

# The Outcome of Infantile Onset Pompe Disease in South of Iran

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Received 2015 August 8; Revised 2015 October 21; Accepted 2015 November 6.

## Abstract

**Background:** Infantile Onset Pompe Disease (IOPD) is a rare autosomal recessive neuromuscular disorder. It is associated with cardiomegaly, hypotonia, paresis, and death in the first year of life. Since 2006, following the use of  $\alpha$ -glucosidase alfa as Enzyme Replacement Therapy (ERT), the patients' survival is improved to a noticeable extent.

**Objectives:** The purpose of this study is to examine the outcome of IOPD patients in South of Iran and the degree of responsiveness to ERT.

**Patients and Methods:** All patients who were diagnosed with IOPD on the bases of clinical symptoms, and enzyme assay on dried blood spot, were included in the study; and were followed up regarding cardiac function, locomotor activity, and cognition.

**Results:** Six patients with IOPD were identified. All these six patients suffered from Hypertrophic Cardiomyopathy (HCM). Four (67%) of them also had generalized hypotonia. Three patients expired during the first weeks due to severe respiratory infection. One of them also got involved with Acute Cardiopulmonary Failure while receiving the fifth dose of ERT; and expired. However, the remaining two patients had a significant improvement after the maximum of 117 weeks of following up both cardiac and locomotor findings. These two patients were the same patients who showed cardiac symptoms from the beginning but did not have generalized hypotonia.

**Conclusions:** Although ERT has a significant effect on enhancing the survival of IOPD patients, it should be associated with meticulous heart-respiratory cares during the first months of treatment and preventing infection especially nosocomial infections.

**Keywords:** Glycogen Storage Disease Type II, Alpha-Glucosidase, ERT, GAA Protein, Inborn Error of Metabolism

## 1. Background

Pompe's Disease (PD) or Glycogen Storage Disease type II (GSDII) is a rare autosomal recessive neuromuscular disorder which arises as the result of deficiency in lysosomal enzyme acid  $\alpha$ -glucosidase (GAA) (1, 2). Pompe patients are not able to decompose the accumulated glycogen in lysosomes. Therefore, glycogen is accumulated in lysosomal vacuoles in various tissues such as smooth muscles, cardiac and skeletal. The accumulation of glycogen disrupts the cell function and causes the cell to grow and the lysosomes to be ruptured (3). The outbreak of Pompe Disease is approximately 1 in every 40000 live births (4). This disease is categorized into two forms of Infantile Onset Pompe disease (IOPD) and Late-Onset Pompe Disease (LOPD) based on the age of outbreak, the organ involved and the rate of the disease's progression (5).

IOPD is of classical and non-classical types. The classical type is a fast progressive disorder which is associated with hypotonia, paresis, cardiomegaly, hepatomegaly, and death in the first year of life following heart-respiratory failure. In the non-classical type, the symptoms appear at the first year of life but the disease proceeds much slower and cardiomyopathy is less severe (3, 6). Complete or near-complete deficiency in lysosomal enzyme acid  $\alpha$ -glucosidase is peculiar to this type of the disease (7).

IOPD patients may also have other symptoms including macroglossia, failure to thrive, and absent deep tendon reflexes (8, 9).

Due to the low prevalence of the disease and the vast range of symptoms, the disease is mostly not diagnosed in time. Thus, it is essential to know more about the natural history of Pompe so that the treatment will be initiated at an appropriate time.

Measuring GAA enzyme activity in cultured fibroblasts of skin and muscle biopsy are two specific standard and reliable diagnostic methods for the diagnosis of this disease (5). However, because of its easiness, the examination of enzyme activity in a blood sample (leukocytes, lymphocytes, or dried blood spot) gradually became one of the common and also reliable techniques for the diagnosis of PD (10).

For a long time, IOPD was incurable and supportive cares such as respiratory protection was the only way to control it. But in 2006, Enzyme Replacement Therapy (ERT) by recombinant human enzyme acid  $\alpha$ -glucosidase (rhGAA) was approved by FDA (11, 12). Of the health benefits of ERT in infants with Pompe, we can refer to the increase of  $\alpha$ -glucosidase activity in skeletal muscle, the improvement of muscle performance and structure, the

reduction in size of the heart, the enhancement of cardiac function, the prevention of respiratory failure, and the increase in years of life in the patients (13). The best results from ERT treatment are achieved when the patient is diagnosed in time and before the outbreak of irreversible damages (9).

