SURVIVAL, QUALITY OF LIFE AND EFFECTS OF ENZYME REPLACEMENT THERAPY IN ADULTS WITH POMPE DISEASE

Outcomes of the IPA / Erasmus MC Pompe Survey

Deniz Güngör

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Overleving, kwaliteit van leven en effecten van enzymtherapie bij volwassen patiënten met de ziekte van Pompe

Resultaten van de IPA / Erasmus MC Pompe Survey

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Voor mijn ouders

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Chapter 1

Pompe Disease

Pompe disease, or glycogen storage disorder type II, is a rare inherited metabolic disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase. This results in accumulation of glycogen in cells throughout the body, particularly muscle cells. The disease presents with (progressive) muscle weakness and can hence be categorized as a lysosomal storage disorder, a glycogen storage disorder and also a neuromuscular disorder.

Pompe disease was the first neuromuscular disorder for which treatment became available, and the development of enzyme replacement therapy for Pompe disease has played a fundamental role in the development of therapies for other rare diseases including neuromuscular and lysosomal storage disorders.

This introductory chapter reviews the history, pathophysiology and clinical characteristics of Pompe disease and provides an overview on the effects of enzyme replacement therapy.

History

"Het hart was geweldig groot en lag met een halve handpalmgroot gedeelte tegen den voorsten borstwand….Wat wij wel zagen was een netwerk van ronde tot ovale of meer langgerekte mazen, waarin dikwijls een kern lag, al dan niet in het midden der holte of aan den kant…. Het bleek namelijk, dat in alle organen, voor zoover nog aanwezig, zich de groote hoeveelheden glycogeen bevonden."

This Dutch passage from the manuscript "*Over idiopathische hypertrofie van het hart*" ("About hypertrophic cardiomyopathy") by the Dutch pathologist Johannes Cassianus Pompe (1901-1945) (Figure 1), describes the heart as being enormous in an infant with Pompe disease "… covering a span of half a palm of a hand".[1]

J.C. Pompe is best known for his discovery and description of a disease that is now known as Pompe disease. In 1932, he described a case of a 7-month-old girl with cardiomegaly and large amounts of vacuolar glycogen storage in all organs. The child was initially thought to have died from pneumonia. He realised that the pathologic findings had something to do with a defect in the child's glycogen metabolism and pointed to other cases of glycogen storage in a number of patients with liver and kidney enlargement, earlier described by von Gierke in 1929. In the same year, 1932, two similar cases of hypertrophic cardiomyopathy were described independently by Putschar and Bisschoff and other reports followed in subsequent years.[2,3] The name Pompe became an eponym for what was later described as glycogen storage disease type II. Sadly, Dr Pompe could not follow up on his important observations; he was executed during World War II for his participation in the Dutch resistance movement.[4]

Figure 1. Johannes Cassianus Pompe. This photo was taken from Zeidman. Johannes C. Pompe, MD, Hero of neuroscience: The man behind the syndrome. *Muscle Nerve* 2012;46:134-8

In the decades following the discovery of the vacuolar glycogen storage in Pompe disease, other developments in the field of cell biology and biochemistry led to a better understanding of the glycogen metabolism and a description of glycogen storage disorders. In 1952 Gerty Cori and her husband Carl discovered the normal metabolic pathway of glycogen.[5] Based on this they proposed a new class of disorders that were all based on defects in glycogenolysis; they called these diseases 'glycogenoses', or glycogen storage disorders, and ranked Pompe disease as number 2.

Also in the fifties, Christian De Duve, a cell biologist from Belgium described the lysosome, a discovery for which he ultimately received the Nobel Prize in Physiology or Medicine in 1974.[6] Lysosomes are subcellular membrane-bound organelles that contain an array of enzymes capable of breaking down all types of biological polymers -proteins, nucleic acids, carbohydrates, and lipids. Lysosomes were seen as the cell's digestive system degrading materials taken up from outside the cell (heterophagy or endocytosis) as well as components of the cell itself (autophagy).

