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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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ARTICLE INFO

Article history:
Received 14 February 2018
Accepted 2 May 2018
Available online xxx

Keywords:
Pompe disease
Enzyme replacement therapy
Follow-up
6MWT

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 ± 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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https://doi.org/10.1016/j.pjnns.2018.05.002
0028-3843/

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 ophalmological 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

Please cite this article in press as: Witkowski G, et al. Enzymatic replacement therapy in patients with late-onset Pompe disease – 6-Year follow up. Neurol Neurochir Pol (2018), https://doi.org/10.1016/j.pjnns.2018.05.002