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CASE REPORT

Pompe's Disease in Siblings Taking Enzyme Replacement Therapy: Skeletal Muscle Magnetic Resonance Imaging Findings

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ABSTRACT

Pompe's disease is a rare inherited muscle disorder resulting from deficiency of lysosomal acid α-glucosidase. This report describes the muscle magnetic resonance imaging findings in two young adults with late-onset Pompe's disease. A specific pattern of muscle involvement has been described in multiple inherited muscle disorders, including Pompe's disease. With the advent of enzyme replacement therapy, increased utilisation of imaging for diagnosis, monitoring of disease progress, and treatment response are expected. This article emphasises the importance of magnetic resonance imaging in screening the skeletal muscle in this disease and describes the development of new imaging techniques.

中文摘要

接受酵素替代療法的一對同胞的龐貝氏症：骨骼肌磁共振成像特徵

單雅怡、羅彪、李昭文

龐貝氏症是因缺乏溶酶體的酸性α-葡萄糖苷酶而導致的一種罕見遺傳性肌肉異常疾病。本文報告兩名晚發型龐貝氏症的青少年患者，描述其肌肉磁共振成像特徵；闡述多種遺傳性疾病（包括龐貝氏症）中肌肉異常病變的特殊模式。隨著酵素替代療法的出現，疾病診斷、病情監測、評價治療反應等過程中影像技術的應用率有望提高。本文重點討論磁共振成像檢查龐貝氏症骨骼肌異常的重要性，並介紹了新型影像技術的發展。

INTRODUCTION

Pompe's disease, also known as glycogen storage disease type II or acid maltase deficiency, is an autosomal recessive lysosomal glycogen storage disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase (GAA). The prevalence of this disease is estimated to be 1:40,000.[1] Without a sufficient amount of functioning GAA, there will be impaired degradation of glycogen to glucose, resulting in lysosomal accumulation of glycogen in most tissues. Excessive glycogen will cause enlargement of the organelles, and eventually results in rupture with leakage of glycogen into the cytoplasm. The structures of the cells are damaged by the excessive cytoplasmic glycogen, leading to functional impairment.

Pompe's disease presents with varying degrees of severity and rates of progression, and may present at

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any time from infancy to adulthood. Pompe's disease is categorised according to age at onset, extent of tissue involvement, and rate of progression. Infantile disease results in severe muscle hypotonia, cardiomyopathy, and death before the age of 2 years if untreated. Late-onset Pompe's disease consists of an overlapping clinical continuum of childhood-, juvenile-, and adult-onset variants, and glycogen accumulation is virtually limited to skeletal muscle in the late-onset variants.[2]

This report presents the skeletal muscle magnetic resonance imaging (MRI) of two siblings with late-onset Pompe's disease, before and after enzyme replacement therapy (ERT). The MRI findings and their clinical significance are discussed, and a review of literature is also performed.

CASE REPORT

A 26-year-old man was noticed to have had muscle weakness since early infancy, with flaccid muscle tone and gross motor delay. He started to have kyphoscoliosis at the age of 6 years. He progressively deteriorated, with muscle weakness, predominantly over the lower limbs, until he was aged 13 years. His creatine kinase level was markedly elevated to 1189 U/L (reference range, 50-200 U/L), and differential diagnoses included muscular dystrophy, myositis, and metabolic myopathy, particularly late-onset Pompe's disease. Finally, a muscle biopsy from the right thigh was performed, and late-onset Pompe's disease was confirmed.

