Floppy Infant-A Case Report of Infantile Pompe Disease With Literature Review

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Research Article

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Abstract

Background: Deficiency of acid-α1,4glucosidase results in lysosomal accumulation of glycogen impairing multiple tissue functions i.e., cardiac, skeletal and smooth muscle functions. First described in 1933 by Pompe who identified glycogen by Best carmine in sections of cardiac muscle of an infant who had died of idiopathic cardiac hypertrophy. Hers in 1963 identified the enzyme – α-glucosidase in lysosomes responsible for cleaving glycogen and maltose. He documented deficiency of this enzyme in tissues of patients with Pompe Disease, and thus launched the field of lysosomal storage diseases. Families have been reported with both infantile and late- onset adult forms. Infantile form of Pompe Disease has a more severe enzyme deficiency than late onset forms. Newborn screening reveals an incidence 1:10,000, much higher than in the past. Appearance of a floppy infant presenting in early infancy invokes a differential diagnosis of hypothyroidism, Down's syndrome, spinal muscular atrophy and less commonly an inborn error of metabolism. History of consanguinity, serial sibling losses and recurrent respiratory infections should arouse suspicion of underlying congenital heart disease. Absence of common structural heart diseases, should focus on functional echocardiography, which was revealing.

Case Presentation: Child is the fourth born of second-degree consanguineous marriage with two sibling losses, presented with breathing difficulty at 1-month age. He has a history of frequent hospitalizations for recurrent respiratory tract infections, suggestive of congestive cardiac failure, possibly due to underlying heart disease. Currently at 6-months age, neuromotor and developmental examination reveals a floppy infant. He has history suggestive of developmental delay more marked in gross motor and fine motor abilities, whereas language and social milestones are less affected. Overall, he has a developmental age of three months. Massive hepatomegaly was observed as cardiac failure set in, but it is not solely due to the storage of glycogen in the liver, being part of generalized glycogenoses.

Cardiac evaluation revealed cardiomyopathy with concentric left ventricular hypertrophy. Biochemical reports also reflect cardiomyopathy. Dried Blood Spot Assay confirmed clinical suspicion of Pompe Disease which is Glycogen Storage Disease type II, *Myozyme* funding being pursued.

Conclusions: Dried blood spot assay holds the key to early and specific diagnosis. Advent of enzyme replacement therapy with early initiation for this rapidly progressive disease is likely to rewrite a brighter future. Immunomodulating agents such as methotrexate, rituximab and intravenous immune globulin can prevent development of immune response to enzyme replacement therapy. Genetic counseling regarding recurrence risk of such inherited disorders in consanguineous marriages should be accorded priority.

Background

Pompe Disease (PD) is caused by deficiency of acid α-1,4glucosidase (acid maltase), an enzyme responsible for the degradation of glycogen in lysosomes.[1] This enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, predominantly affecting cardiac, skeletal and

smooth muscle cells. In PD, glycogen typically accumulates within lysosomes, as opposed to its accumulation in cytoplasm in the other glycogenoses. However, as disease progresses lysosomal rupture and leakage leads to the presence of cytoplasmic glycogen as well.[1] We present here a child of infantile PD suspected in early infancy and confirmed at six months age.

Case Presentation

Currently 6-months age male infant, fourth product of consanguineous marriage, delivered normally weighing 2500gms, said to have cried immediately after birth, presented with breathing difficulty at 1-month age.

Since then, the child has had frequent hospitalizations for recurrent respiratory infections. At presentation coughing was marked with high grade fever. Respiratory distress was evident with difficulty in breast feeding. There was suck-rest-suck cycle. Short periods of feeding were interspersed with short periods of being held up against the shoulder providing rest and relief from breathlessness. Profuse sweating also accompanied the feeding efforts. He is immunized for age. He had history suggestive of developmental delay more marked in gross motor and fine motor abilities, whereas language and social milestones were less affected.

