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Report

Different Responses to Enzyme Replacement Therapy in Two Patients with Childhood-onset Pompe Disease

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Pompe disease is caused by a deficiency of acid alpha-glucosidase (GAA), which results in glycogen accumulation mainly in skeletal and cardiac muscle and the liver. Pompe disease is classified into infantile-, childhood- and adult-onset forms based on onset age and the degree of organ involvement. The infantile-onset form is characterized by marked organ involvement, whereas the childhood-onset form usually presents with muscle weakness and elevation of serum creatine kinase (CK), mimicking the features of progressive muscular dystrophy. Here, we report the clinical courses of two patients with childhood-onset Pompe disease who showed different responses to enzyme replacement therapy (ERT). Computed tomography (CT) images of skeletal muscle in both patients showed a correlation with the respective therapeutic responses. The mean CT numbers of muscles improved with a good response to ERT in our patients; however, focal high-density areas, which were only seen in the non-responding older patient, were not affected by ERT. Evaluation of initial CT images showing focal high-density areas may be helpful for partly predicting the outcome and therapeutic response.

Key Words: Pompe disease, childhood-onset, enzyme replacement therapy, computed tomography (CT), muscle weakness

Introduction

Pompe disease (glycogen storage disease II) is an autosomal recessive lysosomal storage disorder characterized by deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA, EC 3.2.1.20). Pompe disease is progressive, with massive accumulation of glycogen in lysosomes, and is classified into infantile-, childhood- and adult-onset forms based on the onset age and degree of organ involvement[1]. The infantile form has a rapidly progressive course with prominent cardiomegaly, hepatomegaly and muscle weakness[2)3)]. The childhood-onset form usually presents later than the infantile-onset form, with muscle weakness and a high level of serum creatine kinase (CK), similar to the features of progressive muscular dystrophy, and typically does not include severe cardiomyopathy[4].

Treatment of Pompe disease is now possible using enzyme replacement therapy (ERT) with recombinant human acid alpha glucosidase (Myozyme, alglucosidase alpha, Genzyme Corp.), which is beneficial for cardiac pathological changes in the infantile form[4)5)]. However, the efficacy of ERT varies for skeletal muscle involvement, which is the main manifestation in childhood- and adult-onset Pompe disease[5)~7)].

One of the main factors in these variations in efficacy may be the extent of muscle damage at the start of ERT. Here, we evaluated the correlation between the clinical course and changes in skeletal muscle computed tomography (CT) images in two patients with childhood-onset Pompe disease who showed different responses to ERT.

Patient Backgrounds

Case 1: The patient was a 14-year-old boy, who was reported previously[8]. At age 5, low GAA activity allowed a definitive diagnosis of childhood-onset Pompe disease. At 10 years, 3 months of age, he

started to receive ERT. He was treated with IV alglucosidase alfa (Myozyme) at 20 mg/kg every other week. At baseline, he could not jump and needed to hold a rail to climb stairs. Serum CK was elevated (870 U/L). Percent vital capacity (%VC) was 57%. Cardiac echography suggested normal cardiac function. Skeletal muscle CT showed high-density areas in thigh and calf muscles. CT number was markedly higher (138 HU) than normal (30-40 HU). Written informed consent for publication of the case was obtained from the patient's parents.

Case 2: The patient was a 4-year-3-month-old who was also reported previously[9]. At 2 years, 4 months of age, she was referred to our hospital for evaluation of persistent hyperCKemia. Low GAA activity in lymphocytes and genetic analysis of GAA allowed a definitive diagnosis of childhood-onset Pompe disease. At 2 years, 6 months of age, ERT was initiated. At baseline, hypotonicity was apparent, but no muscle weakness was recognized. She showed neither Gower's maneuver nor a waddling gait, but she could not jump perfectly. Skeletal muscle CT showed no focal high-density areas in muscles. CT number was high (94 HU). Written informed consent for publication of the case was obtained from the patient's parents.