He was subsequently treated with nocturnal bilevel

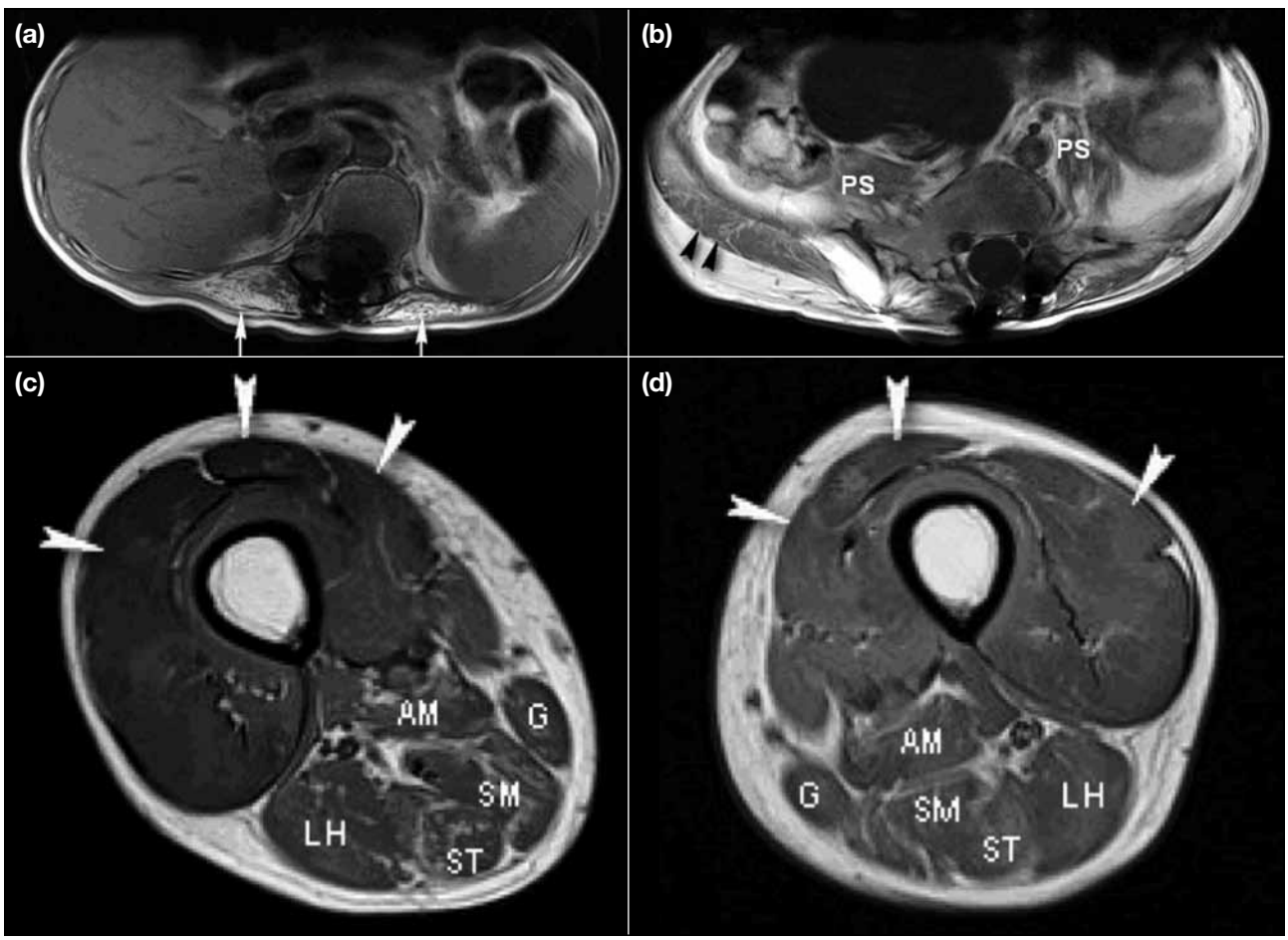

Figure 1. Axial T1-weighted magnetic resonance images of the (a) lower trunk and (b) pelvis of the older brother demonstrating severe fatty infiltration of the paraspinal muscles suggesting stage 3 disease according to Fischer's rating scale (arrows) and stage 2 disease of the psoas and right gluteal muscles (black arrowheads). A moderate degree of muscle atrophy is noted. Note the metallic artefacts along the lumbar spine from posterior spinal fusion. Axial T1-weighted magnetic resonance images of the (c) right and (d) left thighs demonstrating a moderate degree of atrophy suggesting stage 2 disease of the semitendinosus, semimembranosus, and adductor magnus muscles. Involvement of the long head of the biceps femoris, gracilis, and quadriceps muscles (white arrowheads) is mild.
Abbreviations: AM = adductor magnus; G = gracilis; LH = femoris; PS = psoas; SM = semimembranosus; ST = semitendinosus.

positive airway pressure for respiratory insufficiency. Posterior spinal fusion was performed when he was aged 15 years. His disease rapidly progressed and he became wheelchair bound at the age of 16 years. He had been taking L-alanine since the age of 17 years. In 2010, at the age of 25 years, when ERT became available, he was referred for treatment to the Princess Margaret Hospital, Hong Kong.