Family history is significant. Child is the fourth born of second-degree consanguineous marriage i.e., mother of child is married to her maternal uncle's son. The couple's first child i.e., eldest daughter 7-years age is attending primary school, second child daughter expired at 8 months' age due to recurrent pneumonia, third child son expired at 15 months' age due to cardiac failure secondary to pneumonia probably cardiomyopathy, fourth is the present propositus.

General Examination:

The anthropometry parameters were as follows: weight(kg) 6.0(< 3^{rd} centile for age), Crown-Heel Length(cms) 62(<3^{rd} centile for age), Occipito-Frontal circumference(cms) 43(median), Mid-Upper-Arm Circumference(cms) 13, Wt./L is -1 SD, undernourished but not Severe Acute Malnutrition. Child was conscious, temperature 101^{O}F, respiratory rate (RR) 60/min, heart rate (HR) 128/min, Non-Invasive Blood Pressure 85/65mmHg, Capillary Refill Time<3 sec, oxygen saturation 86% on room air. Though overt cyanosis was not present desaturation was noted on pulse oximetry which responded to oxygen by hood box at 6L/min. No pallor, icterus, cyanosis, clubbing, significant lymphadenopathy or pedal edema was noted. Mouth distinct with thick lips and protruding thick tongue.

Systemic Examination:

Cardiovascular examination showed HR 128/min i.e., tachycardia with no chest deformity and cardiac apex at left 5^{th} intercostal space lateral to mid clavicular line, heart sounds S1+, S2+ and no murmur. Respiratory system examination showed RR 60/min i.e., tachypnea, chest symmetrical, movements equal, chest expansion appears limited, intercostal and subcostal retraction as evidence of respiratory

distress, bilateral air entry present and bilateral fine crepitations heard in all areas. Central Nervous System examination revealed a conscious and oriented child with a symmetrical face during both awake and asleep states. Rooting, sucking, swallowing reflexes were present and well-coordinated with no evidence of cranial nerve palsy. Neurodevelopmental examination in various fields revealed the following: Gross Motor- *Supine*: symmetrical posture, arms extended at elbows bilaterally, legs extended at knees bilaterally, head lag on pull to sitting position features as evidence of generalized hypotonia, deep tendon reflexes diminished, superficial reflexes present. *Prone:* legs extended, holds chin up, turns head, unable to support weight on forearm. *Ventral suspension*: head lifted momentarily to plane of body. *Primitive reflexes*: Moro's reflex absent (normal for age), palmar grasp reflex absent (normal for age), plantar grasp reflex present (normal for age), sucking and swallowing coordinated but swallowing slower than before because of respiratory distress and large tongue. Fine motor- *Adaptive*: although spontaneous hand opening achieved and able to grasp rattle with hand, but unable to transfer object from one hand to other. *Language:* coos and babbles. *Social:* smiles to mother, shows likes and dislikes, wide eyed appears excited at sight of food. Neuromotor and developmental examination reveals a floppy infant [Figure 1] which could be due to hypothyroidism or Down's syndrome or Werdnig-Hoffmann disease or Pompe Disease. Though the child is chronologically 6-months age he has developmental quotient of 3-months. Gastrointestinal Tract examination showed mild diffuse distension of abdomen with an abdomino-thoracic type of respiration, umbilicus normal and no hernia, no obvious scars/sinuses, no prominent superficial vessels, massive hepatomegaly with liver span of 11cm, bowel sounds present.

Blood Investigations:

The complete blood count changes over 10 days revealed hemoglobin decreasing from 13.2gm/dl to 10.9gm/dl, total leukocyte count decreasing from 18,720/mm^3 to 11,000/mm^3, differential leukocyte count showed following changes (%): Polymorphs 45 to 27, lymphocytes 45 to 58, eosinophil from 10 to 9, monocytes from 0 to 6, platelet count was steady at 308 x10^3/µl, Liver function tests showed elevated liver enzymes(IU/L) (SGOT: 517(17-59), SGPT: 151(21-72), CPK-MB:62(<25); CPK-NAC:739(55-170); Renal function tests were normal, Thyroid function tests were normal.