Results

Both patients were assessed clinically at every infusion during the first year and then every 3 months during the second year. Serum CK was also measured at every infusion. Anti-recombinant human GAA antibodies were analyzed every 3 months by enzyme-linked immunosorbent and radioimmunoprecipitation assays (Genzyme). Skeletal muscle CT and cardiac echography were performed every 4 months. Skeletal muscle CT scans were obtained at a window level (WL) of 30-45 Hounsfield Units (HU) and a window width (WW) of 300-350 HU.

Case 1: The patient experienced no infusion-related adverse events. After 1.5 months, there was a clear clinical response, that is, he became able to climb steps without a rail. After 4 months, he could climb in an almost normal manner, and also gained the ability to jump slightly, with his feet actually leaving the floor. MMT improved, with a high score of 4/5 in most proximal muscles and 4-5/5 in distal muscles, except those for neck and trunk flexion. However, these steady improvements stopped around 8 months and were followed by deterioration. The patient began supporting his knees with his arms to climb stairs, but was still not using a rail after 18 months. However, he had deteriorated to baseline after 2 years. He also lost the ability to jump after 18 months. After 3 years, he completely lost ambulation without support.

%VC increased to 65% after 4 months and peaked at 71% after 8 months. Overnight saturation monitoring showed a decrease in episodes of diminished oxygen during sleep, and the patient became to attend most physical education classes due to amelioration of fatigue. However, at 18 months, %VC had deteriorated to baseline and continued to decline thereafter. Diminished oxygen episodes during sleep increased again, in parallel with worsening morning lethargy. After 3 years, noninvasive ventilation (NIV) was prospectively applied.

In contrast, the mildly increased cardiac wall thickness had improved after 8 months and had normalized after 20 months.

Skeletal muscle CT showed high-density areas in the rectus femoris, vastus lateralis and gracilis muscles. CT number improved from 138/88 HU (maximum/minimum) at the start of ERT to 100/64 HU after 3 months, but returned to 136/77 HU after 8 months and to 140/80 HU after 1 year of ERT. Increased CT value was found in muscle and partial high-density areas in the thigh rectus muscle and lower thigh in the initial images. CT value decreased after three months of ERT in parallel with improvement of clinical symptoms, but the high-density local areas had expanded independently. CT value then increased again with loss of therapeutic effects, and muscular atrophy started to be observed over time (Fig. 1).

Serum CK increased from 800 to 1,200 U/L after 1.5 months and remained at this level. Anti-recombinant human GAA antibodies remained negative for 1 year. At 15 months, antibodies were finally detectable at a very low titer (100), after