## 2. Objectives

In this study, the clinical symptoms of IOPD patients and their outcome after months of ERT were investigated and compared to the results of previous studies.

## 3. Patients and Methods

The study was carried out on IOPD-diagnosed patients in South of Iran. An enzyme assay was executed on dried blood spot from September 2012 onwards for all patients who according to clinical findings, exhibited typical symptoms of IOPD. The experiments were conducted in Metabolic Laboratory of Hamburg University Medical Center. The patients who had both typical symptoms of the disease and enzyme deficiency were put under investigation.

The cases under investigation were fully examined and specially observed in terms of muscular power, cognition, motor development, and cardiac performance. Then, ECG and echocardiography was taken. After obtaining informed consent from the patients, they started to receive ERT 20 mg/kg/2wk, and were followed up for maximum duration of 117 weeks.

## 4. Results

Based on the clinical symptoms and the enzyme assay,

six infants were recognized as IOPD. Characteristics of the patients are listed in Table 1. All these six (100%) patients had left ventricular hypertrophy along with degrees of hypertrophic cardiomyopathy. Four (67%) patients had generalized hypotonia. Hepatomegaly was found in one (17%) patient. The age range for the onset of symptoms was 1 to 7 (average 3.8) months and the age range for the diagnosis of the disease was 2 to 8 (average 4.7) months.

Three patients expired because of severe respiratory infection while they had received 3 or less doses of ERT. One patient suddenly got bradycardia and then cardiorespiratory arrest, and ultimately expired. The cause of cardiorespiratory arrest was not exactly determined. No evidence in favor of anaphylactic shock was detected in the patient. However, he was running a fever from morning; and received the last dose of the medication in a hospital, personnel of which had no previous familiarity with this medication. Therefore, it seems that he was infected with acute cardiorespiratory failure due to an underlying acute respiratory illness.

Until the preparation of this article, the remaining two patients have been followed for 117 and 65 weeks respectively. They are both normal in terms of growth, motor development, and cognition. They have shown a significant improvement in LVH and HCM. One of them had heart failure at the beginning which is now cured. None of them are on a ventilator. Another significant issue is that the two patients who responded finely to the treatment, only had cardiac symptoms at the beginning; while all four patients who in addition to cardiac involvement also suffered from hypotonia, expired. During ERT, no other side effect of Myozyme, such as fever, body pain and allergic reactions were seen in our patients.

**Table 1.** Characteristics of Patients With Infantile Onset Pompe Disease

	Cardiomyopathy	Generalized Hypotonia	Hepatomegaly	Large Tongue	Age at Diagnosis, mo	Age at Start of ERT, mo	Outcome
1	Yes	Yes	No	No	4	None <sup>a</sup>	Dead
2	Yes	Yes	No	No	3	4	Dead
3	Yes	No	No	No	6	6.5	Alive
4	Yes	Yes	No	No	7	7.5	Dead
5	Yes	Yes	Yes	No	5	5.5	Dead
6	Yes	No	No	No	2	3	Alive

<sup>a</sup>This patient expired before receiving the first dose of ERT.

**Table 2.** Trend of Changes in Echocardiographic Characteristics of Patient No 3, Enzyme Replacement therapy Was Started Since 6.5 Months of Age

	4 Months	7 Months	17 Months	22 Months
IVSD, cm	1.03	0.98	0.99	0.67
IVSS, cm	1.1	1.19	1.21	1.01
IVID, cm	2.37	2.95	3.05	2.99
LVID, cm	2.20	2.05	2.16	1.78
LVPWD, cm	0.57	0.67	0.53	1.01
LVPWS, cm	0.85	0.9	0.96	1.04
EF, %	41.7	59.5	57.3	72.6

Abbreviations: EF, ejection fraction; IVSD, intraventricular septum in diastole; IVSS, intraventricular septum in systole; LVIDP, left ventricular internal diameter in diastole; LVIDS, left ventricular internal diameter in systole; LVPWD, left ventricular posterior wall in diastole; LVPWS, left ventricular posterior wall in systole.

