□ Case Report □

Clinical improvement in a case of atypical infantile onset Pompe disease with enzyme replacement therapy

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Pompe disease is a genetic disorder caused by a deficiency of acid α-glucosidase (GAA). Infantile onset Pompe disease is uniformly lethal. Affected infants generally present in the first few months of life with hypotonia, generalized muscle weakness, and a hypertrophic cardiomyopathy, which is rapidly followed by death, usually by the age of one. The late-onset form is characterized less severe symptoms and prognosis. Therapy for Pompe disease is intended to directly address the underlying metabolic defect via intravenous infusions of recombinant human GAA to replace the missing enzyme. We report a case of atypical infantile-onset Pompe disease that presented symptoms in infancy but had less severe clinical manifestations and improved after GAA enzyme replacement (Myozyme®, Genzyme Co., MA, USA) therapy. It is very important that pediatricians become aware of signs and symptoms of Pompe disease, such as a nasal voice or a waddling gait at an early stage so that these patients can benefit from appropriate GAA replacement therapy as soon as possible. **(Korean J Pediatr 2007;50:213-217)**

Key Words : Pompe disease, Alpha-glucosidases, Replacement therapy

Introduction

Pompe disease, also referred to as glycogen storage disease type II and acid maltase deficiency, is an autosomal recessive lysosomal storage disease caused by deficiency of acid α-glucosidase (GAA, also referred to as acid maltase). This enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, with cardiac, skeletal, and smooth muscle cells the most seriously affected[1, 2]. Pompe disease occurs with an estimated frequency of 1 in 40,000 and encompasses a range of phenotypes[1, 3]. Infantile-onset Pompe disease is uniformly lethal. Affected infants generally present in the first few months of life with hypotonia, generalized muscle weakness, and a hypertrophic cardiomyopathy, followed by death from cardiorespiratory failure or respiratory infection, usually by the age of one. A late-onset (juvenile or adult onset) form is characterized by a lack of cardiac involvement and a less severe short-term prognosis[1]. Enzyme replacement therapy for Pompe disease with recombinant human precursor acid α-glucosidase (rhGAA) is currently in clinical trials[3, 4].

We report here a child with atypical infantile onset Pompe disease who demonstrated clinical improvement after beginning with rhGAA enzyme (Myozyme®, Genzyme Co., MA, USA) replacement therapy.

Case Report

A five-year-old boy presented at our hospital with difficulty in walking and with a cardiac murmur. He was with the product of a normal spontaneous vaginal delivery at 40 weeks of gestation and weighed 2,900 g. He had poor feeding and decreased activity in the first month after birth, and he also had difficulty in standing at 2 years of age. When he was 2 years and 6 months old, he was seen at a private clinic with symptoms of a common cold. The examining physician discovered a cardiac murmur and cardiomegaly. He was diagnosed with Pompe disease after a muscle biopsy by a pediatric neurologist at 4 years of age

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and was referred to our clinic for enzyme replacement therapy. He was the first of two children, and his sister also had low α-glucosidase activity [0.29 nmol/min/mg protein (normal : 0.5-1.5)] in her leukocytes but no symptoms of Pompe disease. When he visited our clinic he was found to have generalized weakness, poor gripping power and a nasal voice. He had difficulty in climbing up or down stairs without using a handrail.

He appeared chronically ill. His vital signs were normal and his weight was 14 kg (10-25th percentile). His height was 92 cm (3-10th percentile) and the head-circumference was 48 cm (10-25th percentile). A loud systolic murmur, grade IV to V, was heard at the left upper and lower sternal border. His liver was enlarged and palpable 4.5 cm below the right costal margin (Fig. 1). His muscle tone was decreased, and muscle strength was graded IV/V in both upper and lower extremities. He had a Gower's sign and a waddling gait. His laboratory result showed an elevated enzymes: aspartate aminotransferase (AST), 281 IU/L; alanine aminotransferase (ALT), 161 IU/L; creatine kinase (CK), 1,235 IU/L; lactate dehydrogenase (LDH), 1,815 IU/L; acid phosphatase, 1.50 IU/L. His α-glucosidase activity in leukocytes was 0.20 nmol/min/mg protein and a muscle biopsy was consistent with glycogen storage disease, lysosomal type. His chest X-ray displayed marked cardiomegaly and his cardiothoracic (CT) ratio was 0.61 (Fig. 2). There was PR interval shortening on the electrocardiogram (0.08 seconds), as well as QRS complex widening (0.12 seconds) and biventricular hypertrophy (Fig. 3). As seen in the echocardiogram, the interventricular septal diastolic dimension