A few years later, in 1963, Henri-Géry Hers identified acid a-glucosidase as one of the many lysosomal enzymes and reported the absence of acid a-glucosidase in tissue samples of five patients suffering from Pompe disease.[7] Thus, he postulated that lysosomal glycogen storage in Pompe disease was caused by the deficiency of acid a-glucosidase and thereby established the concept of lysosomal storage diseases being caused by lysosomal enzyme deficiencies. World-wide this was the first finding of an inherited lysosomal enzyme deficiency. Shortly thereafter, other lysosomal enzyme deficiencies were discovered as the primary cause of storage diseases that had been described decades earlier on the basis of clinical and chemical findings. Following the first report by Hers about acid α-glucosidase deficiency in Pompe disease, the association of lysosomal glycogen storage with acid α-glucosidase deficiency was observed in patients of different ages presenting with progressive muscle weakness, but without cardiomyopathy.[7,8] This led to the recognition of Pompe disease as a clinical spectrum, whereby Andrew Engel introduced the name acid maltase deficiency to make a distinction between patients with onset of symptoms in childhood or adult hood and the infants earlier described by dr. Pompe.[9]

Pompe disease not only played a key role in the basic understanding of the pathophysiology of lysosomal storage diseases (LSDs) but was also paramount for the conception of enzyme replacement therapy in LSDs. A first attempt at enzyme replacement therapy was reported by Baudhuin and co-workers in 1964,[10] who administered a crude extract of the fungus Aspergillus Niger containing acid α-glucosidase to a patient with Pompe disease. Despite this attempt not being successful many new trials were performed in the 1970s and 80s in which enzyme preparations purified from human sources were supplied to patients with Pompe disease, as well as to patients with several other lysosomal storage disorders like Fabry disease and Gaucher disease.[11-13] The results of all these first, experimental, attempts at enzyme replacement therapy were disappointing. Finally in 1990, Roscoe Brady and co-workers succeeded to treat patients with Gaucher disease type 1 by intravenous administration of mannose enriched glucocerebrosidase purified from human placenta.[14]

The first important milestone on the way to enzyme replacement therapy in Pompe disease was the evidence for mannose 6-phosphate mediated uptake of acid α-glucosidase by cultured fibroblasts and muscle cells of patients with Pompe disease.[15-18] The lysosomal glycogen storage was corrected within days. The enzyme used in these experiments was acid α-glucosidase from human urine and bovine testis. Uptake of the latter enzyme by heart and skeletal muscle of mice was demonstrated too.[19] Mannose 6-phosphate receptor mediated enzyme replacement therapy appeared an option for the treatment of other LSDs, like Pompe disease, but enzymes with the proper characteristics could not be extracted from human placenta. It was not until the genes of the various lysosomal enzymes had been cloned that large-scale production of recombinant human enzymes could be realized. Eventually, these efforts led to registered enzyme therapies for Gaucher disease, Fabry disease, MPS I, II, VI and Pompe disease.[13]

After the cloning of the human acid α-glucosidase gene (GAA*)* in 1988 recombinant human enzyme became available. In the following years, trials of enzyme replacement therapy in acid α-glucosidase deficient knockout mice and quail were started using enzyme produced in milk of transgenic mice and rabbits, as well as in Chinese hamster ovary (CHO) cells.[20-25] Finally, in 2006 after completion of successful clinical trials in humans, the application of alglucosidase alfa (Myozyme) for long term enzyme replacement therapy in patients with diagnosis of Pompe disease was approved by the USA Federal Drug Administration (FDA) and the European Drug Agency (EMA).

Clinical manifestations and spectrum

Pompe disease can manifest at any age, with varying symptoms leading to a truly continuous spectrum of disease phenotypes.[26,27] Classic infantile Pompe disease is situated at the very severe end of the spectrum and has a clearly defined disease course.[1,28,29] Other less severe forms of the disease can have onset varying from infancy to late adulthood.[30,31] The level of residual acid α-glucosidase activity resulting from different mutations and combinations of mutant alleles determines, to a certain extent, the clinical phenotype.

In medical practice and in the literature, the terminology for different subtypes of Pompe disease is not well standardized and can be confusing. In my thesis, I will adhere to the use of 'classic infantile' Pompe disease for all cases of infantile-onset Pompe disease with cardiomyopathy, as described by Pompe and Putschar in 1932, and I will use the term 'non-classic' Pompe disease for all other clinical variants.