Electrocardiography (ECG) shows prominent P waves, short PR interval, large QRS complexes in all leads, left axis deviation which is in contrast to the expected right axis deviation for this age, evidence of biventricular hypertrophy seen. ST depression and T-wave inversion changes seen indicative of hypertrophic cardiomyopathy [Figure 2].

Imaging:

Chest X-ray shows massive cardiomegaly and cardio thoracic ratio >70 % [Figure 3].

Echocardiography revealed concentric left ventricular hypertrophy, left ventricular ejection fraction 60%, lateral wall thickness 8.5mm, inter-ventricular septum 8mm, no left ventricular outflow tract obstruction and trivial mitral regurgitation.

Dried Blood Spot (DBS) Assay confirmed our clinical suspicion for the diagnosis of Pompe Disease: Total acid α-glucosidase(A) 4.84nmol/hr/ml (10-60); Lysosomal acid α-glucosidase(B) 0.19nmol/hr/ml (4.51-15.0); Ratio(B/A) 0.04 (0.3-0.8)

Parents were advised follow-up after 1 month.

Management:

Supportive therapy: Propped up, oxygen inhalation, monitoring with pulse oximetry, improved to 94%/120/min. IV Lasix for 3-days, antibiotics administered were Ampicillin-Cloxacillin combination along with Cefotaxime for 9days, followed by Syrup Ampiclox per oral for 5days. Advised immunization with Pneumococcal vaccine along with vaccines in the National Immunization Schedule as well as Rotavirus vaccine. Breast feeding was advised for its numerous benefits along with complementary feeding and multivitamin drops with oral iron therapy. Parents were counselled regarding the need for gentle, graduated physical therapy to strengthen muscles and enable movements which may be beneficial with specific therapy. Follow-up echocardiography showed no change and hemoglobin improved to 11.4gm/dl. *Specific therapy:* Enzyme replacement therapy (ERT) with recombinant human α-glucosidase (Alglucosidase alfa) is available for treatment of PD which is capable of preventing deterioration or reversing abnormal cardiac and skeletal muscle functions. Cost of Myozyme (Alglucosidase alfa) is limiting due to resource crunch and hence funding is being pursued. Parents are keen for follow-up with ERT together with suggested physical and supportive therapy.

Discussion

Discovery of Pompe Disease stands as a milestone in the study of lysosomal storage disorders. A Dutch pathologist J C Pompe, in 1932, first identified glycogen in cardiac muscle sections stained with Best Carmine, of an infant who had died of idiopathic cardiac hypertrophy, and thereafter also in other tissues, as also in other infants from a family [2,3,4]. In 1955, Christian de Duve's discovery of lysosomes (awarded Nobel Prize in 1974) and in 1965 discovery by his co-worker Henri G Hers of deficiency of a lysosomal enzyme α-1,4glucosidase for breakdown of glycogen, could finally explain the symptoms of Pompe Disease [5].

Glycogen Storage Diseases (GSD) are classified numerically in chronological order in which the enzymatic defects were first identified and also on basis of predominant organ affected i.e., muscle and liver glycogenosis.[1] GSD type II could be infantile type or juvenile/adult type. The former is characterized by cardiomegaly, hypotonia, hepatomegaly, with no residual enzyme activity and cardiorespiratory failure leading to death by 1-3years age while the latter is characterized by myopathy, variable cardiomyopathy and respiratory insufficiency.

Infantile PD have a high risk from anesthesia. An ECG is hence mandatory in any patient suspected of having PD, before any procedure requiring anesthesia, including muscle biopsy. The ECG is also helpful in making the diagnosis.[6] Arrhythmias, especially Wolff-Parkinson-White syndrome may occur in Late-

onset Pompe Disease, often associated with mental retardation. Cardiac catheterization or echocardiography shows biventricular hypertrophy.[7]

Close parental consanguinity and affliction of previous siblings confirmed the autosomal recessive nature of the disease. In contrast to the massive and significant hepatomegaly seen in GSD types I &III, it is relatively much less in type II GSD i.e., PD, becoming evident with the onset of congestive cardiac failure.

