CASE REPORT

Enzyme replacement therapy for infantile Pompe disease during the critical period and identification of a novel mutation

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Pompe disease (acid maltase deficiency, glycogen storage disease type II) is a rare progressive autosomal recessive disorder caused by a deficiency of lysosomal hydrolase acid alpha-glucosidase. Historically, infantile-onset Pompe disease presents with cardiomegaly, hepatomegaly, weakness and hypotonia leading to death caused by cardiorespiratory failure in the first year of life. Enzyme replacement therapy has recently become available and has been shown to be effective in prolonging survival and improving respiratory performance. In this article, we report a case of infantile-onset Pompe disease successfully managed with enzyme replacement therapy during the critical period. We would like to highlight the occurrence of sudden cardiac arrest in our patient during the early course of enzyme replacement therapy, which has not been reported before. A novel mutation was also identified in the family.

Case report

A male Pakistani baby was born at term with a birth weight of 3.35 kg. He was the third child in the family and his parents were related. Their first baby suffered from gross hypertrophic cardiomyopathy and died at 7 months of age in Pakistan. He was diagnosed with Pompe disease on clinical grounds. Their second child was healthy.

The baby was well after birth. At 1 month of age, heart failure and hepatomegaly were noted and a chest X-ray showed gross cardiomegaly. His electrocardiogram showed a short PR interval as well as very tall QRS complexes and his echocardiogram revealed hypertrophic cardiomyopathy (Fig 1a). His serum muscle enzyme levels were elevated: creatine kinase was 552 IU/L (reference range [RR], 2-129 IU/L), lactate dehydrogenase was 636 IU/L (RR, 170-450 IU/L), and alanine aminotransferase was 133 IU/L (RR, 4-35 IU/L). An electromyogram showed myopathic changes. A dried blood spot (DBS) was collected and sent for urgent enzyme studies. The DBS analysis revealed no detectable acid alpha-glucosidase (GAA) activity and a urine analysis performed using tandem mass spectrometry showed increased urinary excretion of tetrasaccharide (Glc4) [143; reference level, <24]. These results together confirmed the diagnosis of Pompe disease. Mutational analysis by polymerase chain reaction and direct DNA sequencing of all the exons of the *GAA* gene showed that the patient was homozygous for c.1929_1935dup, which is a novel mutation. The parents and his elder brother were all heterozygous for this nucleotide variation (Fig 2). A heteroduplex study was performed on the DNA samples from 50 normal control subjects. No similar nucleotide changes were found in any of these subjects, ruling out the possibility of polymorphism.

During his hospitalisation, our patient was managed supportively with a beta-blocker (propranolol 2 mg/kg/day) and multidisciplinary care. At 1.5 months of age, he developed a respiratory syncytial virus infection with exacerbation of heart failure, necessitating intensive care and ventilatory support. Although the intensive support improved his condition slightly, his cardiomyopathy progressed rapidly. At 2 months of age, his echocardiogram showed that the left ventricular mass index (LVMI) had nearly doubled, increasing to 293 g/m^2 compared with 154.6 g/m^2 at 1 month of age. His left ventricular cavity was nearly obliterated and impending death was envisaged if no definite treatment was offered. After the diagnosis was confirmed by enzyme studies, he was managed with enzyme replacement therapy (ERT) using Myozyme (Genzyme Corporation, Cambridge, MA, US) 20 mg/kg infusion every 2 weeks. One week after the first dose of ERT, his oxygen saturation dropped suddenly and he developed sinus bradycardia of 50 beats/minute, followed by cardiac arrest. He responded promptly to external cardiac massage. No tachyarrhythmia was detected on continuous cardiac monitoring. The beta-blocker was ceased and an intravenous inotrope was prescribed to counter the deterioration in cardiac output.

