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Trunk muscle involvement in late-onset Pompe disease: Study of thirty patients

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Abstract

Late-onset Pompe disease is characterized by progressive weakness involving proximal limb and respiratory muscles. Recently, treatment with enzyme replacement therapy (ERT) has been introduced partially improving patients' prognosis, but a standard consensus on when to start ERT is still lacking. There is also a lack of biomarkers related to the clinical progression of the disease.

Here we used muscle magnetic resonance imaging (MRI) or computed tomography (CT) to study the abdominal and paravertebral muscles of 30 late-onset Pompe patients at different stages of disease.

We observed a selective pattern of muscle damage, with early involvement of the *Multifidus* muscle, followed by the *Obliquus internus abdominis* and *Longissimus* muscle. Some degree of trunk involvement on MRI occurred even in asymptomatic patients. Severity of muscle involvement in MRI correlated with patients' functional stage.

We suggest that: (a) the combination of paravertebral and abdominal muscle involvement may serve as a useful tool in the diagnostic work-up of patients with a clinical suspicion of Pompe disease; (b) trunk abnormalities appear at very early stages of disease and even in asymptomatic patients, possibly "announcing" the onset of the disease and thus the need for a closer clinical follow-up.

Keywords: Pompe disease; MRI; Paravertebral muscles; Abdominal muscles

1. Introduction

Pompe disease, also known as acid maltase deficiency (AMD) or glycogen storage disease type II (GSD II), is a rare autosomal recessive disorder due to a deficiency of the lysosomal enzyme acid alpha glycosidase (GAA). This deficiency causes intralysosomal accumulation of glycogen

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in several tissues such as skeletal muscle, cardiac muscle or liver [1]. Different clinical patterns have been described, ranging from rapidly progressive infantile forms to slowly progressive adult-onset phenotypes [2]. In general, late-onset Pompe disease is characterized by weakness of the proximal limb and axial muscles associated with respiratory muscles involvement [3]. However, many different clinical presentations have been reported, ranging from predominant respiratory involvement to exclusive limb muscles weakness.

Clinical and muscle biopsy findings can be unspecific in Pompe disease, so that muscle imaging can become a helpful diagnostic tool [1]. Computed tomography (CT) studies in adult patients have shown that the disease spreads over the years from trunk to extremities [4] with selective muscle involvement found in the thighs [5].

The most recent therapeutic progress in Pompe disease has been enzymatic replacement therapy (ERT) with recombinant human GAA (rh-GAA), which has proved to be effective in both infantile and adult forms [6,7]. Although long-term follow-up data in treated patients are still lacking, ERT seems to improve muscle weakness and to stabilize the disease. The response to rh-GAA may be less robust in more advanced phases of the disease [8] and this emphasizes the need for prompt diagnosis and early treatment initiation. Because of the high costs of the treatment there have been controversial discussions about when the therapy should be started [9].

Considering that paravertebral muscles are involved at an early disease stage, we decided: (1) to study both the posterior and anterior trunk muscles in 30 late-onset Pompe patients by muscle imaging in order to evaluate their degree of involvement in a large cohort of patients at different functional stages; (2) to investigate whether there is a correlation between our clinical and imaging data.

2. Material and methods

2.1. Clinical data

A group of 30 adult-onset Pompe patients undergoing regular follow-up assessments at our centres was recruited from April 2006 to July 2011. Pompe disease diagnosis was based on <30% reduction versus controls of GAA activity in peripheral blood lymphocytes/muscle, and was confirmed by molecular analysis of the GAA gene (Table 1).

Muscle MRI was performed as part of the assessment and patients were classified into 4 groups according to the following functional stages:

- *Asymptomatic*: no muscle weakness or respiratory involvement, the only abnormal finding was hyperCKemia.
- *Mild involvement*: patients were able to walk and climb up stairs without help, muscular weakness was detected on clinical examination.
- *Moderate involvement*: patients needed aids (banister, crutch, stick) to climb up stairs, had difficulties to stand up from a chair or required non-invasive ventilation at night.
- *Severe involvement*: patients were unable to walk more than 10 m without help or required non-invasive mechanical ventilation during the day.

We collected the following data from each patient: (1) demographics (age, sex); (2) clinical features (age at onset, age at diagnosis, disease duration at the time of imaging, presence of hyperlordosis, abdominal or paravertebral muscle weakness, presence of lumbar pain, percentage of vital capacity in sitting position, and need for respiratory support); (3) therapeutic data (ERT treatment at time of MRI, time from treatment onset to MRI); (4) mutations found in the GAA gene.

2.2. Muscle MRI

Muscle MRI was performed by a 1.5T MR scanner (1.5T Philips Intera and 1.5T Philips Achieva XR Realeas) and was used to obtain T1-weighted spin-echo axial images from the mid-dorsal segment to the sacrum using the same parameters (TR = 300 ms, TE = 10 ms, thickness = 10 mm). The imaging protocol took 45 min. Five patients were investigated using muscle CT scan. They did not tolerate the MRI protocol due to severe respiratory weakness. CT axial images were performed at the same level with the same thickness. None of the patients of this series had repeated studies.

Two independent observers blind to clinical information examined all the scans and evaluated paravertebral (specifically *Multifidus*, *Longissimus*, *Iliocostal Lumborum*, *Quadratus Lumborum* and *Illiopsoas*) and abdominal (specifically *Rectus Abdominis*, *Transversus Abdominis*, *Obliquus Externus Abdominis*, *Obliquus Internus Abdominis*) muscles (Fig. 1). Muscle atrophy was evaluated by the Mercuri scale [10].

2.3. Statistics

We performed a Pearson test to correlate the functional stage (scored 1–4) in every patient with the degree of muscle involvement (scored as the average value of the Mercuri's scale of all the muscles). It was considered significant if P was lower than 0.05.

3. Results

All patients (17 women and 13 men) had a late-onset form of the disease. All but 5 were symptomatic. Mean age at MRI was 46 years (±16.7 SD); mean age at disease onset was 29 years (±12.9 SD); mean delay in diagnosis was 10 years (±8.4 SD) and average duration of the symptoms at the time of imaging was 7 years (±12).