LETTER TO THE EDITOR

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Is early detection of late-onset Pompe disease a pneumologist’s affair? A lesson from an Italian screening study

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Abstract

Background: Late-onset Pompe disease (LOPD) is a recessive disease caused by α-glucosidase (GAA) deficiency, leading to progressive muscle weakness and/or respiratory failure in children and adults. Respiratory derangement can be the first indication of LOPD, but the diagnosis may be difficult for pneumologists. We hypothesize that assessing the GAA activity in suspected patients by a dried blood spot (DBS) may help the diagnosis of LOPD in the pneumological setting.

Population and methods: We performed a multicenter DBS survey of patients with suspected LOPD according to a predefined clinical algorithm. From February 2015 to December 2017, 140 patients (57 ± 16 yrs., 80 males) were recruited in 19 Italian pneumological units. The DBS test was performed by a drop of blood collected on absorbent paper. Patients with GAA activity < 2.6 μmol/L/h were considered positive. A second DBS test was performed in the patients positive to the first assay. Patients testing positive at the re-test underwent a skeletal muscle biopsy to determine the GAA enzymatic activity.

Results: 75 recruited subjects had outpatient access, 65 subjects were admitted for an acute respiratory failure episode. Two patients tested positive in both the first and second DBS test (1.4% prevalence), and the LOPD diagnosis was confirmed through histology, with patients demonstrating a deficient GAA muscle activity (3.6 and 9.1 pmol/min/mg). A further five subjects were positive in the first DBS test but were not confirmed at re-test. The two positive cases were both diagnosed after hospitalization for acute respiratory failure and need of noninvasive ventilation. Most of the recruited patients had reduced maximal respiratory pressures (MIP 50 ± 27% and MEP 55 ± 27% predicted), restrictive pattern (FEV₁/FVC 81.3 ± 13.6) and hypoxaemia (PaO₂ 70.9 ± 14.5 mmHg). Respiratory symptoms were present in all the patients, but only 48.6% of them showed muscle weakness in the pelvic girdle and/or in the scapular girdle (35.7%).

Conclusions: DBS GAA activity test may be a powerful screening tool among pneumologists, particularly in the acute setting. A simple clinical algorithm may aid in the selection of patients on which to administer the DBS test.

Keywords: Late-onset Pompe disease, Acute respiratory failure, Respiratory high dependency care unit, Noninvasive ventilation, Diagnosis

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Introduction
Pompe disease (ORPHA#365) is a rare autosomal recessive disease due to alpha-glucosidase (GAA) deficiency, leading to glycogen accumulation in multiple tissues with a predilection for the skeletal muscle [1]. Depending on the age of onset, two different clinical forms have been described: infantile and late-onset [2]. Late-onset Pompe disease (LOPD) is a slowly progressive form associated with a residual enzyme activity, which presents with either juvenile or adult onset and shows various clinical phenotypes [3, 4].

Early clinical manifestations of LOPD are usually progressive muscle weakness and/or respiratory failure [5]. In contrast to what happens in other hereditary neuromuscular diseases, in which respiratory failure occurs after the loss of ambulation, respiratory involvement in LOPD may represent the first clinical manifestation of the disease itself, so that patients may have respiratory disorders despite retaining ambulation [6]. Approximately one third of adult patients affected by Pompe disease have an early respiratory phenotype, with a clinical picture that includes dyspnea and/or respiratory failure, sleep-disordered breathing (SDB) and recurrent pulmonary infections [6]. Acute respiratory failure requiring mechanical ventilation in Intensive Care Units (ICU) or in Respiratory High Dependency Care Units (RHDCU) may be the first clinical presentation of the disease [7]. However, LOPD with a prevalent respiratory derangement is not easily and promptly identified during an acute respiratory failure episode because the critical illness itself doesn’t allow a clearly diagnostic electromyographic study [8].

Enzyme replacement therapy (ERT) with alglucosidase alpha was approved for LOPD because it can stabilize lung function and improve walking distance [9]. More-
Data analysis was performed using the GraphPad Prism version 6 software (San Diego, CA, USA). Data are presented as mean (SD) or median (min., max.), as appropriate. The positive and negative predictive values were computed from a $2 \times 2$ contingency table. The association between categorical variables was evaluated using Fisher’s exact test. Differences between groups were assessed using the Student’s $t$ test.

**Results**

The study lasted from February 2015 to December 2017 and recruited 140 patients in 16 out of 19 Italian pneumological participating units with good experience in respiratory failure of neuromuscular origin. Two DBS-positive cases (patients positive in both the test and re-test) were found and confirmed to be LOPD. The cDNA mutations were respectively c.-32-13 T > G (IVS1); c.1564C > G (p.Pro522Ala) and c.32-13 T > G; c.-673C > T. The characteristics of the recruited patients and the two LOPD confirmed patients are described in Table 1.

