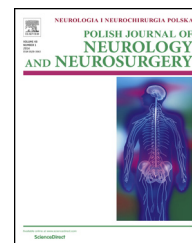


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## Original research article

# Enzymatic replacement therapy in patients with late-onset Pompe disease – 6-Year follow up



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## ABSTRACT

**Introduction:** Late-onset Pompe disease (LOPD) is a progressive metabolic myopathy, affecting skeletal muscles, which, if untreated, leads to disability and/or respiratory failure. The enzyme replacement therapy (ERT) improves muscle strength and respiratory function and prevents disease progression. We present a 6-year follow-up of 5 patients with LOPD treated with ERT.

**Methods:** Five patients with LOPD received ERT: two started treatment in 2008, other two in 2010 and one in 2011. All patients received recombinant human alpha-glucosidase in dose 20 mg/kg intravenously every two weeks. Physical performance was assessed in 6-minute walk test (6MWT) and spirometry was performed to examine FVC and FEV1. Liver enzymes, CK levels were also assessed.

**Results:** The walking distance in 6MWT increased by average  $16.9 \pm 2.26\%$  in the first three years of treatment. Similar changes were detected in spirometry: the most significant FVC increase was observed in two patients with the highest FVC values before treatment, which increased to normal values adjusted for age and sex in three years of treatment, that is by 28% and 34%. In two other patients FVC reached 88% and 76% of predicted values. ERT also improved the liver and muscle enzymes levels.

**Conclusion:** The improvements of exercise tolerance and FVC were observed in all patients in the first three years of treatment and were the most pronounced in the longest-treated patients and with the least severe neurological and respiratory symptoms. Our research suggests that early start of the ERT results in higher improvement of respiratory and ambulation functions.

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## 1. Introduction

Pompe disease belongs to glycogen storage diseases (GSD), in which, due to deficiency or absence of enzyme (lysosomal acid alpha-glucosidase [GAA] or acid maltase) that catalyze the degradation of glycogen, it accumulates in certain tissues (first in the lysosomes and in the case of their damage by excess of glycogen, also in the cytoplasm of cells), particularly in muscles, but also in the heart and other internal organs [1]. Pompe disease is a hereditary autosomal recessive disorder and its symptoms occur in individuals with two abnormal copies of the GAA gene. Yet, about 200 different mutations in GAA gene located on chromosome 17 encoding the GAA protein have been discovered. Mutations can result in the complete absence of enzyme or inactive enzyme (which leads to infantile form of the disease), the correct amount of enzyme with reduced activity, or to reduced enzyme amount with normal activity (which leads to late-onset Pompe disease – LOPD) [2]. Mutation of c.-32-13T>G is most common in late-onset disease form. This mutation leads to a reduction of GAA to 10–20% of normal activity [3]. Despite the later age of symptoms onset and the milder phenotype, adult form of Pompe disease, if not treated, cause progressive physical disability with limbs flaccid paralysis. Some patients would require a wheelchair or respiratory therapy if progressive respiratory failure occurs.

In Poland, in the years 1999–2012, 37 patients were diagnosed with Pompe disease: 25 people with early-onset and 12 patients with late-onset forms of the disease. No relation to gender was found.

The enzyme replacement therapy (ERT) has been shown to improve muscle strength and respiratory function and to prevent disease progression [4]. We present a 6-year follow-up of 5 patients with LOPD treated with ERT.

## 2. Materials and methods

Five patients with late-onset Pompe disease receiving enzymatic replacement therapy: two sisters (current age 39 and 41), another female (current age 32) and two male subjects (current age 48 and 54) have been observed prospectively (Table 1).

Age range of patients was 26–41 years at the beginning of treatment, which is consistent with statistic data concerning symptoms onset, although two youngest patients reported shortness of breath, especially on exercise, recurrent respiratory infections and morning headaches or daytime sleepiness while they were growing up, which suggest that they might

have had juvenile form of Pompe disease. They also complained on difficulties while marching or climbing the stairs. Above mentioned symptoms (which are secondary to respiratory muscle involvement, hypoxia and nocturnal hypoventilation) [5,6] were present in all patients. Two male patients had already been diagnosed with obstructive sleep apnea syndrome, which is very common in LOPD [7,8]. They had been treated with CPAP before Pompe disease diagnosis was made.

Pompe disease was diagnosed as the reasons of progressive muscle weakness and reduced exercise tolerance in four of these patients (all female and the oldest male). The youngest female underwent a detailed diagnostic procedure for liver diseases (including liver biopsy) before LOPD was suspected. In one, diagnosis was made after severe respiratory failure event of unknown cause. In all patients, the diagnosis was confirmed with a genetic test and the assessment of GAA activity in leucocytes and in dried blood spot (DBS) (Table 2).