Classic infantile Pompe Disease

Patients with classic infantile Pompe disease have virtually no residual acid α-glucosidase activity. These infants usually present within the first months of life, at a median age of 1.6 to 2.0 months.[28,29] Untreated, they rarely live beyond the first year of life and have a median life expectancy of 6 to 8 months.[32,33] A persistent and rapidly progressive hypertrophic cardiomyopathy is one of the hallmarks of classic infantile Pompe disease and one of the main causes of death.[34,35] These babies present as 'floppy infants', with failure to thrive and feeding difficulties. Motor development is delayed and major developmental milestones are usually not reached, while respiratory muscle weakness is compounded by recurrent respiratory infections.[26] More recent studies have also revealed hearing loss, speech difficulties, and facial muscle weakness as part of the symptoms of classic infantile Pompe disease.[36-38]

Non-classic Pompe Disease – children and adults

Non-classic Pompe disease comprises all other forms of the disease. As opposed to classic infantile Pompe patients, this group of patients does have some residual acid α-glucosidase activity and can manifest at any age between birth and adulthood. Patients present with

symptoms predominantly related to skeletal and respiratory muscle weakness, and generally do not have cardiac involvement.[9,26,30,39]

Children diagnosed with non-classic Pompe disease comprise a heterogeneous group of patients. Patients can have either a rapid or a more slowly deteriorating course. The heart is sporadically affected, but in contrast to the classic infantile patients this involvement is usually not life threatening. Muscle weakness is a dominating feature. Pulmonary infections followed by respiratory insufficiency are the main causes of death. The disease course seems to be particularly serious in a subset of children with symptom onset under the age of 15, who require intensive respiratory ambulatory and nutritional support at a young age.[33,40]

Patients diagnosed in adulthood are considered to have a milder – but also relentlessly progressive – variant of the disorder. Even in this subgroup the pace of disease progression can vary tremendously. Adult patients generally do not have cardiac involvement. Their main symptoms are those resulting from skeletal and respiratory muscle weakness, which ultimately can lead to wheelchair and respirator dependency. Diagnosis is often made several years, or even decades, after symptoms have started. Some patients may in retrospect have had symptoms as early as in childhood.

In both children and adults with Pompe disease, weakness of limb girdle muscles leads to difficulty with walking, climbing stairs, and rising from the floor.[39,41-43] Eventually, ambulation is lost. Weakened spinal muscles can further cause lordosis, kyphosis, or scoliosis.[44] Impaired respiratory muscle strength can lead to sleep-disordered breathing and respiratory failure.[45-47] Next to respiratory insufficiency, aneurysms due to glycogen accumulation in vascular smooth-muscle tissue have been described as a potential life threatening feature in adults.[42] Another important symptom is fatigue,[48] which has been described as being experienced by all patients irrespective of the severity of their disease.[48] Pain is also frequently mentioned by patients although this has not been described in detail in the literature. Less familiar features described in adults are ptosis, bulbar muscle weakness and scapular winging.[43,49-53] In general, the outcome and course of the disease is difficult to predict because the disease course is variable, even within families.[54,55] Within 10-15 years after diagnosis, about 50% of patients become wheelchair bound and a similar percentage ventilator dependent.[40] These percentages will continue to rise with further years passing.

Pathogenesis and pathophysiology

Pompe disease is characterized by a total or partial deficiency of the lysosomal enzyme acid α-glucosidase, which is needed for the breakdown of glycogen that has entered the lysosome through autophagy. Acid α-glucosidase hydrolyses the α-1,4 and α-1,6 glycosidic linkages in glycogen starting from the non-reducing ends (Figure 2).[56] Deficiency of the enzyme leads to continuous accumulation of lysosomal glycogen, which in turn can cause lysosomes to swell, to lose their function, and to rupture resulting in cellular damage (Figure 3). Lysosomal glycogen

storage also affects autophagy, which contributes substantially to the pathophysiology. Cellular damage can be seen in all cells of the body but is most prominent in the muscle cells.[6,7,27,57,58]