The patient's younger brother was then 22 years old. He had been confirmed to have the same disease when he was 11 years old, following the diagnosis in his elder brother. He had experienced decreased lower limb muscle power when he was aged 13 years, and was treated with L-alanine since the age of 14 years. ERT was also given to him from 2011. Currently, he is still able to walk without aid, and has no significant respiratory symptoms.

Skeletal muscle MRI comprising T1-weighted and short-tau inversion recovery (STIR) images of the pelvis and thighs were obtained for both brothers before and after ERT was started. In the elder brother, axial MRI through the lower trunk and pelvis showed severe atrophy of the paraspinal muscles, with diffusely infiltrative high T1 intensity within these muscles compatible with fatty infiltration (Figure 1). The psoas and gluteal muscles were affected to a lesser extent, with a moderate degree of fatty infiltration demonstrated. Axial T1-weighted MRI through the thigh demonstrated a moderate degree of atrophy and fatty infiltration of the semimembranosus, semitendinosus, and adductor

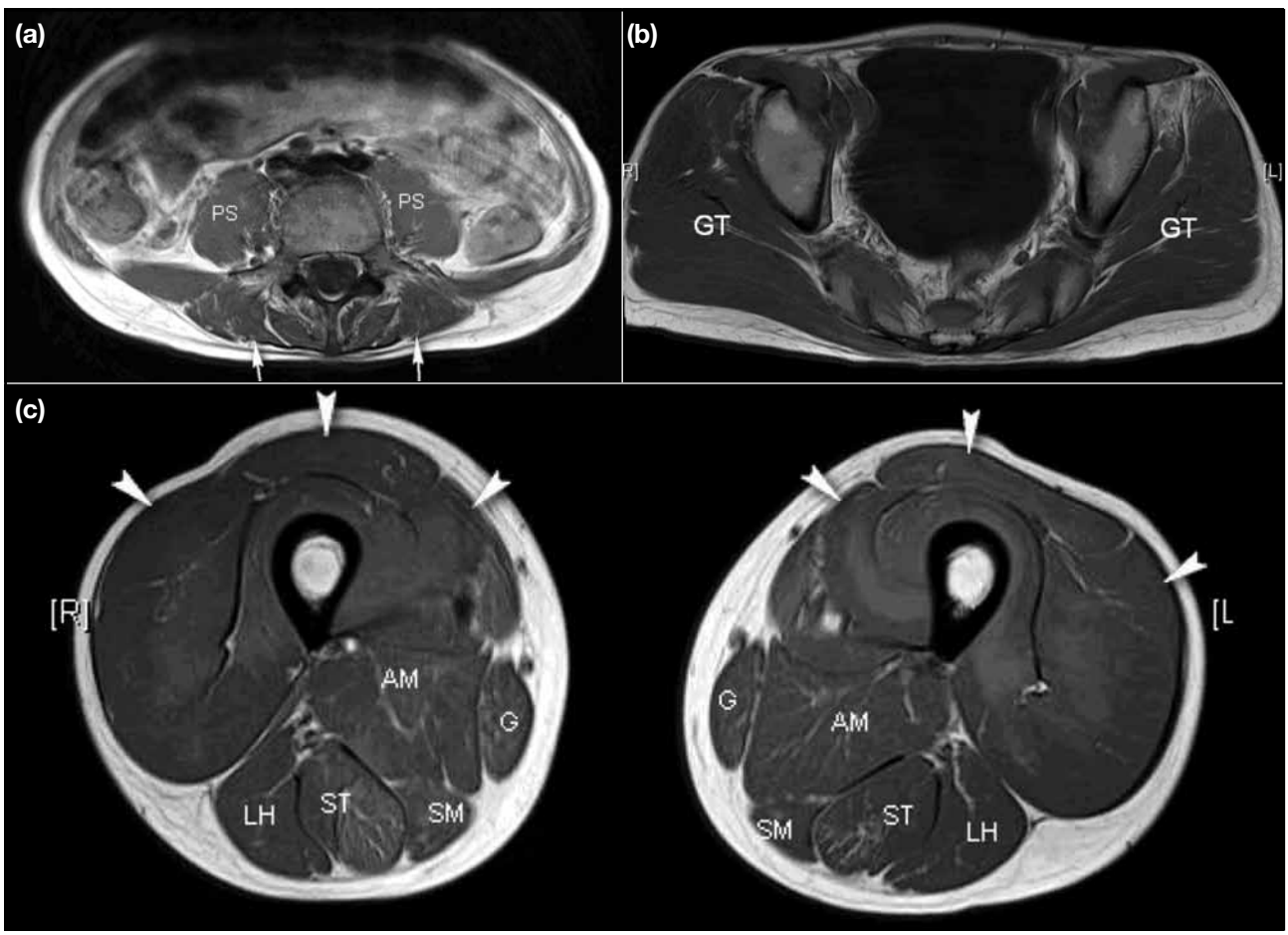

Figure 2. Axial T1-weighted magnetic resonance images of the (a) lower trunk and (b) pelvis of the younger brother demonstrating stage 1 disease with mild fatty infiltration of the paraspinal muscles (arrows) and gluteal muscles. The psoas muscles are not involved. (c) Axial T1-weighted magnetic resonance image of the thighs demonstrating bilateral stage 1 disease in the adductor magnus, semitendinosus, semimembranosus, and gracilis muscles. The long head of the biceps femoris and quadriceps femoris muscles (arrowheads) are relatively spared. No muscle atrophy is detected.
Abbreviations: AM = adductor magnus; G = gracilis; GT = gluteal; L = left; LH = femoris; PS = psoas; R = right; SM = semimembranosus; ST = semitendinosus.

magnus muscles. Involvement of the long head of the biceps femoris, gracilis, and quadriceps muscles was mild. No muscle oedema was detected on STIR images.

In the younger brother, axial T1-weighted MRI of the lower trunk, pelvis, and thigh showed mild fatty infiltration of the paraspinal, gluteal, semintendinosus, semimembranosus, adductor magnus, and gracilis muscles (Figure 2). No muscle atrophy was detected. The psoas, quadriceps femoris, and long head of the biceps femoris muscles that were involved in his elder brother were relatively spared in this patient.

