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Case Report

A rare case of infantile onset Pompe disease with genetic diagnosis

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ABSTRACT

Glycogen storage disease type II, also called Pompe disease or acid maltase deficiency is a disorder of muscle glycogenoses with a wide range of clinical manifestations. It is one of the disorders of glycogen metabolism caused by a deficiency of lysosomal acid α-1, 4-glucosidase (acid maltase) resulting in lysosomal glycogen accumulation in cardiac, skeletal and smooth muscle cells. The pattern of inheritance is autosomal recessive with a gene for enzyme located on chromosome 17q25.2. It is the first recognized lysosomal storage disorder and the first neuromuscular disorder for which enzyme replacement therapy has been approved. We report a case of four month old female child, born to primi gravida third degree consanguineous couple, who presented with history of respiratory illness, hypotonia and developmental delay. Baby was sick needing mechanical ventilation and inotropic support. Echocardiography showed concentric LV hypertrophy with no LV outflow tract obstruction. In view of consanguinity, developmental delay, hepatomegaly and cardiomegaly, provisional diagnosis of a storage disorder, probably infantile Pompe disease was considered. Dried blood spot for α-1, 4-glucosidase enzyme assay confirmed the same. Enzyme replacement therapy was considered, but child progressed to cardiac failure needing prolonged ventilation and expired on day 8 of admission. Whole genome exome sequencing revealed 2 mutations which confirmed the diagnosis. Infantile Pompe disease is fatal without treatment. High index of suspicion and early diagnosis may help in taking advantage of emerging therapeutics, such as ERT which is capable of changing the natural history of the disease.

Keywords: Infantile onset Pompe disease, Alpha-1,4-glucosidase, Enzyme replacement therapy, Hypertrophic cardiomyopathy

INTRODUCTION

Glycogen storage disease type II, also called Pompe disease or acid maltase deficiency is a disorder of muscle glycogenoses with a wide range of clinical manifestations. Incidence of Pompe disease is 1 in 40,000 globally.[1] Incidence in India is unclear.[2] Pompe disease is broadly classified into infantile and late onset forms. Infantile Pompe disease is a rapidly progressive, often fatal disease characterised by significant cardiomegaly, hepatomegaly and hypotonia. Death occurs due to cardiorespiratory failure in the first year of life.[1]

It is one of the disorders of glycogen metabolism caused by a deficiency of lysosomal acid α-1, 4-glucosidase (acid maltase) resulting in lysosomal glycogen accumulation in cardiac, skeletal and smooth muscle cells. It follows an autosomal recessive pattern of inheritance with a gene for enzyme (GAA gene) on chromosome 17q25.2.[1] It is the first recognized lysosomal storage disorder and the first neuromuscular disorder for which a therapy has been approved. Enzyme replacement therapy (ERT) with alglucosidase alpha is presently approved.[1] Prenatal diagnosis using amniocentesis or chorionic villi sampling is possible.

Antenatal diagnosis of Pompe disease by fetal echocardiography is an upcoming option which has a significant impact on outcome as it promotes early initiation of ERT. [3]

The reason for reporting this case is to highlight the fact that infantile Pompe disease is uniformly lethal without ERT at the appropriate time. Current study report a case of a 4 month old child diagnosed as infantile Pompe disease. The option of ERT, though was considered could not be exerted as the child presenting late in the course of illness.

CASE REPORT

Four month old female child was admitted with h/o cough and fever since 3 days. There is history of hurried breathing with refusal to feed since 1 day. Antenatal history was unremarkable. Baby was born to 25 year old primigravida mother out of third degree consanguineous wedlock. Baby's mother was a registered case and had regular antenatal visits. Fetal movements were perceived from fifth month pregnancy onwards. Antenatal ultrasound scan done in each trimester was told to them to be normal. Baby was born at term gestation by normal vaginal delivery. Baby cried soon after birth with a birth weight of 3100 grams. Baby had an uneventful postnatal course & was discharged on day 3 postnatal age. No history of NICU admission. Baby was on exclusive direct breast feeds and regular immunizations were given as per the schedule. Child had an episode of respiratory illness at 2 months of age & was evaluated on outpatient basis at a nearby hospital. No history of cyanosis or feeding difficulty. Echocardiography done showed features of pulmonary hypertension & child was started on oral sildenafil. Development history revealed that social smile was attained; baby recognizes mother & head control is not attained.

At admission, baby appeared ill, hypotonic and not interested in surroundings. Baby had clinical features of respiratory distress with tachypnea (respiratory rate; 50/minute), tachycardia with heart rate: 140/minute, chest retractions and bilateral lung crepitations on auscultation. Baby was pink with blood pressure of 70/40 mmHg and was hemodynamically stable. CVS examination revealed audible S3 with gallop rhythm heard on auscultation. Anthropometry showed weight: 4.6 kg below third centile on WHO chart, length: 62 cms, head circumference: 41 cms which was appropriate for age. Abdomen appeared distended. Hepatomegaly was present 10 cms below right costal margin, which was firm with sharp borders. Liver span was 12 cms suggesting gross hepatomegaly. There was no splenomegaly.