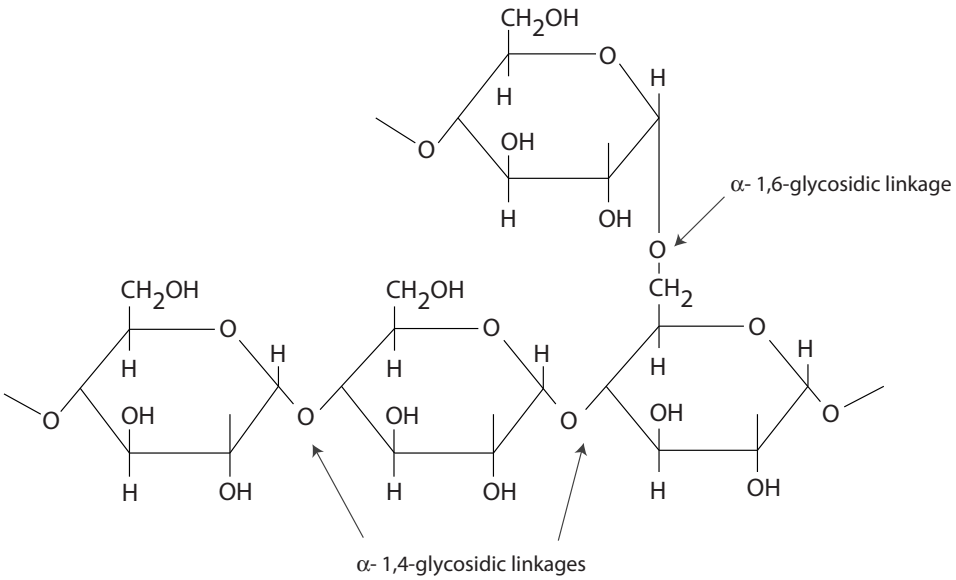

Figure 2. Glycogen degradation. Acid α-glucosidase hydrolyzes the alpha -1,4 and alpha -1,6 linkages in glycogen, maltose and isomaltose and is required for the degradation of 1-3% of cellular glycogen.

The exact mechanism through which muscle damage occurs remains largely unknown. One suggested pathway of muscle damage and wasting involves increased tissue breakdown by autolytic enzymes released from ruptured lysosomes. Another hypothesis is that glycogen-filled lysosomes and clusters of non-contractile material disturb the myofibrillar ordering and thus hamper the transmission of force in the muscle cells. Abnormal macro-autophagy, possibly caused by loss of lysosomal function, also plays a role in the pathogenesis of Pompe disease.[59-64]

Diagnosis

Patients suspected of having Pompe disease will generally first undergo physical examination, laboratory measurements (CK, ALAT, ASAT, LDH), imaging (X-ray), organ function tests (cardiac and pulmonary function), and electromyography (non-specific myopathic activity). The diagnosis of Pompe disease is usually made based on demonstrating the acid α-glucosidase deficiency.

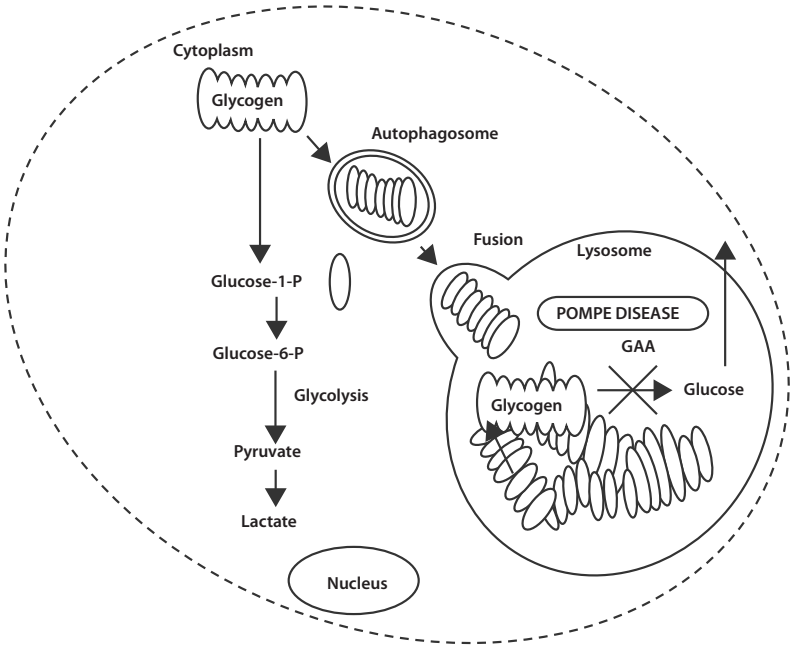

Figure 3. Pathways of glycogen metabolism and effect of GAA deficiency. Acid α-glucosidase (GAA) is responsible for the break-down of glycogen to glucose in the lysosomes. When the enzyme is absent or deficient, glycogen accumulates in the lysosomes. It is not clear how glycogen is transported from the cytoplasm to the lysosomes. If this transport involves the delivery of glycogen by autophagosomes, then suppression of autophagy would reduce lysosomal import and decrease the amount of lysosomal glycogen. The degradation of the cytoplasmic glycogen would proceed unaffected. This figure was adapted from Raben et al. Autophagy and mitochondria in Pompe disease: nothing is so new as what has long been forgotten. *Am J Med Genet C Semin Med Genet* 2012;160:13-21.

