

Muscle MRI in Classic Infantile Pompe Disease

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Abstract

Context: Neuromuscular imaging techniques are helpful tools to create a better understanding of pathophysiological processes of neuromuscular diseases. MRI has been used to study skeletal muscle damage in patients with late-onset Pompe disease. We used this technique to investigate the upper leg muscles of patients with classic infantile Pompe disease.

Case report: Five patients with classic infantile Pompe disease were included. The median age was four months and none of the infants had yet been treated with enzyme replacement therapy. All patients had prominent muscle weakness and strikingly abnormal muscle histopathology sections taken from the lateral vastus muscle.

Conclusions: MR images showed almost no abnormalities except for some hypertrophy of the muscles on T1 and T2-weighted images. The hypertrophic appearance of the muscles demonstrated using MRI in patients with classic infantile Pompe disease is consistent with the degree of muscle firmness palpated on clinical examination. Further investigation is required to establish if the hypertrophic appearance of muscles on MRI in classic infantile patients is related to the glycogen accumulation observed in muscle biopsies.

Keywords: Pompe disease; Lysosomal storage disorder; Glycogen storage disease type II; MRI Muscle biopsy

Abbreviations: AIMS: Alberta Infant Motor Scale; ERT Enzyme Replacement Therapy; GAA Acid α -glucosidase; MRI Magnetic Resonance Imaging; PAS Periodic Acid-Schiff; TR Repetition Time; TE Echo Time

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Introduction

Pompe disease (OMIM 232300: acid maltase deficiency or glycogen storage disease type II) is an inherited metabolic disorder with an incidence of 1:40,000 births per year. It is caused by mutations in the acid α -glucosidase gene (GAA). Deficiency of acid α -glucosidase leads to lysosomal accumulation of glycogen predominantly in muscle tissue [1-4]. The disease has a broad clinical spectrum which is largely determined by residual acid α -glucosidase activity. In infants with the most severe classic infantile form, enzyme activity is virtually absent. These patients present shortly after birth with skeletal muscle weakness, which rapidly progresses to total paralysis within a few months and they eventually die from cardiorespiratory failure [1,2]. Milder forms of the disease may present at any age from infancy to late adulthood [5]. This group has some residual enzyme activity, but usually no more than 30% of average normal activity [4]. Most often they present with limb girdle muscle weakness and

respiratory insufficiency [6,7]. Since 2006, enzyme replacement therapy (ERT) has become available. This has improved survival and motor outcome significantly in infants [4,8], and more recently positive effects have also been demonstrated in adults. These include improved distance walked on the six-minute walk test and stabilization or improvement of pulmonary function, muscle strength, and better survival [9,13]. However, there is a large variation in response between patients.

Neuromuscular imaging techniques may be helpful in creating a better understanding of the pathophysiological process and the severity of muscle abnormalities. Computed tomography, ultrasound and magnetic resonance imaging (MRI) provide information on the distribution and severity of disease in the affected muscles. MRI provides the best soft tissue contrast and information on the shape, volume and tissue architecture of striated muscles [14]. Several cross-sectional studies have been published on muscle MRI findings in adult and juvenile patients with Pompe disease, but as far as we know our group was the first to use MRI in classic infantile Pompe [15-21].

To study if muscle MRI may be a useful tool to investigate the extent of muscle damage in classic infantile Pompe disease, we performed MRIs of the upper legs of five infants with Pompe disease and compared the findings with the pathology found in muscle biopsy sections of the quadriceps muscles of these patients.

Case reports

Patients

Five patients with classic infantile Pompe disease were included in this study (four males and one female). They were diagnosed with Pompe disease between June 2009 and September 2012. In the first months of life all five patients had generalized muscle weakness and the characteristic hypertrophic cardiomyopathy. With the exception of patient 4, they all needed nasogastric tube feeding and supplemental oxygen. On clinical examination, all five patients had a generalized hypotonia characterized by 'slipping through' and head lag. With the exception of patient 2, their muscles felt firm on palpation, especially the calves. Psychomotor development was assessed using the Alberta Infant Motor Scale (AIMS), and was below the 5th percentile in all patients [22]. None of the patients were being treated with ERT at the time the MRIs and muscle biopsies were carried out. Table 1 shows age at time of MRI, acid α -glucosidase activity, GAA genotypes and AIMS of all patients.

