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Kliniczny, ekonomiczny i społeczny wymiar choroby Pompego w Polsce

Direct and indirect costs of Pompe disease

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Streszczenie

Wstęp. Choroba Pompego jest rzadką lizosomalną chorobą spichrzeniową spowodowaną brakiem enzymu alfa glukozydazy. Celem tego badania było oszacowanie kosztów bezpośrednich oraz pośrednich choroby Pompego. Koszty bezpośrednie dzieli się na: medyczne i niemedyczne. Koszty pośrednie odnoszą się do zmniejszenia produktywności, zaliczamy do nich np. koszty pobytu na zwolnieniu lekarskim, koszty utraconego czasu czy utraconych zarobków. ***Materiały i metody.*** Koszty bezpośrednie i pośrednie określono na podstawie badania przy użyciu kwestionariusza pomiaru kosztów specyficznego dla choroby Pompego oraz uzupełniającego badania ankietowego dotyczącego leczenia zastępczą terapią enzymatyczną stworzonych na potrzeby pracy. Analiza została przeprowadzona w dwuletnim horyzoncie czasowym. W tym badaniu specjalną uwagę poświęcono poziomowi współpłacenia przez pacjenta oraz Narodowy Fundusz Zdrowia. Status refundacyjny leczenia chorób rzadkich został również omówiony w tym artykule. ***Wyniki.*** Koszty pośrednie stanowią 3% całkowitych kosztów (wynoszą dla całej populacji 1 447 549.6 PLN w dwuletnim horyzoncie czasowym). Największą składową kosztów pośrednich stanowiły utracone zarobki członków rodziny z powodu konieczności opieki nad chorym. Bezpośrednie koszty medyczne stanowiły 96% kosztów całkowitych (wynoszą dla całej populacji 44 242 541.6 PLN w dwuletnim horyzoncie czasowym). *(Farm Współ 2014; 7: 149-155)*

Summary

Introduction. Pompe disease is a rare lysosomal glycogen storage disease caused by alpha-glucosidase enzyme deficiency. The aim of this study is to estimate the direct and indirect costs of Pompe disease. Direct costs are divided into medical and non-medical costs. Indirect costs are related to decreased productivity resulting from medical leaves, lost time and income. ***Material and methods.*** Costs were estimated based on a questionnaire measuring costs specific for this disease and a survey concerning the enzyme replacement therapy created for this research. The analysis was done over a 2-year time span. In the study special emphasis was put on the patient's and National Health Fund's participation. The reimbursement status of rare diseases' treatment in Poland is also discussed in this article. ***Results.*** Indirect costs constituted 3% of the total costs (amounted to 1 447 549.6 PLN for the whole population in the period of 2 years). The greatest components were the costs of lost income by family members taking care of the patient. 96% of the total direct costs were direct medical costs (amounted to 44 242 541.6 PLN for the whole population in the period of 2 years). *(Farm Współ 2014; 7: 149-155)*

Key words: orphan disease, pompe disease, lysosomal storage disease (LSD), direct and indirect costs, reimbursement of rare disease, enzyme replacement therapy

Introduction

Pompe is a rare and debilitating disease associated with a high medical and economic impact. Although the number of Pompe patients is very low, a lot of discussion has arisen throughout Europe recently over the costs and affordability of the available treatments, and also for rare diseases in general. Treatment options are usually very expensive, and costs associated with rare diseases such as Pompe are taking up an increasingly large part of healthcare budgets. The economic burden of a rare disease on its own would be manageable, if it had not been for the sheer number of rare diseases (There are 6000-8000 known disorders and this number is increasing. It is estimated that 5-8% of society will suffer from rare disorders [1]) and for this reason it makes the economic impact of the treatment a hot topic among healthcare professionals and policy makers.

Objective

The objective of this study is:

- to familiarize the reader with clinical aspects of Pompe disease,
- to estimate the costs associated with Pompe disease in Poland
- to present an overview of the reimbursement status of rare diseases' treatment in Poland

Brief description of Pompe disease

Pompe disease is a rare lysosomal glycogen storage disease caused by alpha-glucosidase enzyme deficiency. People suffering from Pompe disease have an innate 1,4-alpha glucosidase deficiency (GAA – *acid alpha-glucosidase*) [2]. The gene located at the distal end of 17 (q25) chromosome is responsible for the disorder. At present there are over 200 known different mutations of this gene. The most common is c.-32 – 13T> G mutation, which occurs in 2 out of 3 patients with late onset disease [3]. The symptoms can be first observed at any age, from infancy through puberty until adulthood. The onsets can be divided into three major stages:

Infantile onset – the first symptoms are visible until the age of one

Juvenile onset – the first symptoms can be observed between infancy and puberty

Late onset – the first symptoms appear after twenty.

