Case Report

An unusual presentation of metabolic cardiomyopathy due to Pompe's disease

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ABSTRACT

An Omani infant boy who presented in the neonatal period with cardiac failure secondary to hypertrophic cardiomyopathy is reported. He subsequently progressed to show features of a metabolic disorder with multisystem involvement and was diagnosed to have Type II glycogenosis (Pompe's disease). The differential diagnosis and management of metabolic cardiomyopathy are outlined.

Keywords: Metabolic cardiomyopathy, hypertrophic cardiomyopathy, Pompe's disease, heart failure.

Saudi Med J 2002; Vol. 23 (3): 338-340

Cardiomyopathy is an important manifestation of several inborn errors of metabolism,[1] and at times is the presenting problem in such disorders.[2] We report an infant boy who was referred with cardiac failure secondary to hypertrophic cardiomyopathy and later diagnosed to be suffering from Type II glycogen storage disease (Pompe's disease).

Case report. A 3-month old Omani infant boy was referred for problems of heart failure, recurrent chest infections and failure to thrive. Parents were consanguineous and this was their 3rd child, other siblings had been normal. Pregnancy and delivery were uneventful. Respiratory distress was noted soon after birth. The baby was found to be tachypneic, tachycardic and had a hepatomegaly of 3-4 cm. He had clinical cardiomegaly, normal heart sounds and a grade 2/6 ejection systolic murmur best heard over the pulmonary area. He was also noted to be hypotonic but was otherwise normal neurologically. There were no dysmorphic features or large tongue. He required admission to the special care baby unit and was commenced on antiheart failure therapy along with antibiotics and other supportive measures. He was discharged from the hospital at one week and thereafter followed up as an outpatient. The boy was noted by parents to have poor spontaneous activity at one month. He also had 2 further episodes of lower respiratory infection requiring hospitalization, and continued to have poor weight gain. He was then referred to our hospital for further cardiac evaluation. Clinical findings noted here in addition to those described above included clinical evidence of pulmonary hypertension, severe hypotonia with just elicitable deep tendon reflexes and a developmental age of only one month. He also showed bilateral anterior polar cataract. Chest radiograph showed marked cardiomegaly, and electrocardiogram (ECG) revealed biventricular hypertrophy with extreme right axis deviation. PR interval was however normal. Echo Doppler studies showed marked hypertrophy of both right and left ventrilcular free walls and the interventricular septum **(Figure 1)**. Left ventricular ejection fraction was only 55% and there was evidence of diastolic

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Received 27th August 2001. Accepted for publication in final form 14th October 2001.

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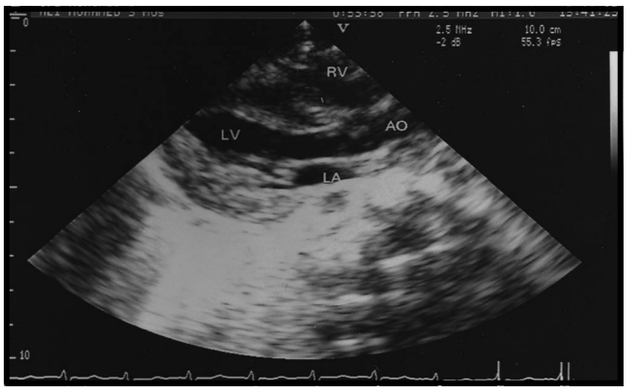

Figure 1 - Two-dimensional echocardiographic picture taken from the parasternal long axis window showing hypertrophied left (LV) and right (RV) ventricles, thickened interventricular septum and a dilated left atrium (LA).

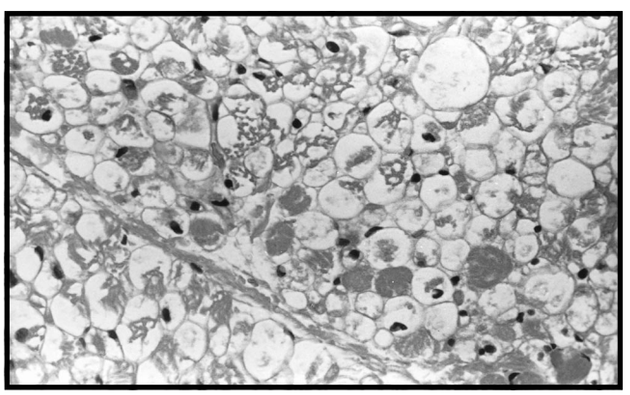

Figure 2 - Transverse section of quadriceps muscle showing numerous vacuolated muscle fibres. Hematoxylin Eosin x 40.

