in the first year of life due to hypertrophic cardiomyopathy and associated complications[8]. The index infant also succumbed to death due to hypertrophic cardiomyopathy.

Symptoms may appear in early to late childhood or even much later in life (between 20-60 years of age). Approximately one-third of those with Pompes disease have the infantile-onset form, while the

majority of patients have the slowly progressive late-onset form. Males and females are equally affected.

Acid  $\alpha$ -glucosidase deficiency can be caused by numerous pathogenic variants in the GAA gene[9]. Carrier parents have 25% chances of having an affected child with each pregnancy. There is a 50% chance to have a carrier child and a 25% chance to have neither a child who is neither affected nor a carrier[7]. Parents who have had a child with Pompes disease are obligate carriers[7].

In most instances, parents of a proband are heterozygotes and thus carry a single copy of a GAA disease-causing mutation [10]. Heterozygotes (carriers) are asymptomatic. So also the younger sibling who was a carrier was asymptomatic. Historically, children with classic infantile Pompes disease have not survived to reproduce, whereas many individuals with later-onset disease survive into their 50's and 60's[7]. Carrier testing for at-risk family members and prenatal testing for at risk pregnancies are possible if the disease-causing mutations in the family are known.

## CONCLUSION

A six month old female infant presented with hypotonia, developmental delay and hypertrophic cardiomyopathy along with elevated CPK, LDH levels and diminished acid  $\alpha$  glucosidase activity. Born of second degree consanguinity, the child was diagnosed to have infantile pompes disease. The infant had failure to thrive and recurrent respiratory infections due to hypertrophic cardiomyopathy and succumbed to death at one year of age. The younger sibling was an asymptomatic carrier for pompes disease.

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