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Infantile hypotonia with failure to thrive

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Summary

Background:

Pompe disease is a lysosomal glycogen storage disease (GSDII) characterized by deficiency of acid glucosidase, resulting in lysosomal glycogen accumulation in multiple tissues, with cardiac and skeletal muscles being the most seriously affected. It manifests itself as a spectrum in multiple age groups including infancy, childhood and adulthood.

Case Report:

We present a case of infantile Pompe disease that was detected at a four month well visit in the presence of hypotonia and failure to thrive.

Conclusions:

Pompe disease can be diagnosed clinically by plotting growth parameters and performing developmental screening accurately. Enzyme replacement is the only available medical treatment for Pompe disease. High index of suspicion is necessary in diagnosing Pompe disease.

key words:

failure to thrive • hypotonia • developmental delay • cardiomegaly

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BACKGROUND

Pompe disease is a lysosomal glycogen storage disease (GSDII) characterized by deficiency of acid glucosidase [1], with cardiac and skeletal muscles being the most seriously affected. It manifests itself in multiple age groups, with a combined incidence of 1:40000 [2]. The screening for Pompe disease is not included in newborn blood screening. It has an autosomal recessive inheritance pattern with the defective gene site localized to chromosome 17q25.2-25.3 [3,4]. Multiple genotypes may produce the disease. It has phenotypic heterogeneity depending on the age of presentation, organ system involvement, degree of enzyme activity, and subsequent rate of progression [5]. The natural history of untreated patients consists of progressive disability, organ system failure, and death primarily due to respiratory causes. Therefore, if the diagnosis is established early, prompt medical therapy may be initiated. The clinician should have a high index of suspicion.

CASE REPORT

A 5-month-old, full-term, African American girl was seen in the pediatric resident continuity clinic and was noted to have significant hypotonia and failure to thrive. She was admitted to the pediatric ward for evaluation of the above complaints. The patient was seen at 2 months of age and was doing well clinically without any evidence of above symptoms. She overcame an upper respiratory infection 3 weeks prior to admission. There were no reports of tachycardia, cyanosis, syncope, febrile illness, rashes, or feeding intolerance over the last week. She was consuming 5 ounces of formula every 3 hours. There was no significant family history of cardiomyopathy, metabolic disorders, sudden cardiac death, arrhythmias, or congenital heart disease. On physical exam, her vitals were stable. Growth parameters are as follows: weight was 5.6 kgs (5th–10th percentile), height was 67 cm (90th percentile) and head circumference was 41 cm (25th percentile). She was alert and did not appear to be in acute distress. A mildly protuberant tongue and a flattened nasal bridge were evident. She was unable to lift her head and had considerable head lag while pulling to a sitting position. She had good air exchange bilaterally with minimal expiratory wheezes. Cardiovascular exam revealed normal first and second heart sounds as well as a gallop. There were good pulses bilaterally in distal upper and lower extremities. Her abdominal exam was significant for a nondistended abdomen with the liver edge palpable at 4 cm below the right costal margin. There was diffuse hypotonia noted in all four limbs, with minimal movement of only the distal upper phalanges. Neurologically, the patient was alert but not playful. Deep tendon reflexes could not be elicited. There was no cervical, axillary, or inguinal lymphadenopathy. Skin exam was unremarkable.

Chest radiograph upon admission revealed a prominent cardiac silhouette and clear lung fields (Figure 1). A pediatric cardiology consult was obtained for evaluation of the cardiomegaly and ventricular hypertrophy. A twelve-lead electrocardiogram showed biventricular hypertrophy, and Q waves were noted in the inferior limb leads and lateral precordial leads (Figure 2). Echocardiography demonstrated biventricular hypertrophy with poor systolic and diastolic function (Figure 3A,B). Blood work showed an elevated

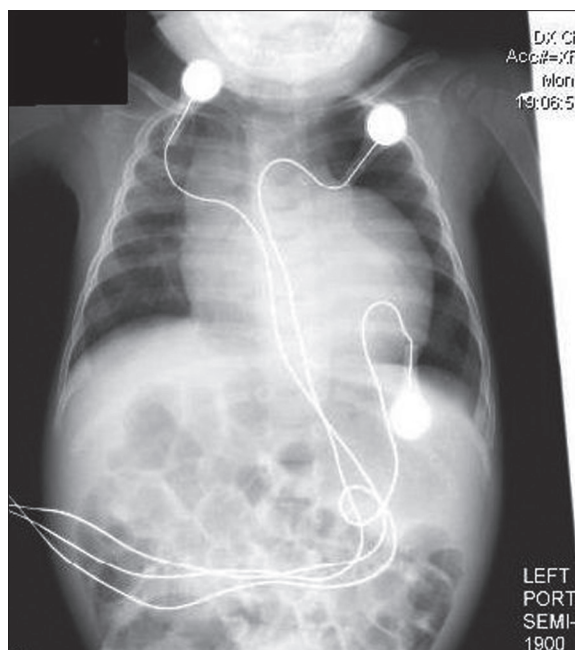


Figure 1. Chest radiogram showing an enlarged cardiac silhouette and clear lung fields.