The infantile form of PD has a more severe enzyme deficiency than the late onset forms.

Skeletal muscle is also prominent in these patients. Hypotonia and absent reflexes may suggest amyotonia congenita. Macroglossia is seen in 50% cases, which together with a protuberant abdomen and possibly an umbilical hernia may suggest diagnosis of hypothyroidism or Down's syndrome.[8]

Suspicion of muscle disease often prompts a muscle biopsy. Though it provides information about glycogen content and storage within and outside lysosomes of muscle cells, a normal biopsy does not exclude PD. Electromyography reveals pseudomyotonia and high frequency discharges with fibrillations in all forms of PD.

Urinary glucose tetra-saccharides can be elevated in the urine of affected patients, and levels are extremely high in infantile patients.

Availability of next generation sequencing panels and whole exome sequencing allows for identification of additional patients of PD especially when the diagnosis is ambiguous. The acid alfa glucosidase (GAA) gene that provides instructions for producing the enzyme acid α-glucosidase has been localized to chromosome 17q25.2.[9] The gene has been cloned and a number of mutations identified. The nature of the disease is quite similar in all affected members of a family. However, families have been reported with both infantile and late-onset adult forms. DBS assay for enzyme deficiency confirmed the diagnosis of PD. New Born Screening now available reveals an incidence 1:10,000, much higher than in the past. Prenatal diagnosis by assay of the enzyme in uncultured amniocytes or chorionic villi is available.[10]

With the advent of Myozyme, a new natural history for infantile PD is emerging. ERT should be initiated as soon as possible across the disease spectrum, especially for the babies with the infantile form, because the disease is rapidly progressive. Myozyme is given as a slow IV infusion 20-40 mg/kg/dose once in two weeks. It has been found to improve survival, ventilator-independent survival, reduce the cardiac mass and significantly improve the acquisition of motor skills.[11] Infants who are negative for cross reacting immunologic material, develop a higher titer antibody against the infused enzyme and respond less favorably to ERT.[1] Treatment using immunomodulating agents such as methotrexate, rituximab and intravenous immunoglobulin have demonstrated efficacy in preventing the development of an immune response to ERT and immune tolerance.

Nocturnal ventilatory support, when indicated, should be used, it has been shown to improve the quality of life and is particularly beneficial during a period of respiratory decompensation.

Conclusion

A high index of suspicion by pediatricians for lysosomal storage disorders must be maintained in the evaluation of floppy infants. There is a need to increase awareness regarding inborn errors of metabolism by investigating sequential sibling deaths for inherited disorders with appropriate and timely genetic counseling including availability of prenatal diagnosis to reduce pregnancy wastage in future.

Abbreviations

PD	Pompe Disease
RR	Respiratory Rate
HR	Heart Rate
ECG	Electrocardiography
DBS	Dried Blood Spot
ERT	Enzyme Replacement Therapy
GSD	Glycogen Storage Disease

Declarations

Ethics approval and consent to participate: Since the patient concerned is an infant, written informed consent was obtained from the parent**.**

Consent for publication: Written informed consent was obtained from the parent for publication of this case report and accompanying images.

Availability of data and materials: Not applicable

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Figures

Figure 1

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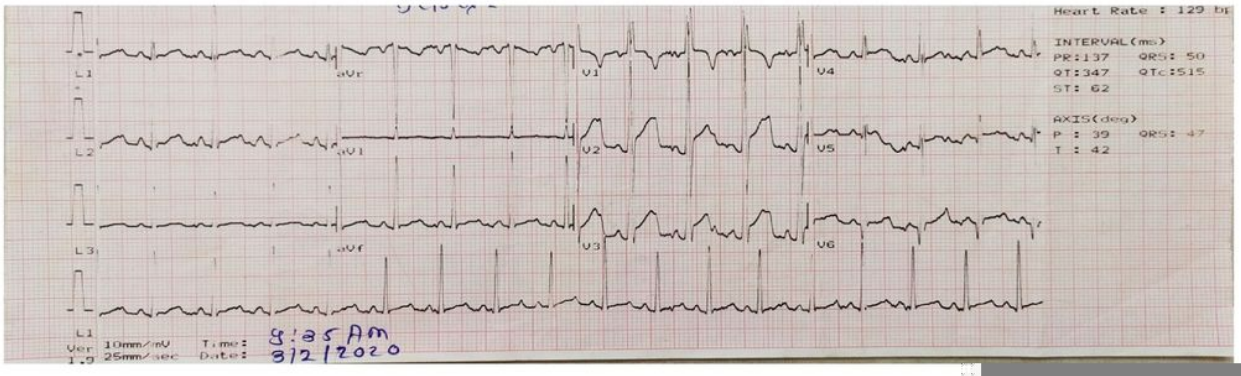