Acid α-glucosidase activity can be determined in skin fibroblasts, muscle tissue, lymphocytes, leukocytes, dried blood spots, and amniotic cells or chorionic villi. The material of choice for diagnosing Pompe disease is fibroblasts obtained from a skin biopsy.[26] The assay in fibroblasts is very sensitive, so that residual activities in the order of 2% of average normal can be measured accurately.[65] While the measurement of enzyme activity in leukocytes and lymphocytes has for long been unreliable, new and reliable tests are now available for diagnosing Pompe disease in leukocytes and lymphocytes.[66,67] Muscle biopsies are usually not merely used for measuring the acid α-glucosidase activity because of the invasiveness of the procedure. Moreover, the α-glucosidase activity in the muscle is relatively low and hence difficult to assess. Muscle biopsies, however, do provide the opportunity to assess pathological changes through the use of light and electron microscopy.[68-70]

Recently, new diagnostic techniques have been introduced that neither require muscle biopsies or skin fibroblasts, nor leukocytes to measure GAA activity. Enzyme testing now can be performed in dried bloodspots using either tandem mass spectrometry or fluorimetric procedures, basically with the idea to apply them in newborn screening, but also as a first-line diagnostic procedure in situations where it is difficult to obtain or transport blood samples or tissue specimens. The development of multiplex systems that can measure the activity of several lysosomal enzymes simultaneously, is an exciting new development that makes neonatal screening possible and affordable.[26,71-76]

Having demonstrated acid α-glucosidase deficiency in either leukocytes or fibroblasts the diagnosis is in fact completed, but is at present usually followed by DNA analysis to facilitate family counselling and prenatal testing.[26]

Genotype-phenotype correlation

The enzyme deficiency in Pompe disease is caused by mutations in the GAA gene that codes for acid α-glucosidase (often abbreviated as GAA). In 1979 this gene was traced to chromosome 17 (location 17q25.3) and was later cloned and shown to contain 19 coding exons.[77-79] Pompe disease has an autosomal recessive mode of inheritance. Most patients are compound heterozygotes meaning that they have inherited two different mutations each located on another GAA allele. To date, the number of GAA sequence variations exceeds 400, 70% of which is pathogenic (see www.pompecenter.nl).

The most frequently reported mutation in Pompe disease is c.-32-13T>G. It is the most common mutation among Caucasians and is located in intron 1, just ahead of exon 2 containing the start codon. The nucleotide change causes aberrant splicing of the GAA messenger in 80%-90% of the splicing events and the same percentage of deficient acid α-glucosidase synthesis. Almost all patients carrying the c.-32-13T>G mutation are compound heterozygotes and have a far more severe mutation on their other GAA allele. They all have a substantial level of residual acid α-glucosidase activity and have non-classic Pompe disease with a slowly progressive course.[43,80-84] Other frequently occurring mutations in Caucasians are c.2481+102_2646+31del (delexon18; p.Gly828_Asn882del), c.525del (delT525; p.Glu176fsX45) and c.925G>A (p.Gly309Arg). c.1935C>A(p.Asp645Glu) and c.2560C>T(p.Arg854X) are common mutations in Asian and African-American populations, respectively.[85-87] All these mutations lead to total loss of acid α-glucosidase activity. To date the genotype-phenotype correlation is not well understood, and significant clinical heterogeneity exists among patients with similar or identical genotypes. There is one clear pattern discernible being that a combination of two mutations (one in each GAA allele) that each lead to total loss of acid alpha-glucosidase results in classic infantile Pompe disease.[88]

Patients with non-classic phenotypes have at least one sequence variation that allows some amount of functional GAA to be produced.[65,88] Although very low enzyme activities have been found in some patients with onset of symptoms in adulthood,[89] most adult patients have more enzyme activity than patients with clinical manifestations in early childhood (aged 0-5 years).[33,90] However, as the phenotype of patients with a similar GAA genotype and haplotype can vary widely with regard to age of symptom onset and rate of disease progression it is obvious that modifying factors -both genetic, epigenetic and environmental- co-determine the clinical course.[88]

Enzyme replacement therapy

Currently, enzyme replacement therapy with alglucosidase alfa (recombinant human α-glucosidase) is the only treatment option available for Pompe disease. In the spring of 2006, both the European and the United States regulatory authorities (EMA and FDA) approved the application of alglucosidase alfa (Myozyme) for long term enzyme replacement therapy in patients with a confirmed diagnosis of Pompe disease. This registration of the first therapy for an inheritable muscle disorder was a major milestone in the quest for therapies for such disorders.[91]

Registration was supported by the outcome of trials performed in patients with classic infantile Pompe disease; for other, less severe, phenotypes therapy was approved conditionally and requiring further evidence to be accrued in the years that followed. Since then clinical studies in adults have been conducted confirming the beneficial effects of enzyme replacement therapy in all forms of Pompe disease. The following paragraphs describe the effects of ERT in classic infantile patients and non-classic patients.

