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Investigation on acute effects of enzyme replacement therapy and influence of clinical severity on physiological variables related to exercise tolerance in patients with late onset Pompe disease

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Abstract

Exercise intolerance is one of the clinical hallmarks of late-onset Pompe disease (LOPD). We studied the acute effects of ERT on the physiological variables associated with exercise tolerance in patients chronically ERT treated. Moreover, we assessed the influence of clinical severity on the investigated variables. The day before (B) and the day after (A) ERT injection, 11 LOPD patients performed on a cycle-ergometer an exercise tolerance test to voluntary exhaustion; VO_2, HR, RPE, and GAA activity were determined in B and A. The disease severity was characterized by Walton scale, 6MWT, and pulmonary function tests. No significant differences in the variables related to exercise tolerance were found in A vs B, despite a significant increase in GAA activity in peripheral lymphocytes. No differences in VO_2 peak were observed between patients with only skeletal muscle impairment and patients with both skeletal and respiratory muscle impairment. Distance walked at 6MWT was significantly higher than VO_2 peak expressed as percentage of normal values. In conclusion, in LOPD patients the exercise tolerance test is not acutely affected by ERT administration; the peripheral muscle component seems more prominent in determining the VO_2 peak decrease than the respiratory component; VO_2 peak might be more sensitive than 6MWT in estimating exercise tolerance in LOPD.

Keywords: Late-onset Pompe disease; Enzyme replacement therapy, exercise tolerance; VO_2 peak

1. Introduction

Glycogen storage disease type II, or Pompe disease, is an inherited autosomal recessive disorder due to the deficiency of the lysosomal enzyme acid alpha glucosidase (GAA), which results in the accumulation of glycogen within the lysosomes of different cells, especially muscle fibres [1]. Two main clinical forms of the disease have been recognized: the classic infantile form and the late onset form. The classic infantile disease is characterized by null or very low GAA activity levels, with a consequent massive impairment of cardiac and skeletal muscles, leading to death within the first year of life, if untreated [2]. The late-onset Pompe disease (LOPD) does not exhibit a cardiac involvement, but affects mainly locomotor and respiratory muscles, determining a progressive muscle weakness and motor dysfunction which can lead the patients to the use of a wheelchair, and to variable degrees of respiratory insufficiency [3]. The specific enzyme replacement therapy (ERT) with recombinant human GAA (Myozyme®) has been introduced and approved for all Pompe patients in 2006. The ERT seems to be able to ameliorate muscle function and slow down the rate of disease progression [4,5].

Exercise intolerance, defined as the inability to produce/maintain adequate force or power to accomplish a task [6], is a key clinical manifestation of LOPD that can be caused by multiple factors including respiratory and peripheral muscle function alterations [7,8]. As in many other diseases [9–12], also in LOPD patients exercise intolerance may contribute to the patients' perception of impaired general well-being. The

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incremental exercise tolerance test, up to voluntary exhaustion, is a validated method to evaluate exercise (in)tolerance in several physiological and pathological conditions, among which metabolic myopathies [11,12]. In 2012 Marzorati et al. demonstrated the positive effect of ERT on some physiological variables associated with exercise tolerance in 4 patients with LOPD, after 1 year of therapy, and proposed this approach for clinical assessment during follow up [13]. Subsequently few other studies have used protocols of incremental exercise tests, with the determination of cardiovascular, pulmonary gas exchange and metabolic variables, to evaluate exercise (in)tolerance in LOPD patients [14–16]. However, the 6 minutes walking test (6MWT) remains the most commonly utilized method to estimate exercise capacity in patients' follow up [17,18].

In clinical practice several LOPD patients long term treated with ERT report a subjective improvement of general well-being, with reduced fatigability and increased exercise tolerance, during the days immediately following the ERT infusion, and a gradual loss of these positive effects during the two week interval between the infusions.

The first aim of this study was to investigate the acute effects of ERT on the main physiological variables associated with exercise tolerance in LOPD patients chronically treated with ERT. The second aim was to assess whether the clinical severity of the disease affects the investigated variables.

2. Patients and methods

Eleven out of twenty-two patients with LOPD followed at the Regional Coordinator Centre for Rare Diseases of the Academic Medical Centre Hospital of Udine, Italy, were enrolled in this study. Six were females and 5 males, with a mean age of 30.9 ± 15.1 years. Two patients (pt 2 and 8) were siblings, the others were unrelated. Anthropometric and clinical characteristics are summarized in Table 1.