After this incident, the patient responded very well to ERT. His cardiomyopathy

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危急階段使用酵素補充療法治療幼年起病的龐培氏症及新型基因突變的發現

龐培氏症（即酸性麥芽糖酶缺乏症，又稱二型糖原累積病）是一種罕見的漸進式常染色體隱性遺傳病，因缺乏溶酶體水解酸α葡萄苷酶導致。文獻記載幼年起病的龐培氏症患者會出現心臟及肝臟肥大、行動時感到疲累、肌肉無力，而患者往往因心臟呼吸系統異常於一歲前死亡。近年酵素補充療法的出現，證實能有效地改善呼吸系統，以致延長患者壽命。本文報告一宗幼年起病的龐培氏症，在最危急的階段用酵素補充療法成功醫治患者。他在接受酵素補充療法的初期出現心臟驟停，這種反應屬首次報告。此外，我們從患者的家人身上發現了新型的基因突變。

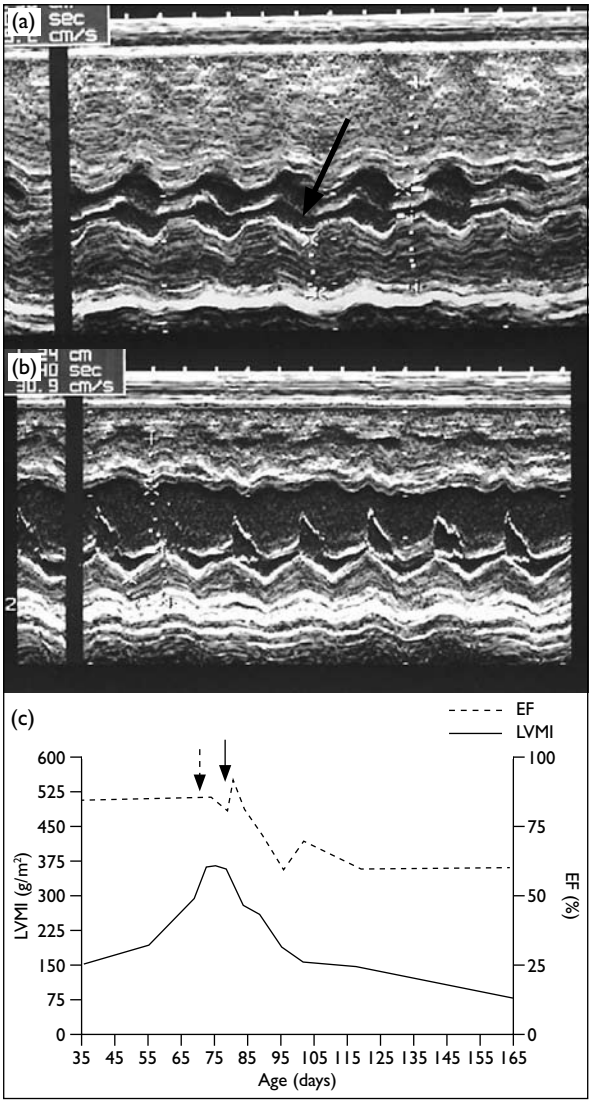

FIG 1. Progress of hypertrophic cardiomyopathy with enzyme replacement therapy (ERT): (a) echocardiogram showing severe hypertrophic cardiomyopathy just before the commencement of ERT at 2 months of age, note the nearly obliterated left ventricular (LV) cavity (arrow); (b) echocardiogram showing marked resolution of hypertrophic cardiomyopathy after three doses of ERT, note the marked decrease of LV wall hypertrophy and the improvement in LV cavity size; (c) the relationship between the left ventricular mass index (LVMI) and ejection fraction (EF) with age, showing the change of LVMI and EF with disease progression and with treatment; dotted arrow denotes the initiation of ERT, and solid arrow cardiac arrest