There were a further five subjects which tested positive in the first DBS test, but were not positive at the re-test. One of these cases could not be retested due to death, seemingly as a result of respiratory failure (the relatives did not authorize autopsy). In the studied population 80 patients were male and 60 were female; the median age at recruitment was 58 years (min.18-max.86). The two positive cases were both diagnosed after hospitalization in RHDCU for an acute respiratory failure with need of noninvasive ventilation and cough assist devices, although they had reported symptoms (dyspnea on exertion, fatigue, sleep disturbances with somnolence during the day, upper and lower girdle weakness with an initial waddling gait and mild hyperlordotic lumbar spine) for at least one year before (mean $1.2 \pm 2$). Other 63 patients were recruited during hospital admission, while the remaining 75 patients underwent ambulatory pneumological visit for respiratory symptoms.

The muscle activity of GAA in the two LOPD patients were 3.6 pmol/min/mg and 9.1 pmol/min/mg. Among the patients admitted to the hospital, 59 out of them required monitoring in a RHDCU, with need of noninvasive ventilation in 31 cases (52.5%). All the recruited patients presented respiratory symptoms, and in fact, the most commonly reported symptoms by the recruited subjects were dyspnoea (121 patients, 86.4% of cases), fatigue (118 patients, 84.3% of cases), orthopnea (61 patients, 43.5% of cases), and further unspecific symptoms with overlapping frequency in our unconfirmed or positive patients. Most of the patients had reduced maximal respiratory pressures (MIP $50 \pm 27\%$ predicted, MEP $55 \pm 27\%$ predicted), and restrictive pattern (FEV$_1$/FVC $81.3 \pm 13.6$) with mild hypoxaemia (PaO$_2$ 70.9 $\pm 14.5$ mmHg). Less than half of the recruited subjects had mild to moderate muscular symptoms including weakness in the pelvic girdle (48.6%) and/or in the scapular girdle (35.7%). There was no adverse effect or delayed
diagnosis due to the administration of the DBS GAA activity test. The prevalence of DBS+ subjects in our selected population was 4.2%, while the prevalence of confirmed LOPD patients was 1.4%. No association between categorical variables was found. The sensitivity of DBS test in our population was 100%, and the specificity 97.1%. The positive predictive value (PPV) of the DBS test in the selected patient population was 0.333 (33.3%), and the negative predictive value (NPV) was 1.000 (100%).

Discussion
A timely diagnosis and treatment of LOPD is important to improve outcome [10], but latency from the onset of symptoms to an established diagnosis may be up to 5–30 years from the onset of symptoms [16, 17]. The delay of LOPD diagnosis is mainly due to the very low incidence (estimated 1 case in 57,000–100,000 in European countries) [18, 19], together with overlapping symptoms with other NMD [3, 18], but also the so-called “respiratory phenotype” might be a confounder [4]. Our national DBS-based screening study demonstrated that also in the pneumological setting it is possible to easily detect patients with undiagnosed LOPD after a patient selection by means of a dedicated clinical algorithm. Particularly, the late-onset form of glycogen storage disease type II or Pompe disease (LOPD) may be suspected in subjects with acute respiratory insufficiency, SDB and

Table 1 Clinical characteristics of the patients

| Characteristics                              | Recruited patients | LOPD patient #1 | LOPD patient #2 |
|----------------------------------------------|---------------------|-----------------|-----------------|
| Gender, M/F                                  | 80 M/60 F           | M               | F               |
| Age at recruitment, mean ± SD                | 57 ± 16             | 69              | 42              |
| Months from symptoms onset, median (min, max)| 6 (0–373)           | 12              | 16              |
| Body mass index, kg/m²                       | 28.5 ± 9.5          | 19.7            | 23.3            |
| Respiratory symptoms                         | 100%                | yes             | yes             |
| • Dyspnea during exercise                    | 86.4%               | yes             | yes             |
| • Dyspnea at rest                            | 35.9%               | no              | yes             |
| • Ineffective cough                          | 41.1%               | yes             | yes             |
| • Oortopnea                                   | 43.5%               | no              | no              |
| • Fatigue                                    | 84.3%               | yes             | yes             |
| • Airways infections                         | 44.1%               | no              | yes             |
| Sleep disorders                              | 36.4%               | yes             | yes             |
| • Nocturnal restlessness                      | 44.2%               | yes             | yes             |
| • Frequent reawaken                          | 40.0%               | no              | yes             |
| • Nocturnal apnoea                           | 41.4%               | no              | no              |
| • Snoring                                    | 30.0%               | no              | no              |
| • Morning sleepiness                         | 25.0%               | no              | yes             |
| • Morning headache                           | 20.0%               | yes             | no              |
| • Day sleepiness                             | 39.2%               | yes             | yes             |
| Acute respiratory failure at recruitment      | 28.5%               | yes             | yes             |
| Myalgia                                      | 52.1%               | no              | no              |
| CPK, IU/L                                    | 345 ± 700           | 206             | 471             |
| AST, U/L                                     | 27 ± 13             | 44              | 57              |
| PaCO₂, mmHg                                   | 43 ± 12             | 54.2            | 46              |
| Upright FVC % predicted                      | 67 ± 25             | 62              | 66              |
| △Upright-Supine FVC%                        | −18 ± 20            | −28             | −31             |
| Lower-girdle muscle weakness, %              | 48.6%               | yes             | yes             |
| Upper-girdle muscle weakness, %              | 35.7%               | yes             | yes             |
| Walton & Gardner-Medwin Scale                | 2.9 ± 3.1           | 7               | 4               |
| GAA activity, microMol/L/h                   | 10.1 ± 6.6          | 0.36            | 0.71            |