## 5. Discussion

ERT with alglucosidase alfa which was approved by FDA in 2006 has the capability to decrease mortality and morbidity in IOPD. Various studies have been conducted on the effectiveness of ERT. A multi-center study on 18 patients with IOPD who received ERT up to 36 months, showed different results.

Their survival rate at age 24 months was 94.4% and at age 36 months it was 72%. Mean left ventricular mass of those patients progressively decreased. Eleven of the 18 patients had significant improvement in motor skills, but other 7 patients were unable to achieve sustained motor gains after 3 years of age (14).

Another study has been performed on 21 IOPD patients who were treated with alglucosidase alfa for about 120 weeks. At the end of the study, 71% of the patients were alive, left ventricular mass improved or remained normal in all of them, and 62% achieved new motor milestones (14).

A new article about different aspects of ERT in IOPD patients has concluded that factors that affect the outcome of IOPD patients include: age at start of ERT, genotype, muscle fiber type and multidisciplinary care (15). However, the results from South of Iran are slightly different. Four out of six (67%) Pompe patients died during the first weeks of the treatment. The reason behind their death was severe respiratory infection; and the cause of another one's death was acute cardiorespiratory collapse during receiving alglucosidase alfa, underlying reason of which was not truly recognized. Only two (33%) patients remained alive, who after 65 and 117 weeks, are perfectly in the age-related normal state in terms of cardiorespiratory and motor performance. Why is the survival rate of IOPD patients in our study poorer than in other studies?

It seems that inattention to infection control skills and multidisciplinary care resulted in death in 3 patients. We did not perform genetic study in some of the patients, therefore, poor survival of our patients can

also be related to their genotype. Thus, it seems that to enhance IOPD patients' survival strict cardiorespiratory care and infection control techniques also must be applied during the first months of ERT. Moreover, special care should be observed not to get nosocomial infections during several hospitalizations in order to receive ERT.

In addition, one of the most important causes of poor response to ERT can be antibody production against the drug. Therefore, according to other studies, it is recommended to determine CRIM negative patients that are highly prone to antibody production, and use immune tolerance induction to diminish the antibody titer and increase the effectiveness of ERT (16, 17).

Six patients were followed up. Two of them who remained alive only had cardiac involvement symptoms at the beginning and did not suffer from generalized hypotonia. However, the four patients who died had both heart muscle involvement and generalized hypotonia right from the beginning. Thus, it is probable that generalized hypotonia worsens the outcome in IOPD patients.

Moreover, since early diagnosis and fast treatment can improve prognosis, it is suggested that a widespread study be conducted to examine the cost-effectiveness of infantile screening for Pompe disease.

In spite of ERT in our patients with IOPD, their survival rate is poorer than in other studies. More attention to infection control skills and multidisciplinary care are needed to improve the outcome of the disease. Additionally, it seems that the patients with generalized hypotonia suffer from a much worse prognosis than the patients who do not show obvious generalized hypotonia.

The most important limitation of this study is the low sample size. According to the rarity of this disease, a multicenter study is needed to get more valuable results.

**Table 3.** Trend of Changes in Echocardiographic Characteristics Patient No 6, Enzyme Replacement Therapy Was Started Since 3 Months of Age

	2 Months	4 Months	6 Months	9 Months	12 Months	22 Months	28 Months
IVSD, cm	0.7	0.7	0.9	0.9	0.81	0.89	0.99
IVSS, cm	0.7	0.8	1.1	0.99	1.24	0.81	0.93
LVID, cm	1.8	2.2	2.2	2.12	2.19	2.03	2.5
LVID, cm	1.2	1.3	1.5	1.28	1.02	1.48	1.44
LVPWD, cm	0.7	0.9	0.7	0.85	0.85	0.6	0.67
LVPWS, cm	0.9	1.2	0.8	0.95	1.17	0.87	0.71
EF, %	69	75	60	67	85	80.5	75.5

Abbreviations: EF, ejection fraction; IVSD, intraventricular septum in diastole; IVSS, intraventricular septum in systole; LVID, left ventricular internal diameter in diastole; LVIDS, left ventricular internal diameter in systole; LVPWD, left ventricular posterior wall in diastole; LVPWS, left ventricular posterior wall in systole.

## Acknowledgments

We would like to thank Metabolic Laboratory of Ham-burg University Medical Center for accurate execution of Enzyme Assay tests. Also we should emphasize that there is no conflict of interest in this article.

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