The time of onset is related to maltase activity. It has been proven that enzyme activity in infants is < 1%, in juvenile < 10% while in adults does not exceed 40%. The higher the grade of enzyme deficiency, the more glycogen is stored in lysosomes. This is especially visible in tissues which need a lot of energy from degrading glycogen, e. g. the heart muscle. Lack of the enzyme can lead to megalocardia in children. Infantile onset causes multiple disorders such as weak muscle tone, problems with breathing, sucking and swallowing, enlargement of organs such as heart, liver and tongue, which can lead to heart and respiratory failure [2]. Pompe is not associated with any mental handicaps in children or adults. It is much easier to diagnose Pompe in infants as maltase deficiency leads to the first symptoms within the first six months after birth and the disease progresses rapidly, often leading to death of the child. Late onset disease is slower and milder, with the age range in which first symptoms appear varying from puberty to sixty. The first symptoms are weakened muscles in leg and hip, leading to a rocking leg motion, a slow walk and stumbling, glycogen storage in the muscles of the back and pelvis causing difficulty maintaining balance, sitting and keeping an upright position, as well as cramps and back bone problems (scoliosis, lordosis and kyphosis). As a result, thorax and diaphragm muscles deteriorate leading to breathing problems. Breathing is shallow and carbon dioxide accumulates in blood which causes difficulty concentrating, shortness of breath, lack of appetite or great hunger, anxiety, morning headache, insufficient sneezing and coughing, needing to use neck and backbone muscles to facilitate breathing, problems with sleeping and frequent nightmares, causing fatigue and sleepiness during the day. The most serious complications of thorax and diaphragm muscle weakening is hyperventilation during the sleep, which can lead to metabolic acidosis and respiratory failure. Additionally, as the throat and tongue cease to work sufficiently, there is a possibility of apnea. Patients suffering from Pompe disease have difficulty expectorating sputum, leading to respiratory tract diseases. In patients with acute respiratory failure the only treatment appears to be tracheotomy-intubation of the respiratory tract to supply the lungs with oxygen while avoiding nose, throat and larynx. Patients at more advanced stages of disease might suffer from difficulty eating, swallowing and digesting and often are bound to a wheelchair.

The estimated frequency of Pompe is one in 40.000 births. In Poland there are 20 patients with Pompe disease, however, according to Institute of Psychiatry and Neurology estimate there are actually about 25-35 sufferers. According to data supplied by the Institute

there are about 3 to 5 children born with insufficient acid α-glucosidase every 10 years [3,4].

In infants, diagnosis is easier as the first symptoms appear quickly and are easily visible. There are a number of examinations and lab tests such as skin and muscle biopsy, blood tests, electromyography and electrocardiogram.

Medical care for Pompe patients requires the cooperation of various specialists such as the pediatrician, neurologist, cardiologist, pulmonologist, gastroenterologist, orthopedist, geneticist, social worker, psychologist and physiotherapist. Some hospitals provide a holistic approach, however, in many cases patients have to instruct medical personnel how to treat them as the knowledge of this rare disease is still insufficient.

At present the only treatment available for Pompe and other lysosomal storage diseases is an enzyme replacement therapy (ERT). It involves giving patients exogenous enzyme produced by DNA recombination technology, using Chinese hamster ovary cells (CHO) and the milk of transgenic rabbits [3]. The Committee for Medicinal Products for Human Use (CHMP) has allowed the drug containing the active substance alpha alglucosidase (rhGAA), called Myozyme®, to be launched onto the market in 2006 [5,6].

Alpha alglucosidase is administered intravenously at regular intervals. The dosage is 20 mg/kg of body mass once every 2 weeks [5]. It has been shown that 90-95% rhGAA reaches the liver and a smaller percentage reaches the heart and skeletal muscles.

