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Muscle imaging data in late-onset Pompe disease reveal a correlation between the pre-existing degree of lipomatous muscle alterations and the efficacy of long-term enzyme replacement therapy

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ABSTRACT

Background: Late-onset Pompe disease (LOPD) is a metabolic myopathy caused by mutations in *GAA* and characterized by proximal muscle weakness and respiratory insufficiency. There is evidence from clinical studies that enzyme replacement therapy (ERT) with human recombinant alpha-glucosidase improves motor performance and respiratory function in LOPD.
Objective: We analyzed quantitative muscle MRI data of lower limbs to evaluate the effects of long-term ERT on muscle parameters.
Methods: Three symptomatic LOPD patients who received ERT for five years and four untreated presymptomatic LOPD patients were included in the study. T1-weighted MRI images were used to determine volumes of thigh and lower leg muscles. In addition, mean gray values of eight individual thigh muscles were calculated to assess the degree of lipomatous muscle alterations.
Results: We detected a decrease in thigh muscle volume of 6.7% ($p < 0.001$) and an increase in lower leg muscle volume of 8.2% ($p = 0.049$) after five years of ERT. Analysis of individual thigh muscles revealed a positive correlation between the degree of lipomatous muscle alterations at baseline and the increase of gray values after five years of ERT ($R^2 = 0.68$, $p < 0.001$). Muscle imaging in presymptomatic patients showed in one case pronounced lipomatous alteration of the adductor magnus muscle and mild to moderate changes in further thigh muscles.
Conclusions: The results demonstrate that fatty muscle degeneration can occur before clinical manifestation of muscle weakness and suggest that mildly affected muscles may respond better to ERT treatment than severely involved muscles. If these findings can be validated by further studies, it should be discussed if muscle alterations detected by muscle MRI may be an objective sign of disease manifestation justifying an early start of ERT in clinically asymptomatic patients in order to improve the long-term outcome.

1. Introduction

Pompe disease (OMIM #232300), also known as glycogen storage disease type 2 or acid maltase deficiency, is a rare autosomal recessive disorder caused by mutations in *GAA* that lead to a deficiency of lysosomal acid alpha-glucosidase [1]. In late-onset Pompe disease (LOPD), skeletal muscle is the most affected tissue. The clinical phenotype of LOPD is characterized by slowly progressive proximal muscle weakness involving axial and respiratory muscles that is associated with significant morbidity and reduced life expectancy [2–7]. Since 2006, an enzyme replacement therapy (ERT) with human recombinant alpha-glucosidase (rhGAA) is available for the treatment of Pompe disease (alglucosidase alfa, Myozyme®, Lumizyme®, Genzyme Corporation, a Sanofi company, Cambridge MA, USA). Clinical studies showed that motor performance, respiratory function and fatigue improved or stabilized in at least two-thirds of LOPD patients who received ERT over 6–36 months [8–15]. The functional outcome seems to be best when ERT starts timely, i.e. at an early clinical stage of LOPD [12,16]. This, by implication, suggests that disease progression has an influence on the efficacy of ERT.

Abbreviations: LOPD, late onset Pompe disease; ERT, enzyme replacement therapy; rhGAA, human recombinant alpha-glucosidase; MRI, magnetic resonance imaging.

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Table 1
Characteristics of LOPD patients included in this study.

	Patient ID						
	1	2	3	4	5	6	7
Gender	Man	Man	Woman	Man	Woman	Woman	Woman
Age	39	51	48	26	22	27	19
Muscle weakness	Yes	Yes	Yes	No	No	No	No
Age at onset [years]	13	37	30	–	–	–	–
Age at ERT onset [years]	31	45	42	–	–	–	–
Age at muscle MRI [years]	33/38	45/50	42/47	25	22	26	18
Able to walk without aid	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Requiring ventilator support	No	No	No	No	No	No	No

An important feature of disease progression in LOPD and many other inherited myopathies is the replacement of muscle fibers by fat cells and connective tissue. This fatty alteration can be detected by magnetic resonance imaging (MRI) because it provides a high soft tissue contrast that allows a noninvasive assessment of striated muscles regarding shape, volume and tissue architecture [17]. Previous MRI studies in LOPD [18–28] revealed changes in quantitative muscle MRI parameters with ERT treatment for between six and 24 months [24,26]. Here we present quantitative muscle MRI data, including assessment of lipomatous alterations in individual thigh muscles, from three LOPD patients who received ERT over a time period of five years and from four untreated presymptomatic patients. The main aim was to investigate if the response to ERT regarding prevention of progressive fatty muscle degeneration depends on the degree of pre-existing alterations.