In all patients at least 2 pathogenic mutations underlying Pompe disease were found. In 3 of them genetic testing confirmed the presence of the above mentioned common pathogenic mutation c.-32-13T>G. This mutation is responsible for a splicing defect. The ability to produce the reduced amount of enzyme is a reason of a relatively mild phenotype [3,9]. In two sisters the same mutation c.1796C>A was found. This mutation relatively rarely found among the Caucasian population was firstly described in 2008 and also is connected with non-severe phenotype of the disease [10].

All patients presented with myopathy, proximal muscle weakness (mainly shoulder and pelvic girdle), hypotonia and reduced tendon reflexes, which severity depended on disease duration. Excessive lumbar lordosis and thoracic kyphosis secondary to paraspinal muscle weakness also were visible in the oldest male patients. Those abnormalities were responsible for changes in the static properties of thoracic and lumbar spine and contribute to characteristic waddling gait. None of the patients had cardiac abnormalities suggesting subclinical cardiomyopathy and signs of cataract on ophthalmological examination.

FVC before treatment introduction were 77% (AG), 78% (UM), 61% (DK) and 63% (AF) (results adjusted for age and sex), consistently with previous observations suggesting that in about 60% of patients with late-onset Pompe disease FVC is of <80% of predicted value, with the remaining 30–40% – down to <60% of predicted [11,12]. Forced expiratory volume in one second (FEV1) was also decreased in all patients (Fig. 1A and B).

Further tests showed increased activity of creatine kinase (CK) and creatine kinase MB (CK-MB) (Fig. 1C), which are indicators of muscle damage, and increased activity of

**Table 1 – Basic demographic and clinical data.**

| Initials | Sex | Age | Age of first symptoms | Age at diagnosis | Age at the beginning of the treatment | Time of the treatment | Time from the beginning of symptoms to the start of ERT |
|----------|-----|-----|-----------------------|------------------|---------------------------------------|-----------------------|---|
| AG       | F   | 32  | 7 (1991)              | 25 (2009)        | 26 (2010)                             | 6                     | 19  |
| DK       | F   | 41  | 25 (2000)             | 31 (2006)        | 33 (2008)                             | 8                     | 8   |
| UM       | F   | 39  | 27 (2004)             | 29 (2006)        | 31 (2008)                             | 8                     | 4   |
| AF       | M   | 48  | 36 (2004)             | 40 (2009)        | 41 (2010)                             | 6                     | 5   |
| ZT       | M   | 54  | 33 (1998)             | 48 (2011)        | 48 (2011)                             | 5                     | 16  |

**Table 2 – Results of genetic testing and GAA activity<sup>a</sup> before ERT introduction.**

| Patient (sex/age) | Pathogenic mutation.  | GAA activity in leukocytes (norm: 0.31–0.52) | GAA activity in DBS (norm: 0.29–0.49) |
|-------------------|-----------------------|--|---------------------------------------|
| F/32              | c.-32-13T>G, c.307T>G | 0.07   | n.d.                                  |
| F/39              | c.1796C>T, c.364A>G   | 0.09   | 0.12                                  |
| F/41              | c.1796C>T, c.364A>G   | 0.07   | 0.05                                  |
| M/48              | c.-32-13T>G, c.307T>C | 0.07   | n.d.                                  |
| M/54              | c.-32-13T>G, c.307T>G | n.d.   | n.d.                                  |

<sup>a</sup> GAA activity ratios measured at pH 3.8 with and without acarbose.  
n.d. – not done.

aspartate aminotransferase (AspAT) and alanine aminotransferase (AlAT), which indicate a subclinical liver damage [13] (Fig. 2). The levels of these abnormalities varied among patients and no relation was found between CK/AspAT/AlAT levels and patient's age (disease duration), their everyday activity or additional physical activity.