In order to assess the clinical efficiency of Myozyme® the patients were subjected to randomized, open, multicenter and international researches [6]. It was discovered that using alpha alglucosidase at an early stage of Pompe disease causes regression of cardiomyopathy which extends patients' lives, improves motoric abilities (the effect on skeletal muscles varies), decreases the amount of glycogen in the quadriceps and enables patients to do without artificial ventilation (in those who before the treatment did not need ventilation).

The first results of one-centered clinical trial on patients with late onset disease (2010) showed effectiveness of the drug in improving skeleton and respiratory muscle activity increased FCV – (*forced vital capacity)* as well as improving motoric muscles (based on a walking distance test) [6].

Side effects are mostly mild and moderate and are strictly connected with the infusion. In some patients there were anaphylactic reactions. In order to decrease (eliminate) the risk of hypersensitivity to the drug patients are given antihistaminic and (or) anti-inflammatory drugs and/or corticosteroids before the infusion [5].

The biggest benefits of using alpha alglucosidase are observed in early onset patients when the treatment was started before irreversible damage to muscles could occur [6]. However, in babies with very high enzyme deficiency suffering also from cardio-respiratory complications, the treatment results are not that impressive.

Myozyme® can stop disease progression, improves quality of life and extends life expectancy, but does not reverse massive destruction of muscle tissue, making early diagnosis and immediate treatment essential [7, 5].

Economic aspects of Pompe disease

Reimbursement situation in Poland

All applications regarding the financing of orphan drugs in Poland are sent to the Ministry of Health and then transferred to Health Technology Assessment Agency (AOTM). The Agency has to evaluate the drug cost-effectiveness and issues a recommendation which helps the Ministry to make a decision on the reimbursement of the orphan drug therapy. The Rare Disease Working Group was established in Poland in 2008 and consists of representatives from the Ministry of Health, National Health Fund, Health Technology Assessment Agency and patient associations [8].

In Poland there are 5 ultra-rare diseases treated within therapeutic health programs supervised by the National Health Fund: Gaucher's syndrome (treatment with imiglucerase, Cerezyme®); Hurler's disease/Mucopolysaccharydosis type I (treatment with laronidase, Aldurazyme®); Pompe disease (treatment with alglucosidase alfa, Myozyme®); Hunter's disease/Mucopolisaccharydosis type II (treatment with idursulfasa, Elaprase®); Maroteaux-Lamy syndrome/ Mucopolisaccharydosis type VI (treatment with galsulfasa, Naglazyme®)[9].

A drug program entitles patients to free access to the drug, free diagnostic examinations and other medical services necessary to stop the development of the disease and to improve the health condition and quality of life, and to limit possible complications connected with the disease. NHF finances health therapeutic programs which include very expensive technologies used by a very small population. For Pompe disease,

Table 1. Reimbursement status of Myozyme used in Pompe disease

State	Reimbursement status	Patients treated early onset (late onset)
Austria	Reimbursed	11 (10)
Belgium	Reimbursed	21 (21)
Bulgaria	None	0
Cyprus	None	0
Croatia	Individual application	1
Czech Republic	Individual application	1 (1)
Denmark	Reimbursed	6 (3)
Esthonia	No patients	
Finland	Reimbursed	1 (1)
France	Infantile onset is reimbursed, late onset – individual application	71 (67)
Greece	Individual application	8 (7)
Spain	Reimbursed	26 (23)
The Netherlands	Reimbursed	84 (75)
Ireland	Individual application	1
Lithuania	None	0
Luxembourg	Refundacja	1 (1)
Latvia	None	0
Malta	None	0
Germany	Reimbursed	130 (120)
Norway	Reimbursed	1 (1)
Portugal	Reimbursed	11 (1)
Romania	Not reimbursed	1 (1)
Slovakia	No patients	0
Slovenia	Individual application	1
Switzerland	Individual application	6 (5)
Sweden	Reimbursed	4 (3)
Great Britain	Reimbursed	68 (61)
Hungary	Individual application	6 (5)
Italia	Reimbursed	75 (61)

only infant onset disease medication is reimbursed in Poland. Treatment is also reimbursed for those with late onset who already started Myozyme® treatment earlier. The following table shows the reimbursement of Myozyme® in Europe.

