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# Late-onset Pompe disease (LOPD): Correlations between respiratory muscles CT and MRI features and pulmonary function

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ABSTRACT

Late onset Pompe disease (LOPD) is a rare muscle disorder often characterized, along the disease course, by severe respiratory failure.
We describe herein respiratory muscles and lung abnormalities in LOPD patients using MR imaging and CT examinations correlated to pulmonary function tests.
Ten LOPD patients were studied: 6 with a limb-girdle muscle weakness, 1 with myalgias, 2 with exertional dyspnoea and 1 with isolated hyperckemia. Respiratory function was measured using forced vital capacity (FVC) in both upright and supine positions, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP) and peak cough flow (PCF) tests.
The involvement (atrophy) of diaphragms, abdominal respiratory muscles and intercostal muscles was ranked by CT and MRI examinations using appropriate scales. Height of lungs and band-like atelectasis presence were also recorded.
Seven out of 10 patients showed a functional diaphragmatic weakness (FVC drop percentage >25%).
In 8 out of 10 patients, involvement of both diaphragms and of other respiratory muscles was seen. The mean height of lungs in patients was significantly reduced when compared to a control group. Marked elevation of the diaphragms (lung height < 15 cm) was also seen in 6 patients. Multiple unilateral or bilateral band-like atelectasis were found in 4 patients. Statistically significant correlations were found between diaphragm atrophy grading, evaluated by MRI and CT, and FVC in supine position, FVC drop percentage passing from upright to supine position, PCF and MIP.
Our data showed that diaphragm atrophy, often associated to reduced lung height and band-like atelectasis, can be considered the CT-MRI hallmark of respiratory insufficiency in LOPD patients. Early recognition of respiratory muscles involvement, using imaging data, could allow an early start of enzyme replacement therapy (ERT) in LOPD.



## 1. Introduction

Pompe disease, also known as glycogen storage disease type II (GSDII), is an autosomal recessive inherited disorder, due to a reduced activity of the lysosomal acid alpha-glucosidase (GAA). The deficiency of GAA results in failure of lysosomal glycogen degradation, leading to a progressive glycogen accumulation in different tissues.

Two clinical forms of GSDII have been described: a severe infantile form with cardiomyopathy, respiratory distress and muscle hypotonia, and a late-onset form characterized by a progressive myopathy [1].

Late-onset Pompe disease (LOPD) patients may present with a quite heterogeneous phenotype ranging from an isolated increase of creatine kinase (CK) level to muscle weakness with a prominent limb-girdle distribution and/or respiratory dysfunction. Disease progression is variable but usually slow. During life, respiratory muscle involvement occurs in up to 60–80% of the patients, with a prevalent diaphragm involvement [2]. However, respiratory failure can also be the initial clinical manifestation and patients may become rapidly ventilator-dependent despite still ambulating.

Since 2006, an enzyme replacement therapy (ERT) for Pompe disease is available: it has been demonstrated that ERT stabilizes or improves muscular and/or respiratory function [3–5]. Early start of ERT

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before the onset of respiratory failure allows a better prognosis [6,7]; thus, an early diagnosis of respiratory muscles involvement in LOPD is highly recommended.

To our knowledge, so far no detailed description of respiratory muscles involvement in Pompe disease by CT or MR is available. In fact, muscle MRI studies in such patients have been mainly focused on the evaluation of muscle involvement pattern as an outcome measure in ERT follow-up [8]. Moreover, LOPD associated with lung abnormalities has been described only in few case reports [9,10].

The aim of this work is to describe respiratory muscles and lung abnormalities in LOPD patients using MRI and CT evaluation looking for possible correlations to pulmonary function tests.

## 2. Materials and methods

### 2.1. Patients

Ten patients with LOPD (5 males and 5 females; mean age: 42.7 ± 18.25 years; age range 8–65 years), not already treated by ERT, were studied. All patients underwent respiratory muscles and lung CT and MRI evaluation and pulmonary function tests in the same day. All patients provided a written informed consent; the study was approved by our University Ethic Committee.

LOPD diagnosis in these patients was based on clinical, morphological (muscle biopsy), biochemical (alpha-glucosidase activity in skeletal muscle), and molecular genetic (GAA mutational analysis) features. All patients harbored the common mutation c.-32-13 T > G (IVS1-13 T > G), associated with a second pathogenic mutation detected in the second allele. Muscle biopsy revealed a vacuolar myopathy with glycogen accumulation in 6/10 patients, an increased glycogen content in 2/10, and unspecific muscle changes in 2/10. Alpha-glucosidase residual activity in skeletal muscle ranged between 0.50% and 22% (Table 1).

Mean age at disease onset, considered as the time of evidence of first symptoms, was 32.5 ± 15.63 years (range: 3–53 years); the diagnosis was performed at 37.5 ± 15.55 years.

When the respiratory muscle evaluation was performed, 6/10 patients presented with a limb-girdle muscle weakness distribution (limb-girdle muscle dystrophy-like), 1/10 had only increased serum CK, 1/10 complained of myalgias and 2/10 patients presented with, respectively, 6 and 10 years of history of exercise intolerance and exertional dyspnoea. All patients were ambulant. Three patients required non-invasive nocturnal ventilation (mean usage time: 8 hours/night). Body mass index ranged between 20 and 33.