### 3. Enzymatic replacement therapy

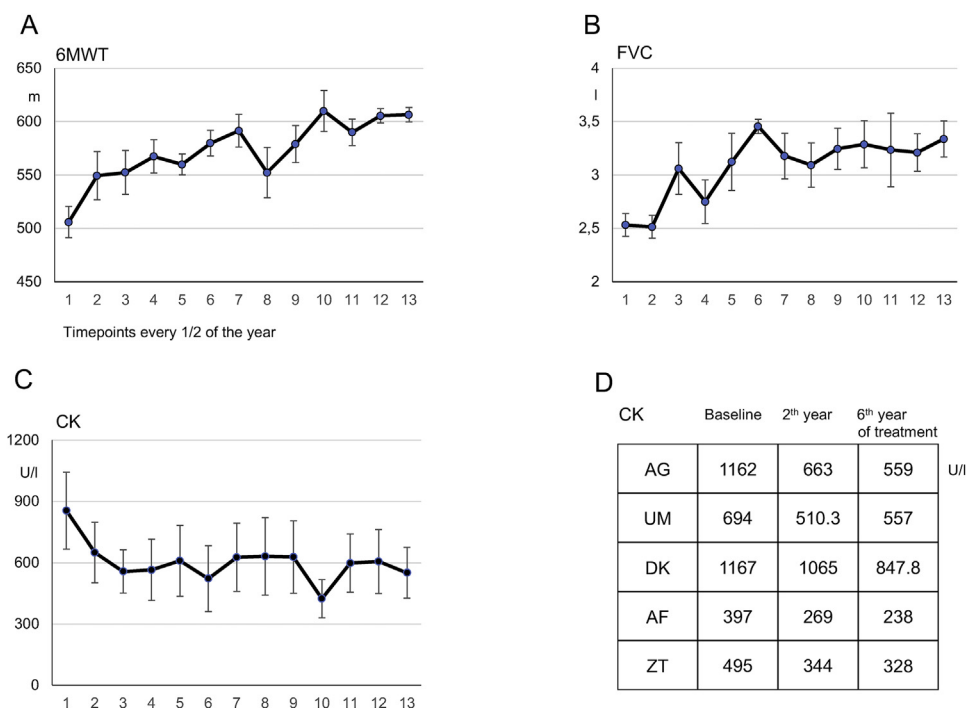
Patients have been treated with recombinant human acid alpha-glucosidase (rhGAA) in recommended dose of 20 mg/kg administered intravenously every two weeks. The treatment was introduced 2 years after diagnosis of Pompe disease in two siblings and within 1-year in three another patients.

ERT overall tolerability was good. Two patients suffered from muscle pain in lower limbs lasting a 2–3 months after

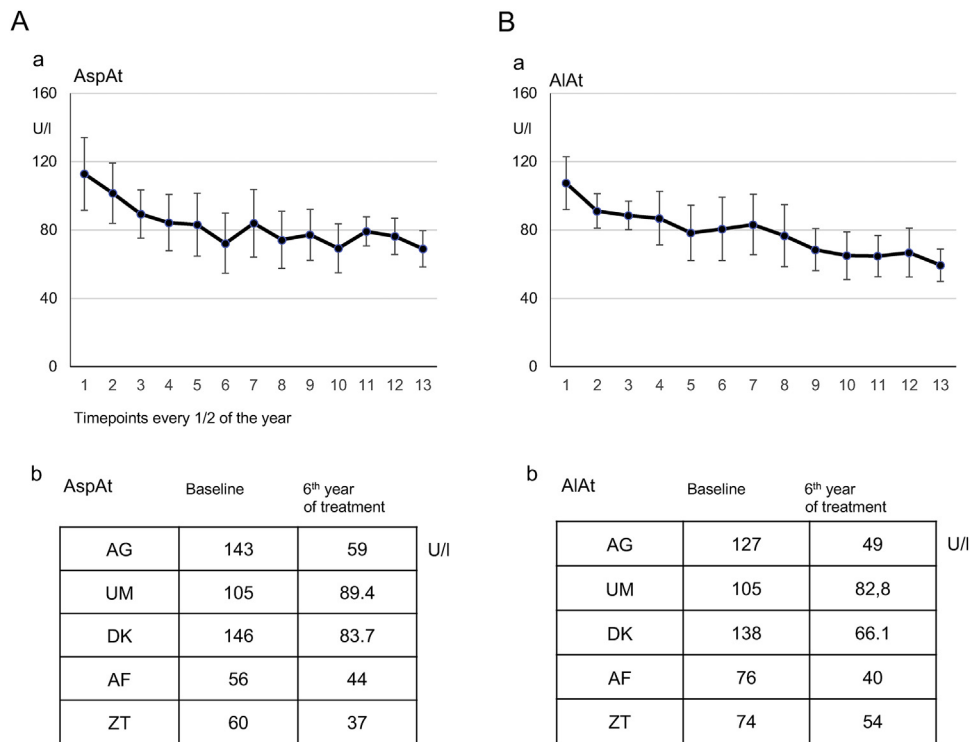
treatment introduction. All patients reported mild dizziness for few hours after drug infusion.

