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Case Report

Pompe's Disease in Infancy: A Case Report

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ABSTRACT

Glycogen storage disorders (GSDs) are inherited metabolic disorders characterized by defects in glycogen metabolism, leading to abnormal glycogen accumulation in various tissues. Pompe's disease, a severe form of GSD, results from a deficiency in the enzyme acid alpha-glucosidase (GAA), causing lysosomal glycogen accumulation, primarily affecting cardiac and skeletal muscles. This case study presents a 45-day-old female infant with Pompe's disease, initially presenting with fever, cough, cold, and respiratory distress. Clinical assessment revealed tachypnoea, elevated heart rate, hypotension, hepatosplenomegaly, elevated liver enzymes, and metabolic acidosis. Diagnostic tests confirmed Pompe's disease through low alpha-glucosidase activity. Despite initiating antibiotic treatment and ventilatory support, the patient's condition worsened, necessitating re-intubation. Pompe's disease presents a broad spectrum of clinical manifestations, with early diagnosis and intervention being crucial for managing the infantile form. Enzyme replacement therapy (ERT) with recombinant human GAA has markedly improved patient outcomes, yet challenges remain, including variability in treatment response and the high cost of therapy. Ongoing research focuses on novel therapeutic approaches and enhancing patient care. This case underscores the importance of early recognition and comprehensive management to improve prognosis in Pompe's disease.

Keywords: Pompe's Disease, Diagnostic approach, Heart

INTRODUCTION

Glycogen storage disorders (GSDs) are a group of inherited metabolic conditions characterized by defects in glycogen metabolism, resulting in abnormal glycogen accumulation in various tissues.[1] These disorders can manifest across a wide age range, from infancy to adulthood, and are classified based on the specific enzyme deficiency involved.[2] The clinical manifestations of GSDs arise from either impaired glycogen utilization or the accumulation of excessive glycogen, leading to various symptoms.[3] Among the GSDs, Pompe's disease is particularly severe and is caused by a deficiency of the enzyme acid alpha-glucosidase (GAA). This deficiency leads to the accumulation of glycogen within lysosomes, primarily affecting cardiac and skeletal muscle cells.[4] The severity of Pompe's disease is closely linked to the age of onset, with classic infantile Pompe's disease representing the most severe form. This form typically presents before the age of 12 months and is characterized by hypertrophic cardiomyopathy, generalized hypotonia, delayed motor development, feeding and swallowing difficulties, and dyspnea.[5] Without treatment, it is often fatal within the first year of life.[6] The pathophysiology of Pompe's disease revolves around the impaired breakdown of glycogen due to deficient GAA activity. The resultant glycogen accumulation disrupts cellular function, particularly affecting muscles essential for movement and respiration.[7] Respiratory muscle weakness is a key feature, leading to respiratory insufficiency and failure.[8] Additionally, cardiac involvement, including hypertrophic cardiomyopathy and progressive heart

failure, significantly contributes to the disease's morbidity and mortality.[9] Diagnosing Pompe's disease can be challenging due to its rarity and variable clinical presentation.[10] Laboratory findings often include elevated creatine kinase levels, indicating muscle damage, and abnormal liver function tests due to hepatomegaly.[11] Imaging studies, such as chest X-rays and echocardiography, may reveal cardiomegaly, diaphragmatic weakness, and hypertrophic cardiomyopathy.[12] A definitive diagnosis is typically confirmed through enzymatic assays showing reduced GAA activity or genetic testing identifying pathogenic variants in the GAA gene.[13] Management strategies for Pompe's disease focus on symptom relief, slowing disease progression, and improving quality of life.[14] Enzyme replacement therapy (ERT) with recombinant human GAA has transformed the treatment landscape for Pompe's disease, significantly enhancing survival and functional outcomes, especially in infantile-onset cases.[15] Supportive care, including respiratory support, physical therapy, and nutritional interventions, is crucial in managing complications and optimizing patient care.[16] Despite advancements in diagnosis and treatment, Pompe's disease remains a devastating condition with significant morbidity and mortality, particularly in its severe infantile form.[17] Ongoing research aims to deepen our understanding of the disease's pathogenesis, explore novel therapeutic approaches, and improve patient outcomes.[18] Continued research and early intervention are essential for mitigating the impact of the disease and improving long-term prognosis.[19]