Follow-up MRI 1 year after ERT showed no significant change in the status of the pelvic and thigh muscles in both siblings, particularly in the atrophy and fatty infiltration.

DISCUSSION

Muscle MRI has been reported to be a useful non-invasive technique for assessment of neuromuscular disorders.[3-9] Among the choices of cross-sectional imaging, MRI has the advantage over computed tomography (CT) of not producing ionising radiation, and thus is better for serial assessment of patients with neuromuscular disorders. MRI is superior in demonstrating high soft-tissue contrast, allowing excellent assessment of striated muscles in terms of the shape, volume, and tissue architecture such as fatty replacement. Skeletal MRI targeting the trunk, pelvis, and thighs is used by many clinicians, as the literature shows that the most common abnormalities in late-onset Pompe's disease are present in the musculature of the trunk and thighs.[10,11]

Although diagnosis of Pompe's disease is based on enzyme assay demonstrating absent or markedly reduced GAA enzyme activity or by genetic analysis, details of the location and distribution of the excess glycogen accumulation and structural tissue damage can only be ascertained using muscle imaging.

Muscle imaging is also important for detection and quantification of dystrophic change. Furthermore, MRI allows evaluation of specific muscle groups that are not accessible for biopsy, such as the diaphragm, in which disease involvement carries important implications in determining a patient's quality of life and mortality.

In Pompe's disease, muscle involvement mainly demonstrates changes in signal intensity related to fatty infiltration of the muscle. It has been reported that T1-weighted images are sufficient for assessment of inherited muscular disorders as they are sensitive enough to detect both muscle atrophy and increased signal related to the increased fatty content.[4]

Several standardised scales for rating the degree of muscular dystrophy in inherited muscle disorders have been established by different authors, most of which are based on the amount of fatty degeneration, ranging from normal appearance to complete fatty degeneration (Table[12-14]). Using standardised rating scales for evaluation of muscle MRI allows a reproducible assessment of degree of involvement of each muscle, resulting in good intra-observer and inter-observer agreement.

At the early stage of the disease before a diagnosis can

Table. Summary of the magnetic resonance imaging rating scales for visual rating of dystrophic changes of striated muscles.[12-14]

