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Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease

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ABSTRACT

Respiratory insufficiency is a serious threat to patients with Pompe disease, a neuromuscular disorder caused by lysosomal acid alpha-glucosidase deficiency. Innovative therapeutic options which may stabilize pulmonary function have recently become available. We therefore determined proportion and severity of pulmonary involvement in patients with Pompe disease, the rate of progression of pulmonary dysfunction, and predictive factors for poor respiratory outcome.

In a single-center, prospective, cohort study, we measured vital capacity (VC) in sitting and supine positions, as well as maximum inspiratory (MIP) and expiratory (MEP) mouth pressures, and end expiratory CO_2 in 17 children and 75 adults with Pompe disease (mean age 42.7 years, range 5–76 years).

Seventy-four percent of all patients, including 53% of the children, had some degree of respiratory dysfunction. Thirty-eight percent had obvious diaphragmatic weakness.

Males appeared to have more severe pulmonary involvement than females: at a group level, their mean VC was significantly lower than that of females ($p<0.001$), they used mechanical ventilation more often than females ($p=0.042$) and the decline over the course of the disease was significantly different between males and females ($p=0.003$). Apart from male gender, severe skeletal muscle weakness and long disease duration were the most important predictors of poor respiratory status. During follow-up (average 1.6 years, range 0.5–4.2 years), three patients became ventilator dependent. Annually, there were average decreases in VC in upright position of 0.9% points ($p=0.09$), VC in supine position of 1.2% points ($p=0.049$), MIP of 3.2% points ($p=0.018$) and MEP of 3.8% points ($p<0.01$).

We conclude that pulmonary dysfunction in Pompe disease is much more common than generally thought. Males, patients with severe muscle weakness, and those with advanced disease duration seem most at risk.
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1. Introduction

Pompe disease is a rare inherited metabolic disorder [1–4] caused by deficiency of the lysosomal enzyme acid α-glucosidase. The spectrum of phenotypes is continuous, but in clinical practice two subtypes can be recognized: 1) the classic infantile phenotype, in which the disease manifests shortly after birth, leading to generalized muscle weakness, cardiorespiratory failure and death within the first year of life [5,6]; and 2) a more slowly progressive phenotype predominantly affecting skeletal and respiratory muscles, in which cardiac involvement is only sporadically present [7,8]. Symptoms in this latter group of patients can become manifest at any age, from as early as the first year of life to as late as the sixth decade [9–12]. The course of the disease can vary substantially between patients [13], and the severity of respiratory involvement is not always related to the degree of skeletal–muscle weakness [14,15].

Due to the disproportionate involvement of the diaphragm, respiratory insufficiency is a serious threat to patients with Pompe

Abbreviations: FEV_1, Forced Expiratory Volume in one second; MEP, Maximum Expiratory Pressure; MIP, Maximum Inspiratory Pressure; MRC, Medical Research Council; VC, vital capacity.

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disease [16,17]; this is also seen in several other neuromuscular disorders such as Duchenne muscular dystrophy or facioscapulohumeral dystrophy. As the disease progresses, many patients ultimately become dependent on mechanical ventilatory support, and respiratory failure is a major cause of death [7,12]. However, most studies have investigated only a small number of patients, or only a selected group; the actual percentage of patients with respiratory dysfunction, who are thus at risk for developing respiratory failure, is therefore not exactly known [11,14,15,17]. Neither is it known which factors are associated with poor pulmonary outcome.

In April 2010, a placebo controlled trial showed that pulmonary function in patients older than eight years may be stabilized by treatment with recombinant human alpha-glucosidase. Early identification of respiratory problems may thus be important for the timely initiation not only of mechanical ventilation, but also of enzyme therapy [18,19].

To establish the proportion of patients with pulmonary involvement, and also the severity of pulmonary dysfunction and the rate of deterioration, we conducted a prospective cohort study in 92 untreated children and adults with Pompe disease. We also aimed to identify predictive factors for poor respiratory outcome.

2. Materials and methods

2.1. Study population and study design

Ninety-two patients (17 children and 75 adults) were included in an ongoing prospective cohort study on the natural course of Pompe disease. Participation was open to all patients who did not have the classic infantile type of Pompe disease. Diagnosis in all patients was confirmed through mutation analysis and by measuring acid alpha-glucosidase deficiency in leukocytes, muscle tissue or fibroblasts.

All patients were examined at Erasmus MC University Medical Centre between August 2003 and August 2009. They were recruited either through neuromuscular centers in the Netherlands and Belgium, or through the Dutch neuromuscular patient organization, or were referred to our center of expertise by their treating physicians. Throughout the study, none of the patients received enzyme replacement therapy. The research protocol was approved by the Central Committee on Research Involving Human Subjects in the Netherlands (CCMO). All patients or their parents provided written informed consent.