Methods of estimating the costs of Pompe disease in Poland

Direct costs are divided into medical and non-medical costs. All costs directly associated with the treatment such as specialist consultations, nursing, rehabilitation, hospital treatment, surgeries, diagnosis, diet and drug purchases are considered direct medical costs. Transport costs, elimination of architectural barriers (e.g. adjustment of house and vehicle), child care are all direct non-medical costs.

Indirect costs are related to decreased productivity resulting from medical leave, lost time or income (absenteeism of patients or care givers) [10, 11].

The population examined in this study was representative - it comprised of 80% (N=16) of all Pompe patients from all over Poland. The most important characteristics of the population are: long and progressive course of illness, and being a small and heterogeneous

group of patients, which at the same time are the very factors which make it difficult to estimate costs.

Direct and indirect costs were estimated based on a questionnaire (consisting of 108 questions), measuring costs specific for Pompe disease, and a survey concerning the enzyme replacement therapy, especially created for this study.

The direct costs of Pompe disease were calculated from the perspective of the patient, the society and the public health care system payer (National Health Fund). Special attention was paid to the level of co-participation in costs borne by the National Health Fund and patients.

The human capital approach methodology was used to measure the indirect costs, including absence from work due to the illness, lost time and salaries of family members taking care of the patients. The analysis was done over a 2-year time span.

Direct costs

Direct medical costs borne by the public payer to finance the purchase of the enzyme replacement therapy depend on:

- The number of Pompe disease patients
- The number of reimbursed patient treatments by the NHF or a pharmaceutical company
- A patient's body mass
- Price of the medicinal product
- The time and frequency of treatment (taking into consideration breaks in treatments).

Twelve out of fifteen questioned patients suffering from Pompe disease stated to being treated with ERT reimbursed by NHF, two were treated with ERT financed by the pharmaceutical company, and one was not treated with ERT at all.

Further analysis involved the twelve patients receiving ERT financed by the public.

Table 2. Average cost borne by the National Health Fund per Pompe patient over a two-year span

Cost type	Average cost born by National Health Fund per patient (in PLN)
Clinical treatment due to Pompe disease (excluding enzyme replacement therapy)	892.50
Tracheotomy	162.00
Muscle and skin biopsy	337.50
Yearly fixed cost of diagnosis	3.723
Specialist consultations	525

Direct non-medical costs

The data on direct non-medical costs were collected based on a questionnaire measuring specific costs of Pompe disease. Three types of costs were taken into account to assess direct non-medical costs, transportation, elimination of architectural barriers (e.g. adjustment of the house and vehicle) and the caregiver's assistance.

Table.3 Costs of products and devices purchased borne by patients, National Health Fund and the public

Medical product or device	Cost per piece born by a patient PLN	Cost per piece born by National Health Fund PLN	Number of pieces PLN	Cost from the public perspective(taking into consideration the number of medical devices and products) per patient in a two-year span-in PLN
Wheelchair	1200	1800	4	12 000 [75]
Splint for stabilizing a knee joint	30	80	1	830 [51,87]
Respirator for home use	25 762	Not reimbursed	2	51524 [3 220,25]
Bi-level device	5 480,72	1 470	4	27 802,88 [1 737,68]
Saliva suction device	1 800	Not reimbursed	4	7 200 [450]
Total cost of all devices	85 476,88	13 880	-	99356,88 [6 209,805]
Average cost per patient in a two year span	5 342,30	867,50	-	6 209,80

Indirect costs

Indirect costs were estimated based on the human capital approach (HCA). According to this method society loses an amount of money which is equal to the potential productivity of the individual and informal providers of care (in the case of Pompe disease most often family members, taking care of sick children) during the whole period of illness. It has been assumed that the average monthly remuneration amounts to 3, 103 PLN (data from 2009) and the number of working days per month is 20. The results of the research based on the questionnaire designed for Pompe disease were used to assess indirect costs.

Results:

Direct costs

The estimated total direct medical costs of the whole Pompe disease population in Poland in a two-year time span (March 2008 to March 2010) amounted to 44 078 002.4 (per patient amounted to 2 189 702. 4 PLN). The enzyme replacement therapy is the main determinant of the direct medical costs and constitutes 99% of the total medical costs.