M males, F females, CPK creatinphosphokinase, AST aspartate transaminase, PaCO₂ arterial partial pressure carbon dioxide, FVC forced vital capacity, GAA alpha glucosidase
proximal muscle weakness without a clinically apparent cardiac involvement. In our study, both of the two patients found to have LOPD has displayed respiratory and neurologic symptoms for more than 1 year, but they were detected only during an episode of acute respiratory failure with the need of RHDCU admission. This latency of the diagnosis may seem too high, but it is much less than other literature reports [8, 16, 17]. In line with our results, Kishnani et al. [19] recently reported that patients with early respiratory involvement can be diagnosed sooner than those presenting with only muscular symptoms and/or hyperCPKemia.

Considering all the subjects included in our survey, most of them had outpatient access, while the other patients were admitted to the hospital with access to the emergency room (ER). Among the 65 patients admitted to the ER, most of them required monitoring in a RHDCU and noninvasive ventilatory support. This is concordant with the findings of the last Italian RHDCU survey, which highlighted the increased number of admissions for acute respiratory failure of neuromuscular origin as compared to the previous national census [20]. Nevertheless, most of the patients in our national screening study were recruited as outpatients visited by a pneumologist for a common symptom like exercise dyspnoea jointly with SDB and a suspected NMD. The execution of a DBS test for the detection of LOPD showed high sensitivity and specificity, without disturbing the correct diagnosis, or harming the patient. The re-test did not confirm four DBS+ subjects at the first test, but this did not influence the respiratory management. One of the two LOPD cases presented only slightly increased blood creatine phosphokinase (CPK) levels (206 IU/L), supporting the observation that CPK levels are almost normal in some cases of LOPD with respiratory phenotype without limb-girdle syndrome [4, 6, 7]. Balancing the potential harms and benefits of diagnosing LOPD in the pneumological setting is not a contentious issue as there are disease-modifying treatments for Pompe disease, and a formal diagnosis may only benefit every patient.

Conclusions
Testing GAA activity by DBS was shown to be a powerful screening tool for pneumologists, particularly in the acute setting. A simple clinical algorithm may help the selection of patients to administer the DBS test in order to diagnose LOPD. Particular attention should be paid when a patient with suspected but undiagnosed NMD and acute respiratory failure without cardiac involvement needs mechanical ventilation and/or cough assist devices.

Abbreviations
ABG: Arterial blood gas; A IPO: Italian Association of Hospital Pneumologists; AST: Aspartate transaminase; COPD: Chronic obstructive pulmonary disease; CPK: Creatine phosphokinase; CTscan: Computed tomography scan; DBS: Dried Blood Spot; ER: Emergency Room; ERT: Enzyme replacement therapy; FEV1: Forced Expiratory Volume in the first second; FVC: Forced Vital Capacity; GAA: Alpha-glucosidase; ICU: Intensive Care Units; LOPD: Late-onset Pompe disease; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; NMD: Neuromuscular disorder; OSA: Obstructive sleep apnea; PaCO2: Partial pressure carbon dioxide; PCEF: Peak cough expiratory flow; RHDCU: Respiratory High Dependency Care Units; SD: Standard deviation; SDB: Sleep-disturbed breathing

Acknowledgements
We thank the other members of the A IPO Pneumoloped Group: Alessio Mattei (Torino), Fausto De Michele (Napoli), Luca Triolo (Roma), Giuseppe Culla (Roma), Peraldo Canessa (Sarzana), Giuseppe Girbino (Messina), Mirco Lusuardi (Correggio), Enrico Peretta (Imperia), Claudio De Micheli (Imperia), Teresa Renda (Firenze).

Funding
Partial support of this study was derived from unrestricted grant by Sanofi Genzyme Italy.

Availability of data and materials
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
MC conceived-designed-coordinated the survey and drafted the manuscript; MV conceived the survey collected data and revised the manuscript, RF conceived the survey collected data and revised the manuscript; MP designed the survey collected data and revised the manuscript, ES collected data and helped to draft the manuscript; GC collected data and revised the final manuscript, PC collected data and revised the manuscript, CA collected data and drafted the manuscript, GS collected data and revised the manuscript, NR performed statistical analysis, reviewed English language, SZ cooperated to statistics and checked lab data, FS collected data and revised the manuscript, AV collected data and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethical approval was given by the C.E.R.U. Friuli-Venezia Giulia (ref # 67/2014).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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