CASE HISTORY

A 45-day-old female child presented with a 5-day history of fever, cough and cold along with difficulty in breathing since that morning. On initial assessment, the patient was responsive, with breathing and pulse present. Given signs of respiratory distress and compensated shock, 100% oxygen was administered with a Non-Rebreathing Mask, and primary assessment was initiated. The patient exhibited tachypnea (respiratory rate of 66/min) with subcostal and intercostal retractions, and grunting. Heart rate was elevated at 190/min with weak peripheral pulses, delayed capillary refill time, and hypotension. Neurological assessment revealed responsiveness to pain, mid-dilated and reactive pupils and a normal temperature. Interventions included continued positive pressure ventilation and fluid resuscitation. With deteriorating vitals, the patient was intubated and ventilatory support initiated. Mild hepatosplenomegaly was noted on examination, with elevated liver enzymes (SGPT - 3502, SGOT - 1065). Investigations revealed anemia (Hb-9 gm/dl), leukocytosis (17,000 /cumm), thrombocytosis (4,37,000), elevated inflammatory markers (CRP-75 mg/dl) and metabolic acidosis and albuminuria (Urine Albumin ++++.). PT - 28.5, INR -2.17, serum Ammonia was 97 and serum Lactate was 2.3. Chest X-ray demonstrated cardiomegaly and consolidation in the right upper and middle zones. 2D ECHO revealed eccentric left ventricular hypertrophy and thickened mitral valve and chordae. With suspicion of an inborn error of metabolism (IEM), alpha-glucosidase activity testing indicated Pompe's disease due to a low ratio 0.1 (Normal range - 0.3 to 0.8) of lysosomal acid alpha-glucosidase to total acid alpha-glucosidase. Antibiotics were initiated and an extubation trial on the 4th day was unsuccessful, leading to re-intubation.

A 45-day-old female infant, who had a normal neonatal period and development without complications, presented with a 5-day history of fever, cough, and cold, along with difficulty in breathing since that morning. On initial assessment, the patient was responsive, with breathing and pulse present. Given signs of respiratory distress and compensated shock, 100% oxygen was administered via a Non-Rebreathing Mask, and a primary assessment was initiated. The patient exhibited tachypnea (respiratory rate of 66/min), subcostal and intercostal retractions, and grunting. Heart rate was elevated at 190/min, with weak peripheral pulses, delayed capillary refill time, and hypotension. Neurological assessment revealed responsiveness to pain, mid-dilated and reactive pupils, and a normal temperature. The infant had a normal course during the neonatal period, showing typical growth and developmental milestones without any complications.

However, recent symptoms included severe respiratory distress and signs of cardiovascular compromise. Interventions included continued

positive pressure ventilation and fluid resuscitation. With deteriorating vital signs, the patient was intubated, and ventilatory support was initiated. Examination noted mild hepatosplenomegaly and elevated liver enzymes (SGPT - 3502, SGOT - 1065). Investigations revealed anaemia (Hb - 9 gm/dl), leucocytosis (17,000 /cumm), thrombocytosis (4,37,000), elevated inflammatory markers (CRP - 75 mg/dl), and metabolic acidosis with albuminuria (Urine Albumin ++++). PT was 28.5, INR was 2.17, serum Ammonia was 97, and serum Lactate was 2.3. Chest X-ray demonstrated cardiomegaly and consolidation in the right upper and middle zones. [Figure.1] 2D ECHO revealed eccentric left ventricular hypertrophy and thickened mitral valve and chordae. [Figure.2] Suspecting an inborn error of metabolism (IEM), alpha-glucosidase activity testing confirmed

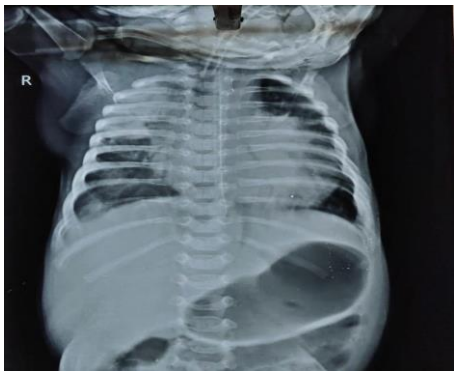


Figure-1: CXR suggestive of cardiomegaly

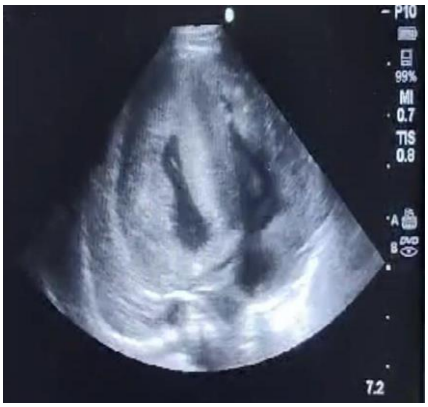
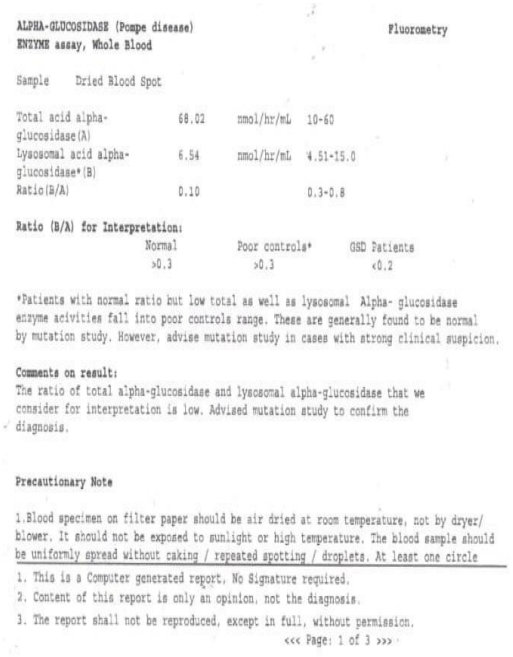