Enzyme therapy in classic infantile Pompe disease

Six infants participated in the very first trial of enzyme replacement therapy that started in 1999 and ended in 2004. They were treated with recombinant human α-glucosidase produced in the milk of transgenic rabbits. After 48 weeks of therapy improvements were observed in the left ventricular mass index (LVMI), cardiac function, and skeletal muscle morphology and function. Patients also survived longer, which was considered the best proof of clinical efficacy and was attributed to the effect of enzyme replacement therapy on respiratory and cardiac muscles.[92-96]

Around the same time 3 infants were enrolled in a three months study investigating the safety and efficacy of recombinant human α-glucosidase produced in genetically engineered Chinese Hamster Ovary (CHO) cells.[32] Two of the three patients were diagnosed prenatally. All three patients survived for more than one year and showed decreased heart sizes at the end of the study. The effect on pulmonary function varied, however. One patient already had a

normal pulmonary evaluation at baseline and remained stable during treatment with respect to pulmonary function. In the other two infants pulmonary function deteriorated rapidly after an initial improvement during the first 3 months of treatment, and these patients eventually became ventilator dependent. The different responses of the three patients were ascribed to the fact that the two poorly responding infants did not produce any endogenous acid α-glucosidase protein and therefore developed high antibody titers against the recombinant enzyme. The third infant that responded well did have some immunologically detectable acid α-glucosidase and had a low immune response. Recent advances confirm that the absence of Cross Reactive Immunogenic Material (CRIM) is a negative prognostic factor for the response to therapy.[32,97]

The registration of alglucosidase alfa came after two larger studies had been performed; one in 18 infants under 6 months with classic infantile Pompe disease and one in 21 children aged 6 to 36 months some of which had non-classic Pompe disease. These trials confirmed the prolonged survival and the reduction of the LVMI seen in the earlier trials, but also showed that treatment responses can vary.[58,98] Later research showed the severity of muscle damage, the amount of glycogen storage, and the antibody response to be prognostic factors for treatment outcome thereby strengthening the importance of starting treatment early.[32,97,99]

Enzyme therapy in children and adults

Since the registration of ERT in 2006, various studies on the effects of ERT in children and adults with Pompe disease have been performed and published. Table 1 presents a summary of the results reported by outcome measure.

The first and longest follow-up study on ERT in non-classic Pompe disease started in our centre in 1999 with 3 patients who were 11, 16 and 32 years old at that time.[100] Two were ventilator and wheelchair dependent. One used a wheelchair and had no respiratory problems. The results of this study, published in 2008, showed that eight years of enzyme replacement therapy substantially improved muscle function and the ability to walk in the youngest, least affected patient.[101] In addition, treatment stabilized pulmonary function and muscle strength of the two more severely affected patients.

Results of the only placebo-controlled clinical trial performed in children and adults with non-classic Pompe disease were published in 2010, providing the best proof of efficacy.[83] In this trial 90 patients were included ranging in age from 10-70 years, 60 of whom received alglucosidase alfa and 30 placebo for 78 weeks. At the end of the trial, distance walked (measured with the 6 minute walk test) and pulmonary function (forced vital capacity, FVC) in upright position were significantly better in the treated patients compared to the placebo arm. After 26 weeks of treatment a plateau phase was reached. All patients developed IgG antibodies, without having any effect on the outcome. Infusion-associated reactions occurred in 28% of the patients in the treatment group. Most of the reactions were not serious or were mild to moderate in severity and resolved with no need to withdraw treatment.[83]

Table 1. Overview of clinical studies on the effects of enzyme replacement therapy in Non-Classic Pompe disease.