Muscle imaging

MR examinations were performed using a 1.5-tesla (1.5T) GE imaging system (General Electric Healthcare, Milwaukee, USA) with an eight-channel receiving only phased-array cardiac coil. Examination areas ranged from the anterior inferior iliac spine to the knee. No intravenous contrast medium or sedative drugs were administered. The infants were placed in supine position and supported by a vacuum mattress. The MRI sequence protocol included axial and coronal images obtained with the following pulse sequences: T1-weighted fast spin-echo images without fat suppression (repetition time (TR) 500-600ms, echo time (TE) 14-23ms, slice thickness 6-8 mm); T2-weighted fast spin-echo images with fat suppression (TR 2500-5000ms, TE 64-85ms, echo train length: six to eight, slice thickness 3-5 mm); and coronal images using a Spin-Echo Inversion Recovery Weighted sequence (STIR) (TR 4500ms, TE 35ms, Inversion Time 155ms, echo train length eight, slice thickness 3-5 mm). In all sequences a matrix of 256 x 192 was used with a slice gap of 1-2 mm and a field of view (FOV) of 20-28 cm. The average scanning time was 25 minutes per patient.

The T1 and T2-weighted images did not show signal intensity changes in the muscles of the upper legs. In patients 1, 3, 4 and 5 the T1-weighted images showed symmetric hypertrophic muscles in the upper legs with little subcutaneous fat. Patient 2 did not have hypertrophic muscles on MRI. Figure 1 shows the muscle biopsies and corresponding MR images of patients 1 and 5.

Muscle biopsy

Needle biopsies were taken from the lateral vastus muscle in accordance with the standard procedure at our center. The muscle sections were fixed in 4% glutaraldehyde, embedded in glycolmetacrylate and stained with periodic acid-Schiff (PAS) [23]. Four of the classic infantile patients underwent muscle biopsies. No biopsy was taken from patient 3 as the parents did not give their consent. In two patients the biopsy was taken within 24 hours of muscle imaging and in the other two patients one day and one week before muscle imaging, respectively. In all patients the muscle biopsy showed a vacuolar myopathy with irregular atrophic and hypertrophic muscle fibers, with positive PAS material in almost all vacuoles (80-95%).

Discussion

In this study it was found that that on MRI, the muscle of the upper legs of patients with classic infantile Pompe disease showed almost no abnormalities except for some hypertrophy of the muscles on T1 and T2-weighted images. To the best of our knowledge this is the first study to describe muscle MRI findings in classic infantile Pompe patients. It was unexpected to find only minor abnormalities on MRI in these patients, since the clinical status was quite advanced in most of them. On clinical examination the muscles had a firm consistency on palpation, most likely attributable to the severe glycogen accumulation that was observed in muscle biopsies [1,2]. Interestingly, the only

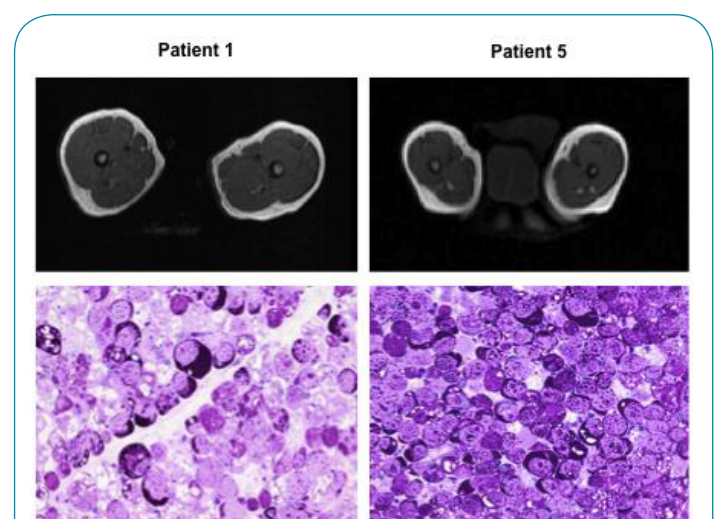


Figure 1 Muscle MRI and histopathology of two classic infantile patients

Muscle MRI of the upper legs and PAS stained biopsies of the lateral vastus muscle of two classic infantile patients (patients 1 and 5). The axial T1-weighted images show hypertrophic muscles and little subcutaneous fat and the muscle biopsies show severe PAS-positive vacuolar changes in almost all muscle fibers.