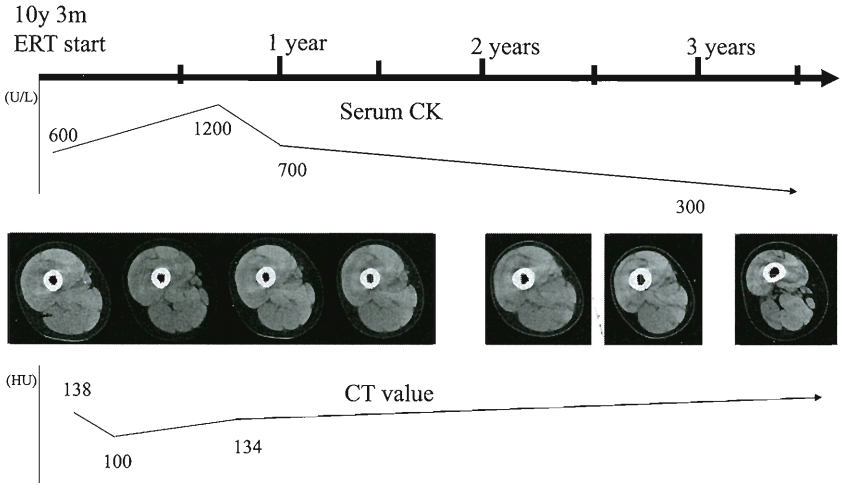

Fig. 1 Changes in skeletal muscle CT images and serum CK level in Case 1

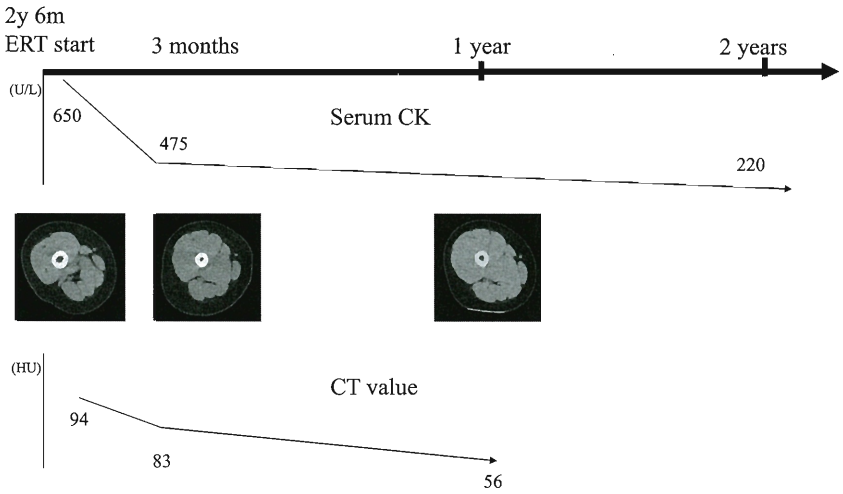

Fig. 2 Changes in skeletal muscle CT images and serum CK level in Case 2

which they remained at this level and then became negative again at 2 years after initiation of ERT.

Case 2: After 1 month, the efficacy of ERT for hepatomegaly was immediately apparent. The liver decreased in size within 1 month and was hardly palpable. Following the reduction in hepatomegaly, the patient gained the ability to jump. This was not due to skeletal muscle involvement, but due to improvement of hepatomegaly, which had caused her to lose her balance by disrupting the body curvature. Abdominal CT revealed a marked decrease in density from 106 HU at ERT initiation to 73 HU after 3 months. ALT and LDH levels decreased to their normal ranges. AST improved to 50 to 60 U/L, but then remained at this level. CT number for skeletal muscle also improved from 94 HU at initiation of ERT to 83 HU after 3 months to 56 HU after 1 year. After 1 year, motor function was almost normal. Serum CK had also improved and stabilized at 220 to 250 U/L, despite increased activity (Fig. 2).

Discussion

Several clinical studies have shown that ERT greatly decreases the incidence of cardiomegaly and significantly improves the survival rate in infantile-onset Pompe disease[7)~11)]. Early intervention with ERT can also give beneficial effects in the childhood- and adult-onset forms, whose major manifestation is skeletal muscle symptoms; however, each therapeutic response is variable[12)~14)]. Our patients showed different responses to ERT. In

Case 2, the effects appeared slowly, but were well maintained. In contrast, Case 1 showed rapid and marked improvement by ERT in the beginning, but after 9 months deterioration started in both pulmonary and motor functions. Maintaining the therapeutic effects for respiratory function was especially difficult.

Production of antibodies is reported to prevent the efficacy of ERT in infantile-onset Pompe disease[10]. However it could not explain the sudden deterioration in Case 1, since antibodies were negative when his improvement stopped. The effects of ERT on cardiac muscle were good compared to those on skeletal muscle, which has been previously reported[12]. In Case 2, childhood-onset Pompe disease was diagnosed before manifestation of skeletal muscle symptoms, based on the findings of hepatomegaly and increased serum CK. Liver enlargement was significantly improved by ERT. The reason for the good therapeutic response in this case may be early initiation of ERT prior to progression of major muscle destruction and development of skeletal muscle symptoms.