Clinical muscle involvement, evaluated by Walton Medwin–Gardner (WMG) scale, revealed a mean WMG score of 3.7 ± 2.16 (median value: 4) with a wide variation range (0–7) (Table 1). CK levels were abnormally high in 9/10 patients (mean value: 500 ± 222 U/L).

### 2.2. Pulmonary function tests

Forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$) were measured from flow-volume curves obtained with a pneumotachograph (Ganshorn Medizin Electronic GmBh, Germany) according to ATS/ERS standards in both upright and supine positions [11]. Values were expressed as percentage of predicted normal values. Reference values were derived from published data [12,13]. A drop in the percentage of predicted FVC upon changing posture from the upright to the supine position > 25% was considered as expression of diaphragmatic weakness [14,15].

As suggested by recent guidelines [14], maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) tests respectively were performed by an experienced operator, who strongly urged the subjects to produce maximum inspiratory (Mueller manoeuvre) and expiratory (Valsalva manoeuvre) efforts at near residual volume and total lung capacity. Reference values were taken into account according to previously published data [16].

Peak cough flow (PCF) was measured in unassisted condition by having the patient cough as hard as possible through a peak flow meter (Mini-Wright; Clement Clarke International LTD; Edinburgh Way Harlow, Essex UK) starting from total lung capacity [17].

### 2.3. MRI and CT features

Muscle MR imaging was carried out in all ten patients. All MR examinations were performed on a 1.5-T superconductive MR scanner (Gyroscan Intera; Philips, Best, The Netherlands) using a four-channel phased array coil. In each patient, axial and coronal T1-weighted turbo spin echo (TSE) images of the thorax and abdomen and respiratory gated coronal T2-weighted TSE images of the thorax were acquired. A magnetic-resonance-proof ventilator was used for the three patients requiring assisted ventilation during MRI procedures.

In 9/10 patients, CT examination of the thorax and abdomen was also obtained. In an 8-year-old male without respiratory symptoms CT was not performed.

All CT examinations were performed with a Somatom Definition AS scanner (Siemens Medical Solutions, Forchheim, Germany). One-

**Table 1**
Clinical and pulmonary function tests data.

| Pts | Gender | Age (years) | BMI | Disease duration (years) | Clinical presentation | Muscle Biopsy | Muscle GAA (%) | WMG | NIV | FVC-U (%) | FVC-S (%) | ΔFVC (%) | PCF | MIP | MEP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 51 | 27 | 6 | Exertional dyspnoea, exercise intolerance | Vacuolar myopathy, + Glycogen | 6.00 | 2 | Yes (8 h) | 52 | 29 | −45 | 250 | −40 | NA |
| 2 | F | 49 | 27 | 10 | LGMD-like | Vacuolar myopathy, + Glycogen | 1.00 | 4 | No | 75 | 49 | −34 | 350 | −30 | 50 |
| 3 | M | 50 | 29 | 10 | LGMD-like | Vacuolar myopathy, + Glycogen | 4.00 | 5 | No | 44 | 33 | −26 | 300 | −45 | 73 |
| 4 | F | 51 | 25 | 12 | LGMD-like | Vacuolar myopathy, + Glycogen | 6.00 | 7 | No | 99 | 61 | −39 | 350 | −60 | NA |
| 5 | M | 47 | 24 | 13 | LGMD-like | + Glycogen | 0.50 | 4 | No | 93 | 79 | −15 | 400 | −70 | 60 |
| 6 | F | 57 | 27 | 19 | LGMD-like | Vacuolar myopathy, + Glycogen | 5.20 | 6 | Yes (8 h) | 64 | 24 | −40 | 250 | −30 | 40 |
| 7 | M | 8 | 20 | 5 | HyperCKemia | Unspecific changes | 3.80 | 0 | No | 97 | 95 | −3 | 430 | −75 | 65 |
| 8 | M | 34 | 33 | 10 | Exertional dyspnoea exercise intolerance | + Glycogen | 4.00 | 4 | No | 56 | 49 | −35 | 350 | −50 | 73 |
| 9 | F | 15 | 22 | 5 | Myalgias | Unspecific chages | 22.00 | 1 | No | 97 | 95 | −5 | 450 | −70 | 60 |
| 10 | M | 65 | 29 | 12 | LGMD-like | Vacuolar myopathy, + Glycogen | 6.30 | 4 | Yes (8 h) | 76 | 39 | −37 | 350 | −60 | 62 |

BMI: body mass index; GAA: acid alpha-glucosidase residual activity; WMG: Walton Medwin–Gardner scale; NIV: noninvasive ventilation; FVC-U: forced vital capacity in upright position (percentage of predicted); FVC-S: Forced Vital Capacity in Supine position (percentage of predicted); ΔFVC: forced vital capacity drop percentage between upright and supine position; PCF: peak cough flow; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; LGMD: limb-girdle muscle dystrophy; NA: not available.