2. Materials and methods

2.1. Patients

Muscle MRI data from seven LOPD patients (diagnosis confirmed by detection of GAA deficiency and genetic analysis) were evaluated with approval of the ethics committee of the Ruhr-University Bochum. Three patients (IDs 1–3, see Table 1 for details) received an i.v. ERT with rhGAA derived from Chinese hamster ovary cells (Myozyme®, Genzyme) in a dosage of 20 mg/kg body weight every other week for at least five years. Four untreated patients were clinically presymptomatic (IDs 4–7 in Table 1). They presented with an elevated serum creatine kinase level but had a normal forced vital capacity and normal muscle strength in manual muscle testing.

2.2. Muscle imaging

Muscle MRI was performed on a 1.5 Tesla scanner with a four channel phased-array coil (Magnetom Symphony Quantum, Siemens Healthcare). Twelve axial slices were obtained through the thighs and lower legs using the following scanning parameters: T1-weighted spin-echo sequence, TR/TE of 500/20 ms, slice thickness of 10 mm, interslice gap of 150%, matrix of 512 × 512, two signal averages, and examination time of 2 min and 44 s. Symptomatic patients (ID 1–3) were examined twice at an interval of five years.

T1-weighted MRI images were used to determine muscle volumes and lipomatous muscle alterations. Slices of examinations at baseline and after five years of ERT were matched by three experienced investigators blinded to the patients' data to ensure that the same segments of thighs and lower legs were included in the analysis. Final measurements were performed by one investigator to prevent bias due to interobserver variability. Total volumes of skeletal muscles in eight consecutive axial slices through the thighs and in eight consecutive axial slices through the lower legs were measured using cellSens Dimension software, version 1.8 (Olympus Corporation, Muenster, Germany). The same slices were used for the assessment of lipomatous alterations of individual thigh muscles (quadriceps femoris, sartorius, gracilis, adductor longus, adductor magnus, biceps femoris, semitendinosus and semimembranosus) by calculating the mean gray values in muscle areas (11-bit grayscale, 2048 tones) with IMPAX software, Version 6.3.1.8000 (AGFA HealthCare N.V., Belgium). On T1-weighted images, the signal intensity of skeletal muscle tissue is much lower than that of fat tissue. The gray value of pixels is a unit-free parameter that depends on the brightness (black = 0, white = 2047). In our MRI setting, healthy muscle tissue has a mean gray value of about 230 and fat tissue a mean value of about 950. An increase of mean gray values of muscle tissue correlates with an increase of fatty replacement. A two-tailed paired t-test (equal variances assumed) at a significance alpha level of 0.05 was used for statistical analysis of differences between baseline and follow-up measurements. The correlation between mean gray values at baseline (of the eight individual thigh muscles in each patient) and changes of these gray values after ERT was assessed using Pearson's correlation coefficient.

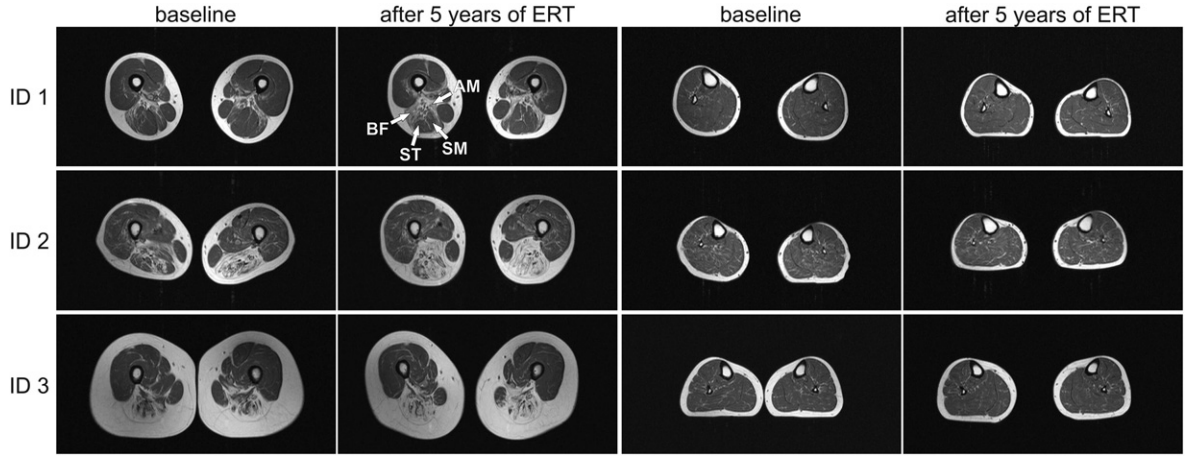

Fig. 1. Transverse T1-weighted muscle MRI images of three symptomatic LOPD patients (IDs 1–3) at baseline examination and after five years of ERT. The pattern of muscle involvement regarding fatty replacement is similar in all patients. On the thigh level (left columns), the semimembranosus (SM), adductor magnus (AM), biceps femoris (BF) and semitendinosus (ST) are most affected at baseline and also after five years of ERT. In lower legs (right columns), muscles show no (ID 1) or only mild lipomatous (IDs 2 and 3) alterations in both investigations.