### 4. Treatment monitoring

Routinely careful clinical assessment is carried, and diagnostic tests are performed every 6 months in patients receiving ERT. Physical performance is assessed in 6-minute walk test and spirometry is performed to examine FVC and FEV1. Gasometry, liver enzymes activity, CK levels are also assessed. ECG and echocardiography are performed to detect potential cardiac disease and pulmonary consultation is carried to detect potential pulmonary abnormalities or diagnose obstructive sleep apnea syndrome. Ophthalmic, orthopedic and laryngological examinations serve for early detection of cataract (which often occurs in patients with Pompe disease) or



**Fig. 1 – Changes of mean value of 6MWT (A), FVC (B) and serum level of CK (C) observed during the 6-years ERT treatment. (D) CK levels for each patient with LOPD at baseline (before the initiation of the ERT treatment), in the 2nd and 6th year of the treatment. 6MWT – 6 min walking test, FVC – forced vital capacity, CK – creatine kinase, ERT – enzymatic replacement therapy, LOPD – late-onset Pompe disease.**



**Fig. 2 – Changes in mean level of AspAt (Aa) and AlAt (Ba) found during the 6-years ERT treatment. AspAt (Ab) and AlAt (Bb) levels for each patient with LOPD present at baseline (before initiation of ERT treatment) and in the 6th year of treatment. AspAt – aspartate aminotransferase, AlAt – alanine aminotransferase, ERT – enzymatic replacement therapy, LOPD – late-onset Pompe disease.**

changes in the static properties of the spine. Abdominal USG and chest X-ray are also repeated.

## 5. Treatment results

The walking distance assessed by 6MWT increased by average  $16.9 \pm 2.26\%$  in the first three years of treatment (from  $507.0 \pm 14.6$  m to  $591.0 \pm 15.5$  m), and then tended to stabilize reaching increase by  $19.5 \pm 1.33\%$  ( $606.0 \pm 6.8$  m) from the baseline at the end of the 6-years observational period (Fig. 1A). Similar pattern of changes was detected in the level of CPK, which significant reduction was present after the first 2 years of treatment ( $34.8 \pm 12.26\%$ ). During the rest of observational period stable values of CPK were found with  $35.6 \pm 14.5\%$  reduction from baseline after 6 years (Fig. 1C and D). Also, FVC values increased in the first 2 years ( $23.3 \pm 11.2\%$ ) and then tended to improve slowly during the rest of observational period ( $31.7 \pm 6.7\%$  from baseline after 6 years) (Fig. 1B). The most significant FVC increase was observed in patients with the highest FVC values before treatment (AG and UM), which reached normal values adjusted for age and sex in two years of treatment, that is an improvement by 28% and 34%. In two other patients FVC increase reached 88% (DK) and 76% (AF) of predicted values.

Both liver enzymes: aspartate aminotransferase (AspAT) and alanine aminotransferase (AlAT) levels showed slow, but continuous reduction during the whole observational period.

AspAT after 6 years of observation dropped from  $112.8 \pm 21.0$  to  $69.0 \pm 10.6$  mg/dl ( $38.0 \pm 4.1\%$  reduction). In one patient (AG) these values reached normal levels (reduction from  $66.0$  to  $44.0$  mg/dl) (Fig. 2Aab).

Similarly, AlAT values decreased from mean value of  $107.4 \pm 15.4$  mg/dl– $66.8 \pm 14.2$  mg/dl ( $44.6 \pm 4.5\%$  reduction from the baseline levels) (Fig. 2Bab).

Consecutive regular examinations did not reveal any abnormalities in cardiovascular system, but mild skeletal abnormalities (scoliosis in 4 patients), liver enlargement (in 1 patient) and cataract (in 1 patient) were found.

During the treatment, all patients maintained their professional activity, and there were no important clinical events observed.

## 6. Discussion

The increase in the walking distance (which indicates the improvement of exercise tolerance) was observed in all patients in the first two years of treatment and was the most prominent in patients with the least severe neurological and respiratory symptoms. The clinical improvement observed in the first 2 years of treatment seemed to be correlated with reduction of creatine kinase levels and improvement of respiratory system function revealed by an increase of FVC. All above measurements remained stable during the follow-up period.

Our observations are in concordance with results of previous studies. In a randomized, placebo-controlled study done by van der Ploeg et al. [14] during 78-week observation period the most prominent increase in 6MWT was documented in first 26 weeks and then was followed by stabilization of the results. The most marked improvement was observed in less severely affected subjects. Similarly, FVC improvement was observed even in a shorter period – during first 12 weeks of treatment. Important study presented by Gungor et al. [4] revealed positive impact of the ERT on survival, which was correlated with improvement of respiratory parameters.

Moreover, regular neurological examination showed improvement in muscle strength, however without impact on reduced tendon reflexes. And despite the fact that in no patient ERT reversed symptoms of the disease totally, initial improvement followed by long-term stabilization, which remained during the whole observation period, have significant positive impact on quality of life and maintaining of their professional activity.

Concluding, similarly to data from other studies [14,15] we showed that long-term ERT positively affects muscle strength, pulmonary function, and daily life activities in adult patients with Pompe disease. The maximal improvement is usually achieved during the first 2 years of treatment.

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### Conflict of interests

None declared.

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