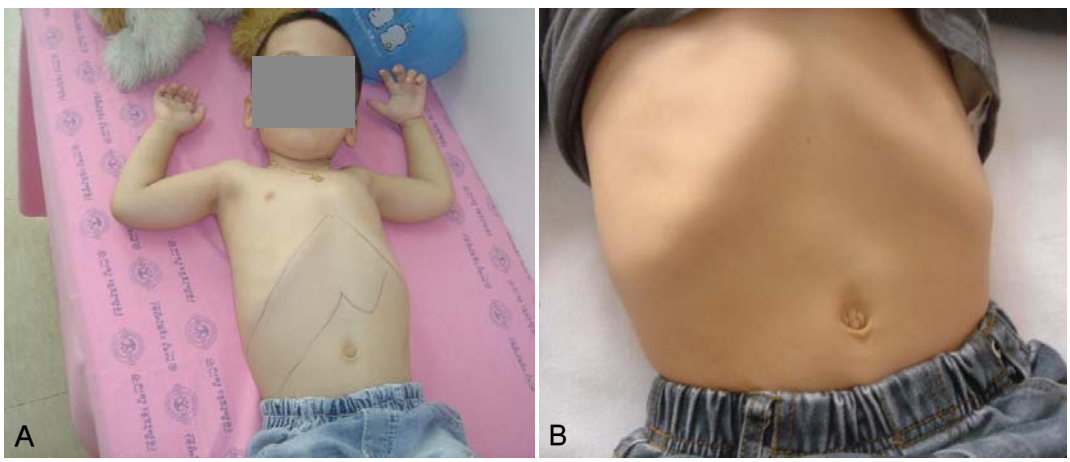

Fig. 1. The patient had hepatomegaly (4.5 cm below the right costal margin) at his first visit (A), but by 38 weeks after the initiation of acid α-glucosidase replacement therapy, he had no hepatomegaly (B).

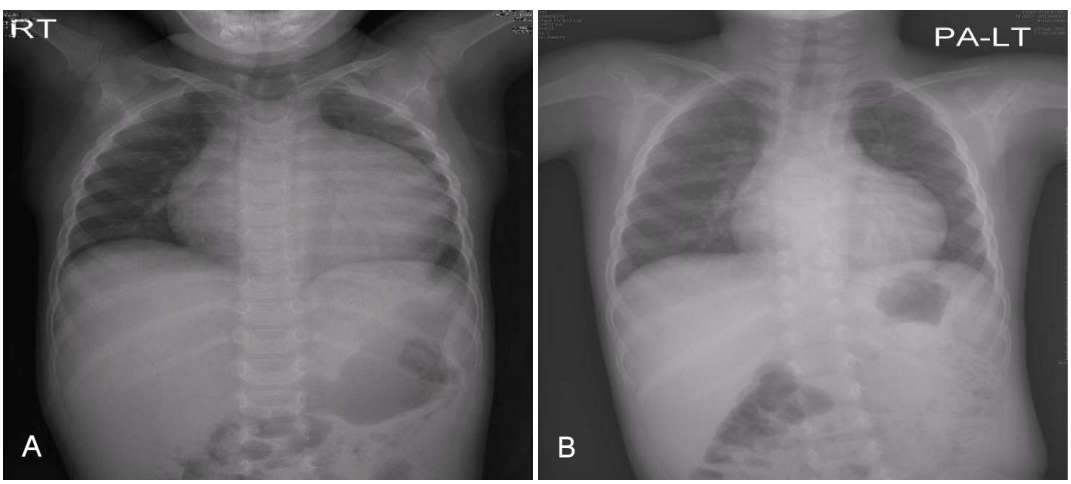

Fig. 2. The patient's chest X-ray showed marked cardiomegaly (cardiothoracic ratio=0.61) at his first visit (A), but 36 weeks after GAA replacement therapy, his cardiomegaly was much improved (B).

was 24.8 mm (normal range 3.3-6.3) and mitral valve regurgitation was observed. There was a 23.4% decrease in the ejection fraction. There was asymmetric septal hypertrophy and the left ventricular mass index was greater than 95 percent (Fig. 4).