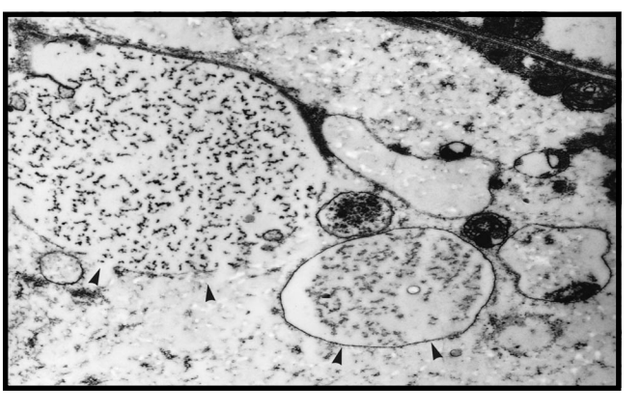

Figure 3 - Electron micrograph with glycogen granules in membrane bound vacuoles - lysosomes (arrrow) x 7000.

dysfunction as well. The left ventricular outflow gradient was normal, excluding significant obstruction. There was evidence of mild mitral and tricuspid valve regurgitations. Blood investigations showed elevated creatine kinase (410 u/L), however the plasma lactate and ammonia were normal. Liver enzymes were elevated, with a normal serum bilirubin. Metabolic screen (including L-carnitine and acyl carnitine) by Tandem Mass Spectometry (TMS) did not yield any abnormality. Serum immunoglobulins and barium swallow for gastro-esophageal reflux were normal. Computerized tomographic scan of the brain and nerve conduction studies were reported as normal. Electromyography revealed a mixed myopathic and neurogenic pattern. Quadriceps muscle biopsy showed a severe type of vacuolar myopathy **(Figure 2)**. P-aminosalycilic acid (PAS) positive glycogen granules in vacuoles almost completely replaced myofibrils in many fibers. Electron microscopy revealed these glycogen granules to be membrane bound **(Figure 3)**, confirming lysosomal storage and thereby the diagnosis of infantile Type II glycogenosis. He was managed with anti-heart failure medications and other supportive and symptomatic measures. He improved and was discharged after counselling the parents. Later at the age of 6 months, he was readmitted to the local hospital with fulminant chest infection and expired.

Discussion. Cardiomyopathy is a disease of the heart muscle of unknown cause that does not represent a response to co-existing or pre-existing diseases of the heart or circulation such as acquired or congenital heart disease, hypertension or pulmonary vascular disease.[3] Three pathophysiologic forms of cardiomyopathy are recognized - dilated, hypertrophic and restrictive.[4-6] Hypertrophic cardiomyopathy (HCM) is in the majority, an isolated cardiac disorder and shows an autosomal dominant pattern or a mitochondrial inheritance.[7] However, many children especially those presenting before the age of 4 years may have associated dysmorphisms or systemic abnormalities that may point to an underlying genetic disorder like Noonan syndrome, Pompe's disease or an infiltrative disorder.[8,9] Our patient had HCM and presented very early in life with clinical features of heart failure. There was no evidence of any congenital heart disease that could have caused the disease, and there was no family history of HCM. The marked hypotonia, sluggish deep tendon reflexes, developmental delay and recurrent chest infections became obvious as age advanced, suggesting an underlying metabolic disorder. Although the typical features of Pompe's disease such as facial dysmorphism and large tongue were absent, the electromyography along with muscle biopsy results

helped us to come to a firm diagnosis. The enzyme deficient being a lysosomal enzyme, glycogen accumulation noted on electron microscopy in membrane bound vacuoles and not in the cytosol is quite characteristic of Type II glycogenosis. Leucocyte assay for acid alpha glucosidase, the enzyme deficient in Pompe's disease could not be performed. Fatty acid oxidase defects and systemic carnitine deficiency which could present similarly were excluded by the normal results of TMS on blood samples.