The costs borne in connection with the diagnosis of the whole population of patients (16 people) in a two-year span amounted to 59 568 PLN (cost borne by NHF for diagnosis in therapeutic health program).

NHF bears the costs connected with diagnosis in the Pompe disease therapeutic program. The annual fixed amount of money spent on diagnosis is 36.5 points (1 point – 51PLN) [7]. The cost of the diagnosis of the whole Pompe disease population under consideration (16 people) in a two year time span amounts to 59 568 PLN. All the patients underwent a biopsy in order to diagnose Pompe disease (87.5%-muscle biopsy, 25% - skin biopsy).

As a result of disease progression some patients had to undergo tracheotomy in order to ventilate the lungs. The patients replace the tube every month, which amounts to 24 procedures of this kind during 2 years. Tube replacement has been estimated to amount to 12 points. The total cost borne by NHF is equal to 2 592 PLN.

Two thirds of patients required orthopedic treatment and one third was taken to the emergency in a hospital. The above mentioned treatments cost 14 280 PLN in total.

The average cost of specialist consultations amounted to 350 PLN per person monthly, which is mostly financed by NHF and totals 8 400 PLN in a two year span.

Direct non-medical costs

The highest cost in non-medical costs is the one connected with elimination of architectural barriers, constituting to 43%, transport 39% and nurse service 18%. The direct non-medical costs per patient in the period of 2 years amounted to 8 226.96 PLN.

Indirect costs

Total direct costs were 72 377 PLN per patient over 2 years, divided into the following categories

1. lost income due to absence from work because of enzyme replacement therapy (given every two weeks which means a one-day stay in hospital - both of patients and caregiver in case of children) (7 447 PLN per patient / 2 years)
2. lost income due to absence from work in connection with Pompe disease and related disease (does not include enzyme replacement therapy) (815 PLN per patient / 2 years)
3. lost income due to retiring in connection with Pompe disease (23 273 PLN per patient / 2 years)
4. lost income of family members having to take care of the patient (32 582 PLN per patient / 2 years)

85% of questioned patients responded they needed help in everyday life. However, only one person hired somebody to help. The others were taken care of by family members who gave up their jobs, generating costs amounting to 32.582 PLN (per patient/ 2 years).

The average monthly patients' salary amounted to 1875 PLN before diagnosis, and 1500 PLN after.

Indirect costs constituted 3% of the total costs. The greatest cost component was the cost of income lost by family members taking care of the patient.

Table 4. Total direct and indirect costs per patient/2 years and for the whole Pompe disease population

Cost category	Costs per patient per 2 years (PLN)	Costs of whole Pompe disease population per 2 years (PLN)
Direct medical	2 203 900	44 078 022
Direct non-medical	8 227	164 539
Direct medical and non-medical	2 212 127	44 242 542
Indirect	72 377	1 447 550

Discussion:

Providing patients with an early access to enzyme replacement therapy leads to the lowering of future indirect and direct costs. The results are a reduced number of patients needing disability pensions, a lowered cost for medical equipment, and higher productivity of those patients that are able to work. Patients who receive the treatment relatively early are able to work and actively participate in society (depending on the time of disease onset) and thus keep a certain quality of life. Early diagnosis is therefore essential, and is this why education and awareness of health professionals is of the utmost importance.

Medical costs associated with Pompe patients indeed are relatively high, and any discussion on the affordability of treatment is well justified. However, the fact remains that the number of patients born with Pompe disease is very low, and the total economic burden of this disease on the healthcare budget is only marginal.

In general, it seems there is a need to introduce an atypical, specific approach for rare diseases in Health Technology Assessment, reimbursement, and the registration processes of medicines. Patients with debilitating diseases should have access to the best methods of treatment as soon as possible. Shortening the timelines for medicine approvals (so called "conditional approvals") could be a large step forward. Also, a collective European approach to dealing with the costs of rare diseases could prove to be beneficial.

In the end, the discussion boils down to a question of ethics: why could we, as human beings, not afford to treat those patients with a rare and hereditary disease, but on the other hand we are willing to treat millions who have a self-chosen lifestyle directly contributing to their condition. Solidarity with the minorities who are born with a rare disease would show the real meaning of civilization, and focusing on the actual major components of healthcare systems and its inefficiencies in general, will prove much more rewarding.

Conflict of interest
None

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