Since January 2005, recombinant acid α-glucosidase (GAA), Myozyme® (Genzyme Co., MA, USA) was infused to the patient every other week with a dose of 20 mg per kg. Following the first infusion of GAA, his appetite increased and after six weeks hepatomegaly had improved by 2 cm (Fig. 1). After 10 weeks of treatment, he was able to walk downstairs without using the handrail. At the 12th week, his cardiac murmur was still heard but was less loud, and the echocardiogram revealed improved cardiac function. By 20 weeks, his grip strength had improved and he was able to climb up the slide ladder in the playground. After 32 weeks, he could jump. At 38 weeks of therapy, we could palpate only the tip of his liver. After 40 weeks, the patient was able to walk for 1 hour, and by 42 weeks he was able to climb up the stairs from the 1st to the 13th floor. We had also checked Pompe-PEDI (pediatric evaluation of disability inventory)[5], a development test for Pompe disease, before the first injection and at the 12th week, 26th week, and 38th week. The score at the 12th week was no higher than the initial score but the score at the 26th week and 38th week were significantly increased from baseline (Table 1). Up until now, there have been no side effects of GAA replacement therapy.

Discussion

Pompe disease is a genetic disorder caused by a deficiency

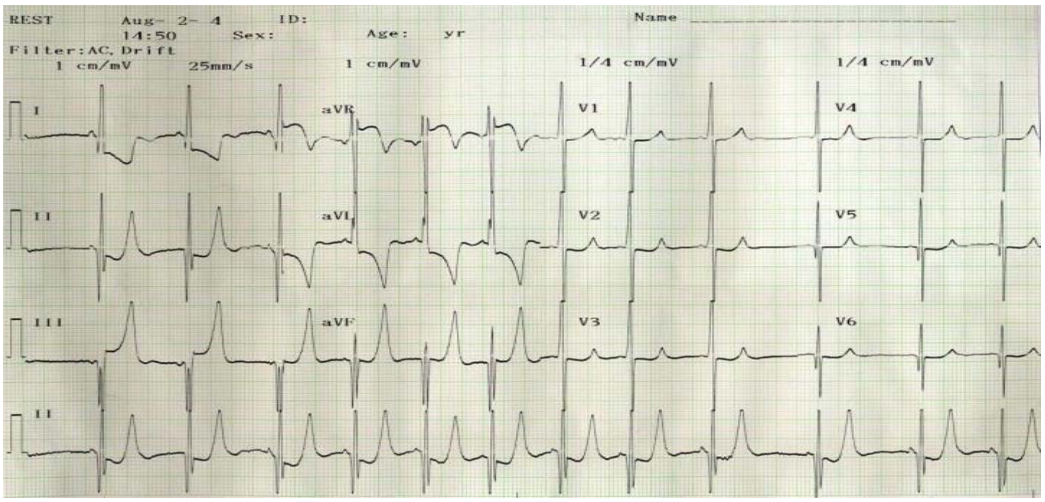

Fig. 3. The patient's electrocardiogram showed a short PR interval (0.08 seconds), a widened QRS complex (0.12 seconds) and biventricular hypertrophy.