Metabolic cardiomyopathy of infants and children accounts for 15-20% of all cardiomyopathies presenting at these ages, and majority of these are of the hypertrophic type.[8,9] These may or may not be associated with significant subaortic obstruction.[10,11] Unlike the new born with HCM secondary to maternal diabetes mellitus which mostly resolves in due course, the majority of the HCM are progressive in nature. Hereditary HCM without any demonstrable metabolic abnormality may also occasionally present at an early age and family screening for the disease and genetic studies will then be helpful to establish the diagnosis. Our patient had hypertrophy of both right and left ventricles, and also of the interventricular septum, and evidence of systolic and diastolic left ventricular dysfunction. However, there was no evidence of any subaortic obstruction. The metabolic evaluation of pediatric hypertrophic cardiomyopathy is aided by keeping in mind that the heart is often only one of the many organs affected in what should be seen as a systemic disease. Cardiomyopathy due to glycogen (Pompe's disease) or mucopolysaccharide (Hurler's disease) disorders are generally easy to diagnose because of obvious extracardiac manifestations. The confirmation of enzyme deficiency can be performed by enzyme assay on a blood or urine sample. Cardiomyopathies due to a deficit of oxidative metabolism are usually associated with multi-system abnormalities but may be isolated or the presenting sign of the deficit. The diagnosis should be suspected in cases of a positive family history of cardiomyopathy or sudden death, of consanguinity, of unusual or unexplained extracardiac disease, of atypical ECG changes or of hypoglycemia. Chromatography of organic acids, analysis of acyl carnitines and fatty acids are also helpful. The diagnosis of mitochondrial cardiomyopathy is based on the ratios of oxidoreduction and, above all, on spectrophotometric analysis of the respiratory chain complexes in skeletal or cardiac muscle (when the heart is the only organ involved). At times the systemic features are atypical or not full blown in early infancy, and the baby may present with heart failure as the predominant manifestation. Our patient serves to emphasize this point.

The confirmation of etiology helps to establish a prognosis which is often poor, and, above all, for family counselling. Treatment is rarely curative except in case of primary carnitine deficiency, which responds promptly to oral supplements of L-carnitine.[12] Recently recombinant human acid alpha glucosidase enzyme therapy has been tried in early infancy in Pompe's disease with marked subsidence of the cardiomegaly and cardiac failure by one year of age. Both genetically engineered Chinese hamster ovary cells[13] as well as recombinant human alpha glucosidase from rabbit milk[14] have been used, and were well tolerated. Early initiation of therapy is essential for satisfactory results.

References

1. Kelly DP, Strauss AW. Inherited cardiomyopathies. *N Engl J Med* 1994; 330: 913-919.
2. Ferencz R, Neill CA. Cardiomyopathy in infancy: observations in an epidemiologic study. *Pediatr Cardiol* 1992; 13: 65-71.
3. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. *Circulation* 1996; 93: 841-842.
4. Benson LN, Freedom RM. Classification of cardiomyopathies of childhood. *Prog Pediatr Cardiol* 1992; 1: 4-7.
5. Codd MB, Sugrue DD, Gersh BJ, Melton LJ. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. *Circulation* 1989; 80: 564-572.
6. Ablemann WH. Classification and natural history of primary myocardial disease. *Prog Cardiovasc Dis* 1984; 27: 73-94.
7. Schwartz ML, Cox GF, Lin AE, Korson MS, Perez-Afayde A, Lacro RV. Clinical approach to genetic cardiomyopathy in children. *Circulation* 1996; 94: 2021-2038.
8. Servidei S, Bertini E, DiMauro S. Hereditary metabolic cardiomyopathies. *Adv Pediatr* 1994; 72(Suppl): 1-32.
9. Towbin JA. Molecular genetic aspects of cardiomyopathy. *Biochem Med Metab Biol* 1993; 49: 285-320.
10. Rees A, Elbl F, Minhas K, Sohinger R. Echocardiographic evidence of outflow tract obstruction in Pompe's disease (glycogen storage disease of the heart). *Am J Cardiol* 1976; 37: 1103-1106.
11. Gussenhoven WJ, Bush HF, Kleijer WS, de Villeneuve VH. Echocardiographic features in the cardiac type of glycogen storage disease II. *Eur Heart J* 1983; 4: 41-43.
12. Helton E, Darragh R, Francis P, Fricker FJ, Jue K, Koch G, et al. Metabolic aspects of myocardial disease and a role for L-carnitine in the treatment of childhood cardiomyopathy. *Pediatrics* 2000; 105: 1260-1270.
13. Amalfitano A, Bengur AR, Morse RP, Majure JM, Case LE, Veerling DL, et al. Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. *Genet Med* 2001; 3: 132-138.
14. Van den Hout H, Reuser AJ, Vulto AG, Loonen MC, Cromme-Dijkhuis A, Van der Ploeg AT. Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. *Lancet* 2000; 356: 397-398.