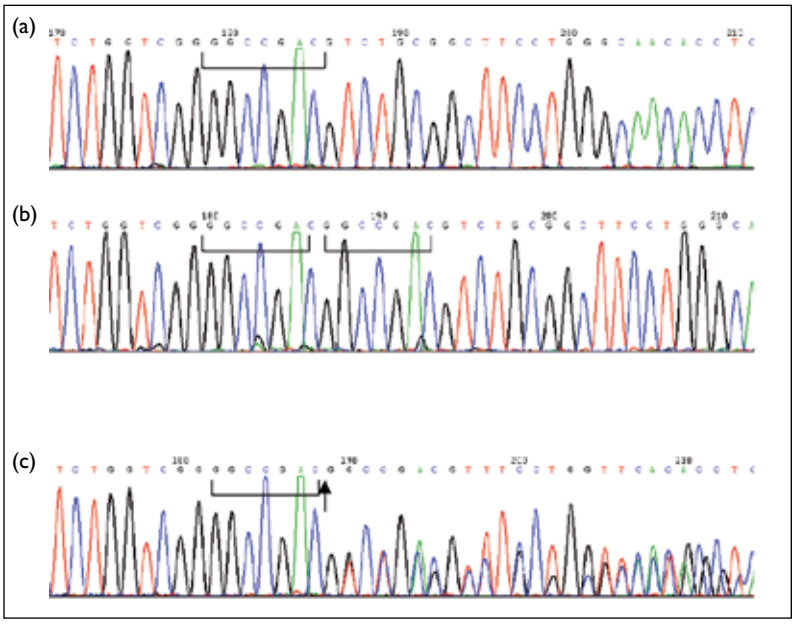

FIG 2. Electropherograms of a segment of the *GAA* gene showing the mutation c.1929_1935dup in the patient and his father. (a) Control, wild-type sequence, (b) patient, homozygous for c.1929_1935dup, and (c) father, heterozygous for c.1929_1935dup

The duplicated nucleotides 1929 to 1935 are indicated by brackets and the starting point of the mutation is indicated by an arrow. All in sense direction

resolved favourably. He was taken off intensive support and inotropes from the age of 3 months. At 5.5 months, after eight doses of ERT, his LVMI had decreased to 75 g/m^2, which was within normal limits (70-75 g/m^2) and his left ventricular cavity size had increased. Before ERT was commenced, his ejection fraction (EF) was 86% and decreased to 60% at 3 months of age (normal range is around 60-75% depending on age at the time of data collection). All cardiac drugs were ceased. His echocardiographic findings are shown in Figure 1.

His skeletal muscle also responded to ERT, although less favourably than the cardiac muscle response. He required a combination of oral and tube feeding to ensure adequate nutritional intake and permit oral motor development. His total score on the Alberta Infant Motor Scales improved to 14 (5th centile) at 5 months of age compared to a total score of 4 (<5th centile) at 2 months of age. He could hold his head in the midline, tuck in his chin, and bring his hands to the midline and to his knees. He could sit and stand with support transiently. This motor development was not expected without ERT.

Discussion

Pompe disease is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid GAA. In Pompe disease, lysosomal glycogen accumulates in many tissues especially in skeletal, cardiac, and smooth muscle.[1] The steady accumulation of glycogen substrate in target tissues leads to progressive debilitation, organ failure and/or death. There is a spectrum of disease severity. In infantile-onset Pompe disease, the most severe and rapidly progressive form, patients present with hypertrophic cardiomyopathy, hepatomegaly, generalised weakness, hypotonia and death due to cardiorespiratory failure in the first year of life.[2]

Until recently, there has been no specific treatment for Pompe disease other than supportive care. Enzyme replacement therapy is now available for treatment. Several studies involving patients with infantile-onset Pompe disease have shown that ERT significantly prolongs survival, decreases cardiomegaly, and improves cardiac and skeletal muscle function.[3-5] In most cases, the cardiac response appears to be good. Reduction in the LVMI has been demonstrated in all patients. Reverse remodelling occurs in varying degrees, leading to changes in cardiac systolic function as measured by the EF. With thinning of the walls, the overall heart size decreases and intracavitary volume increases. The sudden increase in intracavitary volume in the early course of therapy will cause a transient drop in EF during the first 12 weeks of ERT but as the left ventricular cavity size normalises over time, so does the EF.[6] Our patient's EF rose to 86%, indicating that his systolic function was hyperdynamic initially. With ERT he experienced a transient drop in EF, but it was generally within the normal range all along.