In Case 1, a poor responder to ERT, the initial CT images of skeletal muscles already revealed not only increased CT value of whole muscles, but also focal high-density areas in the rectus femoris and anterior tibialis. CT value of whole muscles decreased after ERT initiation in parallel with improvement of clinical symptoms, but the focal high-density areas expanded independently. Then, CT value increased again with loss of therapeutic effects, and muscular atrophy started to be observed over time. In Case 2, a good responder to ERT, only an increased CT value of the whole muscles was detected at the start of treatment, but without focal high-density areas. We previously reported these specific CT findings in childhood-onset form and concluded that increased CT value of whole muscles reflects accumulation of glycogen, whereas focal high-density areas are due to calcium accumulation in autophagic vacuoles[15]. Therefore, it is reasonable to think that the increased CT value of muscles was reversed by ERT in Case 2, whereas the focal high density areas found in Case 1 may suggest irreversible pathologic changes in spite of ERT. Cases with focal high-density changes in initial CT images of skeletal muscle can be predicted to have a poor response to ERT. Furthermore, CT values during treatment are sensitive to changes in clinical symptoms including motor function, and thus changes in CT values are useful for monitoring the course of Pompe disease.

The variation in efficacy of ERT in the childhood- and adult-onset forms is thought to be due to the extent of muscle damage at the start of ERT[4)~6)]. The best motor function outcomes have been achieved after early initiation of ERT, which underscores the need for early diagnosis. Neonatal screening for Pompe disease is being established in Japan[16], but childhood-onset Pompe disease may show no clinical signs or symptomes even they have screened by measurement of enzyme in neonatal mass screening. Thus, a consensus on when treatment should be started has yet to be established. In Case 2, ERT was started before the development of skeletal muscle symptoms. In such cases, CT may be an informative tool that serves as the first step in differential diagnosis. CT is less invasive than muscle biopsy, facilitating both diagnosis and assessment of the efficacy of ERT. The risk of radiation in CT should always be kept in mind, especially for children, and the radiation dose can be reduced by adjustment of scan parameters such as mA, kVp and imaging times.

In summary, skeletal muscle CT in childhood-onset Pompe disease may be helpful not only for differential diagnosis, but also for partly predicting the outcome and therapeutic response through the detection of focal high-density areas.

The authors declare no conflict of financial interest.

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酵素補充療法に異なる治療反応性を示した小児型 Pompe 病 2 症例

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佐藤（サトウ） 孝俊（タカトシ）・梶野（カジノ） 幸子（サチコ）・吉川（ヨシカワ） 陽子（ヨウコ）・大澤眞木子（オオサワマキコ）

Pompe 病は酸性 α-グルコシダーゼ欠損により，著明な筋力低下や呼吸筋障害，心肥大を来たす難治性の先天性代謝異常症である．酵素補充療法により治療可能な疾患となり，早期診断，治療指標の検討が重要になってきている．我々は酵素補充療法に対して異なる治療反応性を示した小児型 Pompe 病患者 2 例の臨床経過と骨格筋画像の変化を検討した．症例 1 は 14 歳男子．2 歳頃より易転倒性，鼻声などの症状が出現し，5 歳時に酵素活性低下より小児型 Pompe 病と確定診断された．10 歳時より酵素補充療法を開始し，早期には治療反応性を示したが，開始後 9 ヵ月ころから徐々に運動，呼吸機能が低下した．治療前の骨格筋 CT では全体的な CT 値上昇と局所的な高吸収域が認められた．治療開始後，臨床経過の改善とともに全体的な CT 値は一旦低下したが，症状増悪とともに再び上昇した．一方で，局所的な高吸収域は治療経過に無関係に拡大した．症例 2 は 4 歳女児．2 歳時に高 CK 血症に対する精査の結果，Pompe 病と確定診断され，酵素補充療法を開始した．治療開始前に筋力低下はなかったが，肝腫大を認めた．治療 3 ヵ月で肝腫大は改善し，その後も筋力，運動機能低下なく保たれている．治療前の骨格筋 CT では全体的 CT 値上昇を認めるのみで局所的高吸収域は認めなかった．治療開始後には臨床経過の改善とともに CT 値は低下した．筋全体の CT 値上昇はグリコーゲン蓄積を反映していると考えられ，治療に対して反応があり可逆的であった．一方，局所的な高吸収域は，自己貪食空砲内のカルシウム蓄積を反映しており，治療による改善を認めなかった．治療前の骨格筋 CT において局所的な変化が認められる症例に関しては病理的に不可逆変化が生じており，治療前にある程度の治療反応予測が可能であると考えられた．また筋全体の CT 値は治療指標に有用であることが示唆された．