2.2. Pulmonary function tests

Vital capacity (VC) and Forced Expiratory Volume in one second (FEV_1) were measured using a Lilly type pneumograph (Viasys Healthcare, Würzburg, Germany) according to ATS/ERS standards [20]. Patients were tested in upright seated or supine position while wearing a nose clip. Three repeated flow volume curves were made; in case of a non-characteristic curve, an extra measurement was performed. The best effort, determined as the measurement with the highest sum of VC and FEV_1, was used in further analyses. Values were expressed as percentage of predicted normal values (based on able-bodied persons of the same age, gender, and height) or as z-scores, calculated as the difference between the observed and predicted value divided by the standard deviation from the reference value. Z-scores <-1.64 (5th percentile of the reference population) were considered abnormally low. Reference values were derived from published data [21,22]. For vital capacity a further subdivision was made to categorize the severity of lung function impairment: mild (z-score -3 to -1.64), moderate (z-score -4 to -3) and severe (z-score <-4). A drop in percentage predicted VC upon changing posture from the upright to the supine position of more than 25% was considered as diaphragmatic weakness [23–25].

Maximum static inspiratory (MIP) and expiratory (MEP) pressures were recorded using a differential pressure transducer (Viasys Healthcare, Würzburg, Germany) according to ATS/ERS standards [23]. Patients were comfortably seated, wearing a nose clip. Pressures were measured against an obstructed mouthpiece with a small leak to prevent glottic closure during the MIP maneuver and to reduce the use of buccal muscles during the MEP maneuver. In addition, the patient held the cheeks during the MEP maneuver. MIP was measured at residual volume after maximal expiration and MEP at total lung capacity after maximal inspiration. Pressures had to be maintained for at least one second. Maneuvers were repeated until three reproducible measurements were recorded. At least 1 min was taken between consecutive measurements. The highest value obtained was taken for analysis. Reference values were taken from published data [26]. MIP below the lower limit of the normal predicted value was interpreted as diaphragmatic weakness.

The carbon dioxide fraction in the expired gas was measured with a capnograph (ms-capno, Viasys Healthcare, Würzburg, Germany) at maximum expiration ($P_{EE,CO2}$). In the absence of ventilation irregularities, the $P_{EE,CO2}$ approximates the arterial carbon dioxide pressure ($P_{a,CO2}$). A daytime $P_{EE,CO2}$ over 6.0 kPa suggests hypercapnia and chronic alveolar hypoventilation [27].

2.3. Additional clinical information

Information was gathered on the following: 1) age at symptom onset, 2) age at diagnosis, 3) disease duration since first symptoms, 4) height, 5) weight, 6) gender, 7) use of wheelchair or walking aids, 8) muscle strength, 9) use of ventilatory support, 10) number of hours of ventilatory support per day, 11) presence of sleep disorders, 12) presence of scoliosis and scoliosis surgery, 13) smoking habit, 14) concomitant diseases such as chronic obstructive pulmonary disease or asthma, and 15) family history of pulmonary disease.

Muscle strength was graded through manual muscle testing using the Medical Research Council (MRC) grading scale [28] (range 0–5; all patients were assessed by the same examiner (NvdB) without having access to the pulmonary function data). A muscle sumscore was calculated for the following muscle groups: neck extensors, neck flexors and bilateral shoulder abductors, elbow flexors, elbow extensors, hip flexors, hip abductors, knee flexors and knee extensors. This sumscore ranges from 0 ("total paralysis") to 80 ("normal strength").

2.4. Statistical analyses

Continuous variables are presented using median and range. For categorical variables, percentages or frequencies are given. Pulmonary function testing could not be performed in six patients who were ventilated 24 h a day through a tracheostomy tube. In the statistical analyses these patients were considered to have the most severely affected pulmonary function, and were artificially given a VC of -8.5 SD (just below the least observed value), since their omission might have led to biased results.

Baseline differences between males and females were assessed using χ^2 tests (wheelchair use and ventilator use) or Mann–Whitney tests (age, disease duration, mobility, age at first symptoms, age at diagnosis and MRC sumscore).

The relationships between disease duration, MRC sumscore, mobility, gender, MIP, MEP and vital capacity were calculated using the Spearman's rank correlation coefficients (ρ).

Multiple linear regression analysis was used to further explore the relationship of VC versus gender and disease duration, with adjustment for age, MRC sumscore and mobility.

Longitudinal analysis of pulmonary function was performed using random coefficient models for repeated measurements, allowing for irregularly measured data. For subgroup analyses, patients were divided into groups on the basis of disease duration (<5, 5 to 10, 10 to

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