creatinine kinase (CK 1173 U/L). In addition, reduced serum acid-alpha-Glucosidase (GAA) activity on dried blood spot screening was suggestive of infantile onset Pompe Disease. On quantitative analysis of GAA, there was complete absence of activity. Skin biopsy showed intracellular vacuoles filled with glycogen. Serum amino acids, carnitine, lactic acid, acyl carnitine analysis, and SMA gene were all within normal limits. The diagnosis of Pompe Disease was established after serum qualitative and quantitative analysis and a skin biopsy were performed. The patient developed mild tachypnea and was placed on oxygen via nasal canula. She was transferred to the intensive care unit for worsening respiratory distress. A family meeting was arranged and the decision was made to provide enzyme replacement therapy. Due to the complete absence of GAA activity, she was transferred to an outside institution for enzyme replacement therapy and management of potential anaphylaxis associated with enzyme administration. She required intubation for carbon dioxide retention prior to the transfer.

DISCUSSION

The differential diagnosis for this hypotonic infant is vast. The presence of a high CK (more than 1000 U/L) limits the differential to predominantly muscular diseases, especially those with muscle necrosis. Muscular involvement is seen in congenital muscle dystrophy (syndromic and non syndromic), congenital myotonic dystrophy, and metabolic dystrophy (Pompe and other storage diseases). Cardiac involvement further limits the differential diagnoses to congenital myotonic dystrophy and Pompe Disease. Given that the child was of nonconsanguineous conception and had no significant family history, Pompe Disease was considered to be the primary diagnosis. In the classic infantile form, onset of symptoms is at the median age of 1.6 months with the majority of patients dying at the median age of 6 to 7.7 months. Generally, 5 to 8 percent survive beyond one year and even fewer past 18 months [6]. Furthermore, GAA

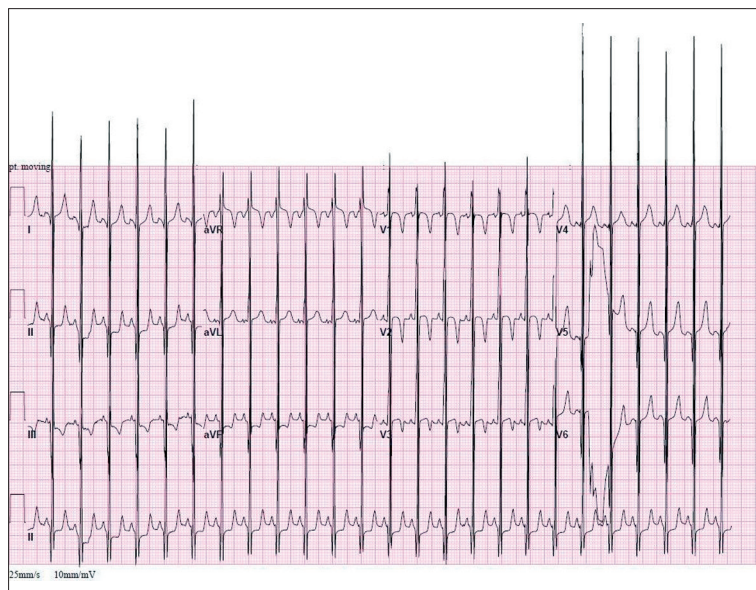


Figure 2. Electrocardiogram showing biventricular hypertrophy and Q waves in inferior limb leads and left lateral precordial leads. The PR interval measures 100 milliseconds.