Routine blood investigations including complete blood count, liver function test and renal function tests were normal. Chest radiograph showed cardiomegaly with bilateral lower lobe opacity & features suggestive of consolidation (Figure 1). ECG done showed a PR interval of 0.1 seconds with features of left ventricular (LV) hypertrophy (Figure 2). Echocardiography showed concentric LV hypertrophy with no LV outflow tract obstruction. Provisional diagnosis of a storage disorder, probably infantile Pompe disease was considered.

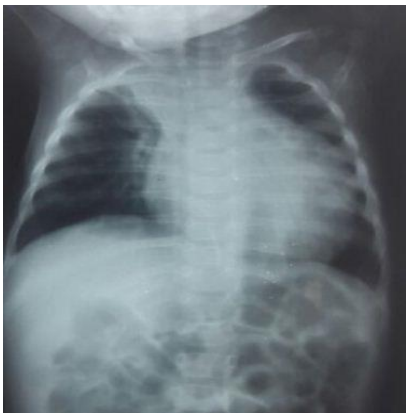

Figure 1: Chest radiograph showing cardiomegaly.

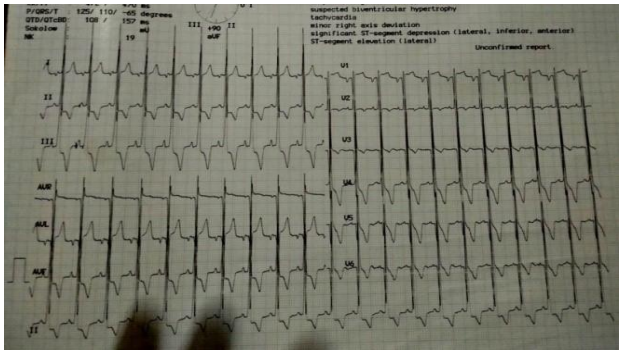

Figure 2: ECG with features of biventricular hypertrophy.

Child was treated with anti failure medications and intravenous antibiotics. By day 2 of admission, child developed increasing respiratory distress. Dried blood spot was sent for α-1, 4-glucosidase enzyme assay. Bystanders were explained regarding the option of enzyme replacement therapy with alglucosidase alpha after contacting the concerned authorities. Muscle biopsy was not attempted due to increased risk of anaesthestic complications. Subsequently, child deteriorated & was put on mechanical ventilation by day 3 of admission. In view of shock, child was started on inotropic support. Child continued to deteriorate further and was ventilator dependent. However, on day 8 of admission, child progressed to catecholamine resistant shock and cardiorespiratory failure. In spite of extensive resuscitative efforts, child could not be revived & expired on day 8 of admission.

Parents were explained regarding the underlying genetic cause of the disease and recurrence risk for future pregnancies. The parents were referred to a clinical geneticist for genetic counselling. The DNA extraction

from dried blood spot by PCR amplification and whole genome exome sequencing showed gene/locus: GAA on chromosome 17q25.3. Two heterozygous mutations were detected; a missense mutation in start codon: c.(A>G); (2608C>T) and a stop (nonsense) mutation: p.(M1V); (R870*), which confirmed the diagnosis of Pompe disease.

DISCUSSION

Floppy infant with failure to gain weight, feeding difficulty, delayed motor milestones, recurrent respiratory infections and massive cardiomegaly gives us a clue to infantile Pompe disease. In infantile Pompe disease, heart is one of the main organs that are affected by lysosomal glycogen accumulation. It results in a significant amount of cardiac hypertrophy that may begin in utero and that is significant even at 4-8 weeks of age and results in hypertrophic or hypertrophic and dilated cardiomyopathy.[1] In the study done by Jegdeeswari et al two cases presented early in infancy with decompensated cardiac failure and hypertrophic cardiomyopathy was diagnosed as infantile Pompe disease.[2]

The confirmatory step is enzyme assay demonstrating deficient acid α-glucosidase and gene sequencing.[3] Specific enzyme replacement therapy with recombinant human acid α-glucosidase (alglucosidase alfa) is available. It is capable of preventing deterioration or reversing abnormal cardiac and skeletal muscle function.[4,5] In study done by Lokesh et al in South India with 6 patients with infantile Pompe disease, all had motor delay with severe hypotonia and head lag with respiratory distress, similar to the case that we described.[6] Two of the six cases were able to receive ERT through the India charitable access program (INCAP) programme on a compassionate basis.[7] These cases were the first to receive ERT for Pompe disease but was started at the later ages of 8 and 15 months, hence was not effective in infantile onset Pompe disease.

In multi centric cross-sectional study done by Gupta et al, out of 77 patients with infantile onset Pompe disease, alpha-glucosidase gene variant analysis was done for 48 patients showed missense variants similar to our case.[8] Along with ERT, other factors such as under nutrition, feeding difficulties and recurrent respiratory infection are possible factors influencing clinical outcomes in these patients. Organization for rare diseases India (ORDI) is doing exceptional work in providing ERT free of cost to the deserving in India.[9]

CONCLUSION

Early diagnosis and treatment are necessary for optimal outcomes in Pompe disease. Awareness of this condition helps in screening and diagnosis, so that patients can take advantage of emerging therapeutics. The history of consanguinity, presence of developmental delay, hypertrophic cardiomyopathy and hepatomegaly in infancy warrants workup for infantile Pompe disease. Genetic diagnosis is helpful in counselling the family regarding recurrence risk in future pregnancies. Early specific enzyme replacement therapy is capable of changing the natural history of the disease.

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