Clinical studies author and year (number of patients, ERT duration)	Outcome measures							
	Physician driven			Patient reported				Survival
	Motor performance/ Muscle function	Muscle strength	Respiratory function	Quality of life	Participation in daily life	Fatigue	Depression and Anxiety	
Winkel *et al*. 2004 (n=3, t=36 mo)	GMFM: (n=1) ≈, (n=2)↑ PEDI: (n=3)↑	MRC: (n=2)↑, (n=1)↓ HHD: (n=2)↑, (n=1) ≈	FVC: (n=3)↑					
Rossi *et al.* 2007 (n=3, t=5, 17, 30 mo)	GMFM: (n=2)↑ WGM: (n=2) ≈ PEDI: (n=1) ≈, (n=1)↑	MRC: (n=1) ≈, (n=1)↓						
Van Capelle *et al.* 2008 (n=3, t=96 mo)	GMFM: (n=3) ≈	HHD: (n=2)↑, (n=1) ≈	VC: (n=3) ≈	SF36: (n=2)↑	RHS: (n=2)↑	FSS: (n=2)↑		
Angelini *et al.* 2009 (n=11, t=3-18 mo)	6MWT: (n=11)↑/≈		FVC sitting: (n=11)↑/≈	SF36: (n=2)↑				
Merk *et al.* 2009 (n=4, t=6 mo)	6MWT: (n=1)↑, (n=1) ≈		FEV1: (n=2)↑, (n=2) ≈ MIP: (n=3)↑	SF36: (n=4)↑				
Strothotte *et al.* 2009 (n=44, t=12 mo)	Arm function test/ 6MWT/ Timed tests/ WGM: (n=44) overall ↑/≈	MRC: (n=44) overall ≈	FVC sitting: (n=44) overall ≈	SF36: (n=44) overall ≈				
Bembi *et al*. 2010 (n=24, t=36 mo)	6MWT: (n=24) overall ↑ WGM: (n=24) overall ↑		VC: (n=24) overall ≈ FEV1: (n=24) overall ≈					
Kobayashi *et al*. 2010 (n=4, t>12 mo)	WGM: (n=4) ≈	MRC: (n=4)↑						
Ravaglia *et al.* 2010 (n=11, t>24 mo)	6MWT: (n=11) overall ↑ Walton score: (n=11) ≈	HHD: (n=11) overall ↑/≈	FVC: (n=11) overall ↑					
Van der Ploeg *et al.* 2010 (n=90 (n=60 treatment arm), t=18 mo)	6MWT: difference in favour of alglucosidase alfa QMT leg and arm: no significant difference between groups		FVC sitting: difference in favour of alglucosidase alfa MIP: no significant difference between groups MEP: difference in favour of alglucosidase alfa	SF36 (PCS): no significant difference between groups				
Furusawa *et al.* 2011 (n=5, t=24 mo)	GMFM: (n=5)↑/≈ Barthel index: (n=5) ≈	MRC: (n=5) ≈	(F)VC/FEV1: (n=5) ↑/≈					
Orlikowski 2011 (n=5, t=12 mo)	MFM: (n=3)↑, (n=2)↓ Arm function test: (n=5) ≈ Leg function test: (n=5) ≈ WGM: (n=5)↑/≈ QMT: (n=5) ≈		VC sitting: (n=2)↑, (n=3)↓ VC supine: (n=2) ↑/≈, (n=1)↓ MIP: (n=4)↑/≈, (n=1)↓ MEP: (n=3)↑, (n=2)↓	SF-36: (n=3)↑		FSS: (n=4)↑, (n=1)↓		

Van Capelle *et al*. 2011 (n=5, t=36 mo)	6MWT: (n=1)↑, (n=4) ≈ Timed tests: (n=5)↑ QMFT: (n=5)↑	MRC: (n=5)↑ HHD: (n=5)↑	FVC sitting: (n=2)↑, (n=3) ≈ FVC supine: (n=3)↑, (n=2) ≈					
Yang *et al*. 2011 (n=13, t=5-59 mo)	WGM: (n=13) overall ≈		FVC: after 1 year (n=5)↑/≈ after 4 years (n=2)↑					
Angelini *et al*. 2012 (n=74, t=12-54 mo)	6MWT: (n=58) overall ↑ WGM: (n=68) overall ≈		FVC sitting: (n=69) overall ≈					
Regnery *et al*. 2012 (n=38, t=24 mo)	6MWT: (n=38) overall ↑ Arm function test: (n=38) overall ≈ WGM: (n=38) overall ≈ Timed tests: (n=38) overall ≈	MRC: (n=38) overall ≈	FVC sitting: (n=38) overall ≈	SF-36: (n=38) overall ≈				
Van der Ploeg *et al*. 2012 (n=55, t=24 mo)	QMT arm: (n=52) overall ↑ QMT leg: (n=53) overall ≈ 6MWT: (n=53) overall ≈		FVC sitting: (n=53) overall ≈ MIP: (n=53) overall ↑ MEP: (n=53) overall ↑					
De Vries *et al*. 2012 (n=69, t=5-47 mo)	QMFT: (n=69) overall ≈	MRC: (n=69) overall ↑ HHD: (n=69) overall ↑	FVC (n=69) overall ≈ FVC supine: (n=69) overall ↓					
Güngör *et al*. 2013 (n=283, median t=4 yrs) Chapter 5								(n=204) overall ↑ (HR 0.41)
Güngör *et al*. 2013 (n=163, median t=3 yrs) Chapter 7						FSS: (n=163) overall ↑	HADS depression: (n=59) overall ↑	
Güngör *et al*. (n=174, median t=4 yrs), Chapter 8				Sf36: (n=174) overall ↑	RHS: (n=174) overall ≈			