Inclusion criteria were confirmed diagnosis by the assessment of GAA activity and/or genetic testing; chronic (at least 2 years) ERT at a standard dosage of 20 mg/kg every 2 weeks; willingness to participate in the study. Exclusion criteria were wheelchair bound; severe cardiac disease (assessed by electrocardiogram and echocardiography) or respiratory assistance 24 h/day. All recruited patients, or their parents when under 18 years of age, provided written informed consent. The study was approved by the local institutional ethics committee. All procedures were in accordance with the recommendation found in Declaration of Helsinki (2000) and its following amendments (2008).

Clinical history was collected from clinical records. Before performing the study tests, patients were asked to indicate how they usually felt, in terms of general subjective well-being and fatigability, the day before and the day after the ERT infusion.

Full neurological examination, 6MWT, and pulmonary function testing (PFT) in the sitting position were performed using standard methods. Distance walked at 6MWT and forced vital capacity (FVC) at PFT were calculated as a % of predicted values [19,20]. Patients were classified as having a respiratory involvement if FVC was <90% and/or if they were treated with non-invasive nocturnal ventilation (NIV). Global motor disability was assessed by the modified Walton scale (WS) [21].

The day before (BEFORE) and the day after (AFTER) the ERT infusion, patients underwent to blood sample collection and then performed a modified exercise test (see below) to the limit of tolerance on a cycle ergometer. In all patients ERT was administered intravenously at the usual dosage and at the scheduled day (14 days after the previous injection).

GAA activity was measured in lymphocytes using the fluorogenic substrate 4-methylumbelliferyl-α-D-glucopyranoside (Glycosynth, Cheshire, England) [22]. Protein concentration of the samples was determined by the Lowry method. Enzymatic activity was expressed as nanomoles of substrate hydrolysed per milligram of total protein per hour. All assays were done in triplicate.

Serum levels of muscle enzymes (creatine phosphokinase CK, lactate dehydrogenase LDH, alanine transaminase ALT,

Table 1
Anthropometric and clinical characteristics of patients.

Patient code	Age, years	Gender	Genotype, c−/c−	Height, m	Weight, kg	BMI, kg/cm^2	Years on ERT	WS	NIV	FVC, %	Subjective well-being
1	46	F	IVS1(-13T>G)/2481 + 102_2646 + 31del	1.64	50	18.6	2	3	No	108	Better in A
2	47	M	IVS1(-13T>G)/2646_2646 + 1delTG	1.90	112	31.0	4	0	No	112	Unchanged
3	19	M	IVS1(-13T>G)/unknown	1.78	60	18.9	7	2	No	107	Unchanged
4	17	M	IVS1(-13T>G)/2481 + 102_2646 + 31del	1.88	66	18.7	7	0	No	91	Better in A
5	43	F	IVS1(-13T>G)/2237G>A	1.68	80	28.3	7	6	Yes	64	Better in A
6	21	M	IVS1(-13T>G)/unknown	1.74	71	23.5	7	0	No	99	Unchanged
7	43	F	N.A.	1.66	70	25.4	2	3	No	126	Better in B
8	53	M	IVS1(-13T>G)/c.2646_2646 + 1delTG	1.85	106	31.0	7	3	Yes	55	Better in A
9	20	F	692 + 1G>C /1645G>C	1.57	41	16.6	8	3	Yes	22	Better in A
10	15	F	IVS1(-13T>G)/307T>G	1.60	59	23.0	8	0	No	106	Unchanged
11	16	F	IVS1(-13T>G)/1465G>A	1.62	57	21.7	7	0	No	102	Unchanged
Mean	30.9			1.7	70.2	23.3	6.0			90.2	
SD	15.1			0.1	21.9	5.1	2.2			30.7	

BMI, body max index; ERT, enzyme replacement therapy; WS, Walton scale score (0 = preclinical, all activities normal; 2 = defect in posture or gait, climbs stairs without using the bannister; 3 = climbs stairs only with the bannister; 6 = walks only with aids); NIV, nocturnal non-invasive ventilation; FVC, forced vital capacity. A: the day after the ERT injection; B: the day before the ERT injection.