Figure-2: 2D ECHO showing LVH



ALPHA-GLUCOSIDASE (Pompe disease) Fluorometry
ENZYME assay, Whole Blood

Sample Dried Blood Spot

Total acid alpha-glucosidase(A)	68.02	nmol/hr/mL	10-60
Lysosomal acid alpha-glucosidase*(B)	6.54	nmol/hr/mL	4.51-15.0
Ratio(B/A)	0.10		0.3-0.8

Ratio (B/A) for Interpretation:

Normal	Poor controls*	GSD Patients
>0.3	>0.3	<0.2

*Patients with normal ratio but low total as well as lysosomal Alpha- glucosidase enzyme acivities fall into poor controls range. These are generally found to be normal by mutation study. However, advise mutation study in cases with strong clinical suspicion.

Comments on result:
The ratio of total alpha-glucosidase and lysosomal alpha-glucosidase that we consider for interpretation is low. Advised mutation study to confirm the diagnosis.

Precautionary Note

1.Blood specimen on filter paper should be air dried at room temperature, not by dryer/ blower. It should not be exposed to sunlight or high temperature. The blood sample should be uniformly spread without caking / repeated spotting / droplets. At least one circle

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Figure-3: Alpha-glucosidase enzyme assay

Pompe's disease due to a low ratio of 0.1 (Normal range - 0.3 to 0.8) of lysosomal acid alpha-glucosidase to total acid alpha-glucosidase.[Figure.3] Antibiotics were initiated, but an extubation trial on the 4th day was unsuccessful, leading to re-intubation.

DISCUSSION

Pompe's disease presents with a wide range of clinical manifestations, from severe infantile forms to milder late-onset phenotypes.[20] In severe cases, early diagnosis and intervention are crucial to preventing rapid disease progression and improving outcomes.[21] Diagnostic testing, including enzyme activity assays and genetic analysis, is vital for confirming the diagnosis.[22] Treatment strategies encompass supportive care, enzyme replacement therapy, and a multidisciplinary approach to address the diverse manifestations of the disease.[23] Enzyme replacement therapy (ERT) with recombinant human GAA has significantly improved the prognosis for patients with Pompe's disease, especially those with the infantile form.[24]

ERT has been shown to enhance survival rates, cardiac function, and delay the progression of motor and respiratory symptoms.[25] However, responses to ERT can vary, and some patients may develop an immune response to the treatment, necessitating additional therapies to manage these reactions.[26] Supportive care, including respiratory support and physical therapy, is a cornerstone of Pompe's disease management.[27] Respiratory support, such as non-invasive ventilation or mechanical ventilation, is often required as the disease progresses and respiratory muscles weaken.[28] Physical therapy and regular exercise can help maintain muscle function and improve overall quality of life.[29] Nutritional support is also critical, particularly in infantile Pompe's disease, where feeding difficulties can lead to poor growth and nutritional deficiencie.[30] Despite these advancements, managing Pompe's disease presents several challenges.[31] The high cost of enzyme replacement therapy, the need for lifelong treatment, and variability in patient response highlight the need for continued research into more effective and accessible treatments.[32] Additionally, the rarity of the disease and its variable presentation can result in diagnostic delays, underscoring the importance of increasing awareness and improving diagnostic techniques.[33] Ongoing research focuses on developing new therapeutic approaches, including gene therapy and pharmacological chaperones, which aim to enhance the stability and activity of the deficient enzyme.[34] Early results from gene therapy trials have shown promise, with some patients experiencing sustained improvements in muscle function and reductions in glycogen accumulation.[35] As these treatments evolve, they have the potential to significantly alter the management and prognosis of Pompe's disease.[36] Pompe's disease poses significant challenges in diagnosis and management, particularly in its severe infantile form.[37] Early recognition and intervention are essential for improving outcomes and quality of life for affected individuals.[38] Continued research into novel therapeutic approaches and a comprehensive, multidisciplinary approach to patient care are crucial for addressing the complex needs of patients with Pompe's disease.[39]

CONCLUSIONS

This case highlights the challenges in managing Pompe's's disease, particularly in the infantile form, where early recognition and intervention are paramount. Despite advances in diagnostic techniques and treatment modalities, the prognosis remains guarded, emphasizing the need for further research and therapeutic advancements in this rare metabolic disorder. Comprehensive care involving a multidisciplinary team is essential to optimize outcomes and improve the quality of life for affected individuals.

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