Stage	Mercuri et al,[12] 2002	Kornblum et al,[13] 2006	Fischer et al,[14] 2008
0	Normal	Normal	Normal
1	Early moth-eaten appearance with scattered small areas of increased T1 signal	Discrete moth-eaten appearance with sporadic T1 hyperintense areas	Mild: traces of increased T1 signal
2	2a: Late moth-eaten appearance with increased T1 signal with beginning confluence, comprising <30% of volume of the muscle	2a: Moderate moth-eaten appearance with numerous confluent T1 hyperintense areas	Moderate: increased T1 signal with beginning confluence in <50% of the muscle
	2b: Late moth-eaten appearance with numerous discrete areas of increased T1 signal with beginning confluence, comprising 30-60% of volume of the muscle	2b: Late moth-eaten appearance with numerous confluent T1 hyperintense areas	
3	Washed-out appearance, fuzzy appearance due to confluent areas of increased T1 signal with muscle still present at the periphery	Complete fatty degeneration with replacement of muscle by connective tissue and fat	Severe: increased T1 signal in >50% of the muscle
4	End-stage appearance with muscle replaced by increased T1 signal and only a rim of fascia and neurovascular structures distinguishable	-	End-stage disease: increased T1 signal replacing the entire muscle

be made, pattern recognition of muscle involvement may be helpful in narrowing the differential diagnosis.[3] In these patients, the absence of oedema makes the different kinds of myositis unlikely differential diagnoses. The relatively symmetrical muscle involvement also helps to exclude some myopathies with significant asymmetry such as Miyoshi myopathy and inclusion body myositis.

A specific pattern of muscle involvement has been reported in patients with different inherited muscle disorders. These patients demonstrated the myopathic pattern consistent with Pompe's disease described by various authors, which tends to include fatty infiltration of the muscles in the lower trunk and pelvis (particularly the paraspinal, psoas, and gluteal muscles), and muscles in the posterior and medial compartments of the thigh (including the adductor magnus, semimembranosus, semitendinosus, and gracilis muscles), although a similar pattern of muscle involvement is also seen in some muscular dystrophies such as Becker muscular dystrophy and limb-girdle muscular dystrophy. de Jager et al[10] found that CT in adult patients shows a characteristic distribution of CT changes with the axial and thigh muscles being more severely affected than the lower leg and shoulder girdle muscles. Del Gaizo et al[15] reported involvement of the paraspinal muscles, psoas and gluteal muscles in the pelvis, vastus medialis, vastus intermedius, adductor magnus and, later, the long head of the biceps femoris muscles in the thigh. A similar pattern of muscle involvement has been reported by Arai et al[16] and Dlamini et al,[17] and Pichiecchio et al[18] have demonstrated a selective progressive pattern of muscle involvement.

However, a later study by Carlier et al[19] showed that thigh involvement was more heterogeneous than previously described, in terms of distribution across muscles as well as with respect to the overall clinical presentation. These authors reported that the tongue muscle was heavily involved independent of disease severity, and changes in the scapular girdle muscles were seen in patients with advanced disease. The use of whole-body MRI provides a global assessment of muscle degeneration, while also localising a specific group of muscles involved, allowing quantification of the degree and distribution of muscle involvement.

The use of L-alanine decreases amino acid catabolism and may conserve muscle protein and function, but the evidence remains controversial.[20] The efficacy of ERT in patients with Pompe's disease has been confirmed in many studies, and improvement was most prominent during the first 2 years of treatment.[21-24] These patients demonstrated static disease in terms of fatty infiltration of muscles in MRI after 1 year of treatment.

Studies have shown limited improvement in muscle function after the first 2 years of treatment, probably because of the irreversible muscle destruction caused by glycogen storage, so early initiation of ERT is very important to achieve the best outcome.[25-27] This again emphasises the role of muscle MRI at an early stage of the disease in helping to suggest the diagnosis of Pompe's disease and to direct the most appropriate enzyme and / or genetic investigation.

With the advancement of treatment, it is expected that there will be increased utilisation of imaging for assessing disease progression and treatment response. A study performed by Ravaglia et al[28] showed that MRI demonstrated increased mass in the anterior thigh, but the response of the posterior thigh muscles to treatment was limited and accumulation of intramuscular fat progressed during ERT. New techniques using carbon-13 nuclear magnetic resonance (NMR) spectroscopy have been used to elucidate muscle energetics and metabolite changes, yet there is still a lack of reproducible data for acceptance into clinical practice.[29,30]

In conclusion, MRI offers a non-invasive approach in assessment of disease severity in Pompe's disease. This imaging modality is invaluable in the early stage of the disease in helping to make a specific diagnosis, thus early treatment, which is essential for an improved outcome, can be prescribed. A specific pattern of muscle involvement has been described, emphasising the biogenetic basis of such findings. The newer imaging technique, NMR spectroscopy, may provide more data in this respect. With the advent of ERT, increased utilisation of imaging for helping diagnosis, monitoring of disease progress, and treatment response are expected.

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