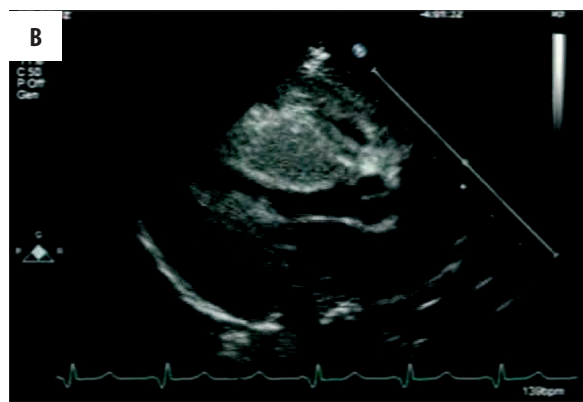
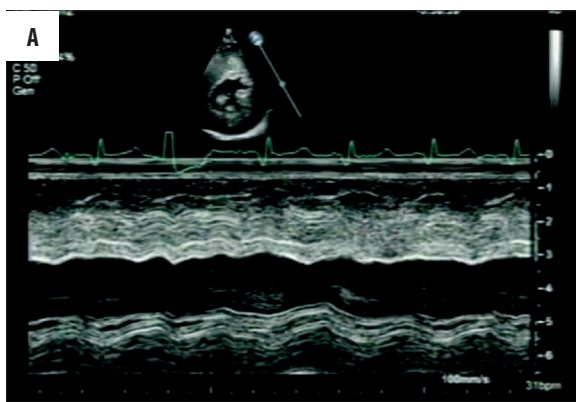


Figure 3A,B. M-Mode and parasternal long-axis views. Note the severely thickened interventricular septum and the left ventricular free wall.

activity is severely, and often completely, deficient in the infantile form. Predominant symptoms at presentation include feeding problems, failure to thrive, muscular weakness, gross motor delay and lack of voluntary movements [6]. Pathogenesis involves accumulation of lysosomal glycogen predominantly in skeletal, cardiac, and smooth muscle as well as other organs. Less severe cardiomyopathy, absence of left ventricular outflow obstruction and less than 5% of residual acid maltase activity are characteristics of a milder subtype of infantile form. A complete and thorough physical exam is of the utmost importance. The physical exam findings of a patient with classic infantile Pompe's Disease were described above in this patient; however, the physical exam findings may vary depending on the timing of presentation. Investigations for Pompe Disease must include serologic and noninvasive testing. Blood work should consist of CK, CK-MB, LDH, AST, ALT, dried blood spot screen, and quantitative and qualitative analysis of GAA activity. Usually, the aforementioned markers are elevated except for the GAA activity which is decreased or absent. Noninvasive testing must include a chest radiogram, an electrocardiogram and an echocardiogram.

The prognosis has been poor prior to the advent of recombinant human GAA (rhGAA). The key to successful palliation of severe muscle damage is to institute the enzyme

replacement therapy (ERT) prior to development of severe muscle damage. There is a significant positive cardiac response to rhGAA with decreased left ventricular mass index, left ventricular posterior wall thickness, and left ventricular dysfunction, independent of the disease severity [7]. However, the skeletal muscle response to rhGAA has been variable. Among the studies involving patients with classic infantile Pompe Disease and enzyme replacement therapy, the life span was extended up to 51 months with a median age of survival being 21.7 months, which is significantly longer than those untreated [8]. Regardless of the benefits of ERT on cardiac structure and function, most patients are ventilator-dependent at the end of life and succumb to respiratory failure. ERT with rhGAA has been accepted as more than an experimental therapy and is approved in the United States of America since 2006. The administration of recombinant acid-alpha-Glucosidase is not without significant risks. A Black Box warning exists for the therapy with particular attention to risk of anaphylaxis and risk of exacerbation of cardiopulmonary dysfunction. Other adverse reactions include upper respiratory infection, febrile illness, otitis media, gastrointestinal upset, rash and pneumonia. There is also development of IgG antibodies to acid-alpha-Glucosidase in a majority of the patients. The degree of elevated antibody titers varies between cross-reactive immunological material (CRIM) positive and negative individuals;

those with residual functioning or non-functioning enzyme are said to be CRIM positive and have lower antibody titers [9]. Those who were CRIM-negative developed antibodies earlier and had a poorer prognosis compared to those who were CRIM-positive. Additional clinical trials need to be done to identify those at higher risk with early elevation of antibody titers.

CONCLUSIONS

Early diagnosis and intervention will alter the prognosis and life expectancy in patients with Pompe disease although death is certain. A high index of suspicion, adequate differential diagnosis, complete physical exam and subsequent work up is mandatory to identify patients with Pompe Disease early. With the availability of rhGAA, the life expectancy is prolonged, although the individual response to therapy may vary depending on multiple host factors.

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