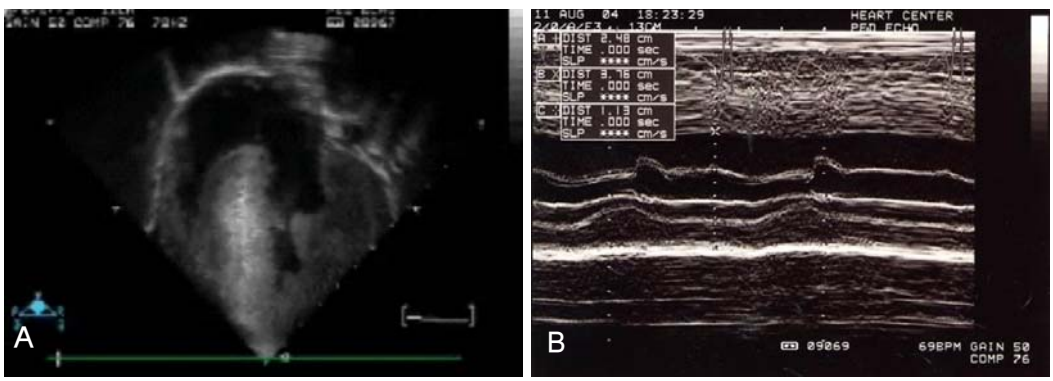

Fig. 4. (A) The patient's echocardiogram showed a high interventricular septal diastolic dimension (24.8 mm), a high left ventricular mass index (>95 percent) and asymmetric septal hypertrophy. (B) Mitral valve regurgitaion was observed and there was a 23.4% decrease of the ejection fraction.

Table 1. The Patient's Pompe-Pediatric Evaluation of Disability Inventory (PEDI) Score* at Baseline, 12th Week, 26th Week and 38th Week

	Baseline	12th wk	26th wk	38th wk
Functional scale				
Self-care	69.39	69.00	73.00	77.13
Mobility	58.23	58.23	62.50	65.14
Social function	57.2	57.2	65.1	66.2
Caregiver assistance				
Self-care	72.7	71.1	71.1	89.7
Mobility	70.5	70.5	82.5	89.4
Social function	59.3	59.3	72.5	75.3

*This Pompe-PEDI score was based on Haley SM, et al. Pediatr Rehabil 2003;6:77-84.

of GAA. The responsible gene has been localized to chromosome 17q25 and is designated GAA on the human gene map. Pompe disease is inherited in an autosomal-recessive manner; thus, both parents of a child with the disease must be carriers of the mutant gene. More than 120 mutations in the GAA gene that give rise to Pompe disease have been identified[1].

Patients have been classified as infantile or late onset (juvenile or adult) types. In general, the age of onset appears to correlate with residual GAA levels, which tend to correlate inversely with disease severity. Infants with Pompe disease have virtually no GAA activity, and they present in the first few months of life with feeding problems, poor weight gain, respiratory difficulties frequently complicated by pulmonary infection, and delayed motor milestones. Most infants have profound muscle weakness and are unable to hold up their heads or to move normally, resulting in floppiness and head lag. More than half of the infants also have macroglossia, moderate hepatomegaly, or both.

Other cardinal features are apparent in the laboratory results, which include a markedly elevated plasma CK. Glycogen accumulation is found in cardiac, skeletal, liver and smooth muscle tissues. Most infants with Pompe disease develop massive and progressive cardiomegaly before 6 months of age. Glycogen accumulation in cardiac muscle causes thickening of the walls of both ventricles and the interventricular septum, resulting in a hypertrophic cardiomyopathy, which eventually progresses to a dilated cardiomyopathy. Electrocardiographic findings are striking, revealing a shortened PR interval and large QRS complexes, a feature that can differentiate Pompe disease from other causes of cardiac disease in infants. Infantile-onset Pompe disease results in very early death, particularly for those infants with significant cardiac manifestations before the 6 months of age. These classic or typical symptoms appear in the first few months of life, and infants rarely survive beyond their first birthday.

A subset of infants, referred to by Slonim et al[6] as "atypical," present with symptoms a few months later. They have less severe cardiomyopathy and a somewhat better prognosis, with likely survival to two years of age. Late-onset Pompe disease can present at any time from the toddler years to adulthood. Virtually all children who present with Pompe disease symptoms after the age of two have no significant cardiac manifestations, a slower progression of muscle disease, and a less grim prognosis than infantile-onset cases. Residual GAA activity can be as much as 10 % of normal in patients who present in childhood or adolescence, and as much as 40% of normal in patients who present in adulthood. Proximal muscles (trunk and proximal muscles in the lower limbs) are usually affected first, followed by involvement of the diaphragm and other muscles that aid in respiration, leading to pulmonary insufficiency and difficulty breathing in sleep. Weakness of hip muscles leads to trouble walking. Toddlers can present with delayed motor milestones. Lordosis or kyphosis/scoliosis is common in older children[1].