Figure 2

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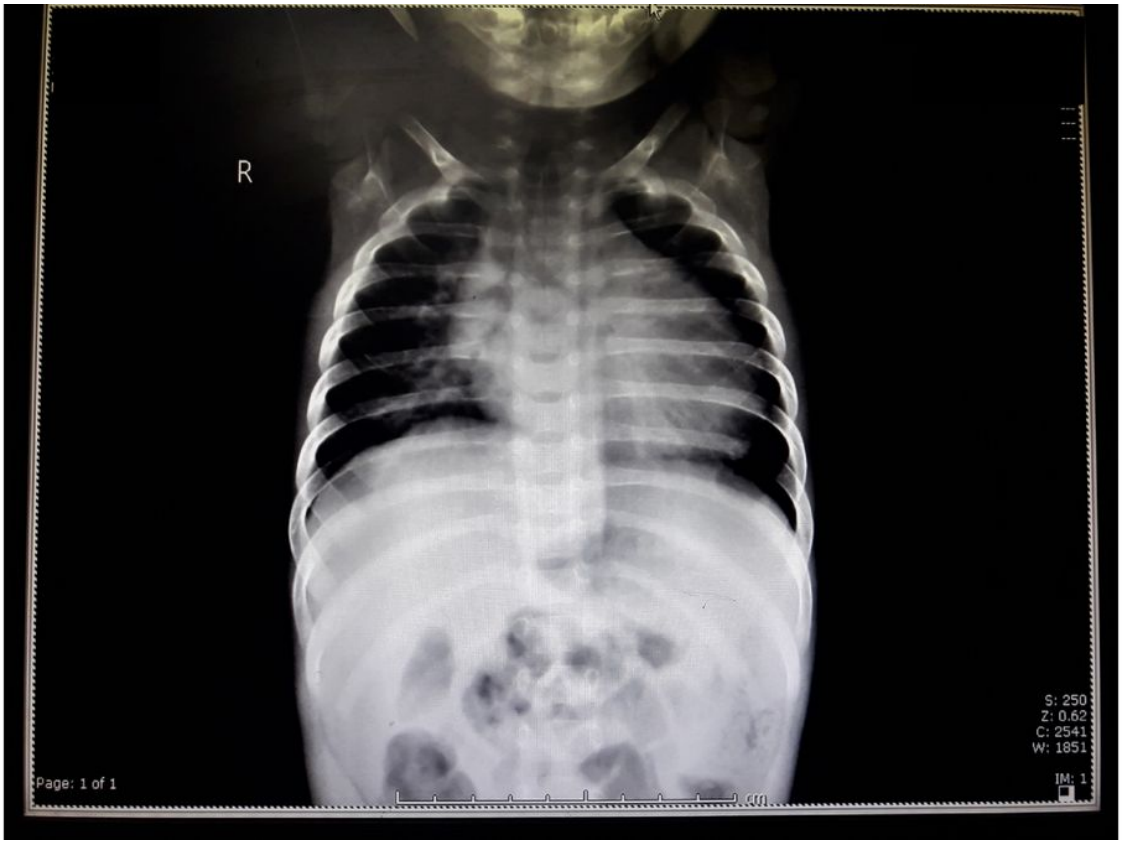

Figure 3

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