This case illustrates a good short-term result with ERT but also the negative effects of ERT in the early phase of treatment. Patients with infantile Pompe disease are at high risk of arrhythmia. A death from ventricular fibrillation arrest during the early phase of ERT, after general anaesthesia for a skin biopsy and central venous catheter placement has been reported.[7] The underlying mechanisms were thought to be the hypertrophied heart, labile coronary perfusion pressure and abnormal conduction velocities.[8] The period of highest risk may be early in the course of ERT when there is a substantial decrease in left ventricular mass and an initial decrease in the EF.[9] Our patient developed sudden bradycardia followed by cardiac arrest 1 week after the initiation of ERT but no tachyarrhythmia was detected on continuous cardiac monitoring. This phenomenon has not been reported before. We do not know the exact cause of his sudden cardiac arrest. It may have been the effect of the ERT or it may have been caused by the use of beta-blockers, which may have further depressed the decreasing cardiac contractility during the early course of treatment. High doses of beta-blockers (propranolol) are associated with an increased risk of sudden death in hypertrophic obstructive cardiomyopathy.[10] Several anecdotal unreported cases of sudden death associated with the use of beta-blockers in patients with Pompe disease suggest that beta-blockers should be used carefully.[11] In retrospect, it may be wise to decrease or stop beta-blockers once ERT has commenced. Fortunately our patient responded well to cardiac massage and recovered without any significant sequelae after the beta-blockers were ceased. Thus, cardiomyopathy in Pompe disease should be treated carefully and the choice of cardiac medications should be based on the stage of disease. The use of digoxin, inotropes, diuretics, and afterload-reducing agents may exacerbate the left ventricular outflow tract obstruction and should be avoided but these agents are indicated in the later phases of the disease, when the ventricle becomes dilated and functions poorly.[1,11]

As ERT is extraordinarily costly, a diagnosis confirmed by enzyme studies is often required for initiation of treatment. Blood tests may give a false-negative result as blood contains maltase glucoamylase, a GAA, whose activity can mask a deficiency of GAA. Measurement of GAA activity in skin fibroblasts is the current diagnostic gold standard but cultured fibroblasts can take up to 4 to 6 weeks to grow to confluency prior to the enzyme assay, causing a delay in diagnosis. Patients with infantile Pompe disease often progress rapidly, resulting in fatality, and they are at increased risk of complications of anaesthesia. Rapid and non-invasive diagnostic tests that assay GAA activity in DBS extracts using maltose[12] or acarbose[13] as inhibitors of maltase glucoamylase have been developed to save valuable time in patient care and treatment. A DBS can be conveniently collected and shipped from locations where enzyme studies are not available to the analytical centres, as in our case. Combined with an analysis of urinary Glc4, the diagnostic sensitivity is close to 100% for infantile Pompe disease.[14] Genetic testing, which is available locally, plays an important role in confirming the diagnosis and provides valuable information for family studies and for prenatal diagnosis. Indeed, earlier diagnosis of affected patients using newborn screening to determine GAA activity in DBS extracts using a fluorometric enzyme assay[15] is feasible and allows the initiation of ERT before patients become symptomatic.

Conclusion

Infantile Pompe disease is a rare inherited metabolic disease and is fatal in the first year of life without ERT. Early diagnosis followed by treatment with ERT

is crucial to optimise patient outcomes. This is made possible by assaying GAA activity in DBS extracts and analysing urinary Glc4. Earlier detection by newborn screening is feasible. Great care must be taken during the early course of ERT as arrhythmias or sudden cardiac arrest may occur. Genetic testing, which is available locally, plays an important role in diagnosis and genetic counselling.

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