Blood tests in infants and children should include a serum CK examination as an early step to determine whether more invasive testing is necessary, because CK elevation is a sensitive marker for Pompe disease. The greatest elevation is usually found in infantile-onset patients (as high as 2,000 IU/L). Approximately 95% of late-onset patients have an elevated CK. The diagnostic test for Pompe disease is the GAA enzyme assay from muscle or cultured skin fibroblasts. Infantile-onset Pompe disease is usually recognized because of the unique and acute constellation of findings. But in older children, symptoms are more subtle and diminished, and the diagnosis can be elusive. CK measurements can help in the diagnosis of Pompe disease. A CK elevation is a sensitive but nonspecific marker for Pompe disease[8]. Serum enzymes such as AST, ALT or LDH may also be elevated and may reflect enzymes released from damaged muscle tissue[9]. In many cases, the chest radiograph shows massive cardiomegaly. Echocardiography may reveal thickening if both ventricles or the interventricular septum or left ventricular outflow tract obstruction and electromyography generally reveals a myopathic pattern[1].

Until recently there has been no treatment other than

supportive care for Pompe disease. Supportive therapy can improve the quality of life and reduce complications of the disease, but it does not alter the course of the disease. Therapies that alter the synthesis of glycogen, such as high-protein diets and alanine, can produce transient clinical improvement in some patients, but they do not reduce intracellular glycogen accumulation[1]. Enzyme replacement therapy (ERT) is currently undergoing clinical trials. ERT for Pompe disease is intended to directly address the underlying metabolic defect via intravenous infusion of recombinant human GAA (rhGAA) so as to provide the missing enzyme[4]. Such therapy is already commercially available for Gaucher's disease, Fabry's disease, and mucopolysaccharidosis (MPS) type I. There is a report of four critically ill patients with infantile Pompe disease who all improved their cardiac function and gained muscle strength during follow-up studies of more than 3 years of intravenous treatment with rhGAA[3].

Our patient has a milder, atypical infantile type of Pompe disease. A diagnosis of atypical infantile onset Pompe disease is more difficult than that of typical infantile onset Pompe disease because symptoms are more subtle. However, as Pompe disease was diagnosed, we were able to try ERT. In our case, the effect of rhGAA replacement therapy was very significant and rapid. In our view, the degree of impairment of skeletal muscle function at the start of treatment may play a role in the outcome, and therefore ERT for atypical infantile onset Pompe disease may be more effective than when used in the more typical infantile onset cases. Thus, it is very important that pediatricians and pediatric specialists become aware of signs and symptoms of glycogen storage diseases, including Pompe disease, such as nasal voice or waddling gait at an early stage so that these patients can benefit from appropriate GAA replacement therapy as soon as possible.

한 글 요 약

효소 보충 치료로 호전을 보인 비전형적 영아형 Pompe 병 1례

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Pompe 병(Glycogen storage disease type Ⅱ)은 acid α-glucosidase (GAA)의 결손에 의한 질환이며 열성으로 유전한다. 전신적인 근육약화와 비후성 심근병이 생긴 후 대개 1년 안에 사망하게 되는 영아기 발병형과 상대적으로 임상양상이 경한 후기 발병형이 있다. Pompe 병의 국내 보고는 드문 상태이나 최근 GAA 효소 보충 요법이 개발되어 임상적으로 시도 중이다. 저자들은 발병은 영아기에 있으나 비교적 임상증상이 심하지 않은 비전형적 영아형 Pompe 병을 진단받고 심한 간비대와 비후성 심근병증, 보행곤란의 증상을 보이던 4세 남아에게 재조합 인간 GAA 효소(Myozyme®, Genzyme Co., MA, USA) 치료를 하여 운동능력과 심기능의 현저한 호전을 경험하였기에 보고한다. 비전형적 영아형 Pompe 병에서는 ERT의 효과가 더욱 큰 것으로 생각되며 소아과의사들이 비전형적 Pompe 병 초기의 특징인 비음이나 동요성 보행같은 증상을 이해하고 있어 이를 빨리 진단하고 효소보충요법을 조기에 시행한다면 Pompe 병 환아의 예후를 호전시킬 수 있겠다.

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