Table 1: Patient characteristics.

Patient	Age at MRI	α -glucosidase activity	Mutation 1	Mutation 2	AIMS [†]
1	5	0	c.2104C>T	c.379-380delTG	6
2	4	0	c.2481+102_2646+31del	c.del525T	8
3	3	0	c.1209C>G	c.del525T	0
4	3	1.4	c.925G>A	c.2608C>T	5
5	5	0	c.del525T	c.del525T	4

[†]AIMS = Alberta Infant Motor Scale, reference values in children aged three to four months are 12.6 and in children aged four to five months 17.9. The age at MRI is expressed in months. Acid α -glucosidase activity was measured in leukocytes with glycogen as substrate in the presence of acarbose, and expressed as nmol/mg/h (normal range 30-160 nmol/mg/h).

patient whose muscles did not feel firm on palpation also did not have hypertrophic muscles on the MR images.

In an earlier histopathological study based on electron microscopy, five stages in the pathological process of classic infantile Pompe disease were distinguished [24]. Stage 1 was described as small glycogen-filled lysosomes between intact myofibrils, Stages 2 and 3 as stages with increased lysosomal glycogen with leakage into the cytoplasm and fragmentation of myofibrils and abnormal mitochondria. At Stage 4 most glycogen was cytoplasmatic, while the contractile elements were severely damaged. By Stage 5 - the end stage- there was complete loss of myofibrils, while the cells were bloated due to water influx. The muscle biopsies from the patients in this study showed extensive glycogen accumulation contained in vacuoles in virtually all muscle fibers, and there was no obvious replacement of muscle tissue by fat or connective tissue. It seems likely that the hypertrophic aspect seen on MRI is due to glycogen accumulation and a reactive increase of organelles, with signs of severe myopathy and beginning of fibril dissolution as observed in the histopathological study of Thurberg et al. (resembling Stages 2-3) [24].

Muscle MRI in adult patients with Pompe disease has been described in detail previously. In adults MRI shows fatty infiltration particularly in the spine extensors, abdominal belt and scapular and pelvic girdle muscles [16,19,25]. Although the disease in adults is considered to be slowly progressive and the process of glycogen accumulation to be spread over many years, MRI shows that it results in considerable muscle atrophy, fat infiltration and replacement of muscle by connective tissue over longer periods of time. In adult patients glycogen storage can vary extensively between muscle fibers, even within the same muscle. Also the extent of tissue damage between muscle groups varies greatly [26-28]. Why some muscles are more severely affected than others would be an interesting topic for further study as would investigating the effects of ERT in adult patients by means of muscle MRI. A recent study shows that quantitative whole-body MRI is a feasible technique to use [21].

A limitation of this study was that only the upper legs were scanned and that only T1 and T2-weighted sequences were used. This was due to limited scanning time and taking the risks of anaesthetic to these infants into account, we did not want to administer sedative drugs. Although it might have been more informative to perform a total body MRI, taking the homogeneous process of muscle destruction in infants into account, it was considered unlikely that the results would have been completely different. Now ERT means that patients are living longer, it will be certainly of interest to repeat MRI scans in long-term surviving patients with classic infantile Pompe disease. Other MRI techniques

could also be of additional value to objectively quantify disease severity and progression in Pompe disease; these include C-NMR spectroscopy, T2 mapping and 3-point Dixon imaging [29-33]. It has been shown that C-NMR spectroscopy can demonstrate glycogen accumulation in muscle in patients with glycogenosis type III and in adult patients with Pompe disease, indicating that this technique could also be useful in infants with Pompe disease [32,33].

In conclusion, MRI in patients with classic infantile Pompe disease showed the upper leg muscles to be of hypertrophic appearance, which is consistent with the degree of muscle firmness on clinical examination. Further investigation is required to establish if the hypertrophic appearance of the muscles is related to glycogen accumulation only and if MRI will prove to be an effective tool in evaluating the effects of ERT in classic infantile Pompe disease.

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