↑=improvement; ↓=decline; ≈=stable or no further changes; N=number; ERT=Enzyme-Replacement Therapy; t=ERT duration; mo=months; yrs= years; 6MWT=6-minute walk test; WGM= Walton Gardner Medwin Scale; MFM=Motor Function Measure; QMFT=Quick Motor Function Test; PEDI=Pediatric Evaluation of Disability Inventory; MRC=Medical Research Council; HHD=Hand-Held Dynamometry; QMT=Quantitative Muscle Testing; FEV1=Forced Expiratory Volume in 1 second; FVC=Forced Vital Capacity; MIP=Maximum inspiratory pressure; MEP=Maximum inspiratory pressure; VC=vital capacity; SF-36=Medical Outcomes Study 36-item short-form health survey; RHS=Rotterdam Handicap Scale; FSS=Fatigue Severity Scale; Overall=the effect at group level is presented for studies with larger numbers of patients. Only studies with 3 or more patients are mentioned.

Overall, results from the range of clinical studies indicate that muscle strength and muscle function/ motor performance and respiratory function either improve or stabilize under treatment in the majority of children and adults.[83,102-111] Considering the progressive nature of Pompe disease, stabilization should be considered a positive outcome of treatment. Few studies investigated the effects of ERT on quality of life and fatigue, and at the time of starting this thesis no data were available on the effect of ERT on survival and participation in daily life.

Individuals patients show a variable response to therapy. Gender, age, disease duration and disease severity are considered as potential prognostic factors, but a plethora of yet to be identified other factors will undoubtedly play a role.[107] Despite the variable response of patients, the clear benefits of ERT have led to the exploration of improved modes of treatment including optimization of ERT and gene therapy.[112-128]

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Chapter 2

Research in rare diseases and the IPA / Erasmus MC Pompe Survey

This chapter discusses the challenges of doing research in rare disorders, introduces the rationale and the design of the IPA / Erasmus MC Pompe Survey, and summarizes previous results from the Survey that were available on the natural course of Pompe disease in children and adults at the time that the studies described in this thesis started.

Challenges of studying rare diseases

Pompe disease, with an estimated frequency ranging from 1 in 40.000 to 1 in 300.000 in different parts of the world is a rare disease.[1-6] Rare diseases, or orphan diseases, are diseases that affect less than 5 to 8 people per 10.000. The exact definition varies and depends on the legislations and policies adopted in each country: in Europe a disease is called rare, when no more than 5 in 10.000 of the population are affected,[7] but in the United States a disease is called rare when the prevalence is less than 200.000 affected individuals (7-8 per 10.000 inhabitants).[8]

Studying rare diseases poses a number of challenges that are not encountered when studying common diseases. With rare diseases the available pool of patients is naturally small, which complicates statistical analyses due to insufficient power while the geographical dispersion of patients complicates the collection of data. A third complicating factor is that rare diseases do not attract broad scientific attention so that elementary mechanisms underlying the disease may not have been studied or discovered, making it difficult to identify therapeutic targets. Finally, physicians may not be familiar with the disease, which causes diagnostic delay and difficulty in identifying patients for studies. Even when therapy is available, the low frequency of the disease and the clinical diversity within the disease make it difficult to establish therapeutic efficacy.[9-13]

Despite these difficulties, significant advances were made in the field of orphan diseases over the last few decades including increased public awareness and political will, development of new drugs and expansion of knowledge. Being the first inherited neuromuscular disease to be treatable, Pompe disease is an example of a rare disease in which this progress has changed patients' prospects remarkably.[14] Increased public awareness has placed rare diseases on the political agenda, resulting in several countries implementing legislations and directives to stimulate academic researchers to participate in research on drugs for the treatment of rare diseases and to encourage the pharmaceutical industry to invest in the development of medicinal products for orphan diseases.[13,15,16] The incentives provided by the Orphan Drug legislation include benefits for drug companies such as several years of market exclusivity, accelerated marketing procedures, reduced fees and tax credits for conducting clinical trials, and support for research purposes (scientific and technical support). These legislations have allowed many patients to access treatments. This has not been without caveats, as the exclusive rights have, for instance, resulted in extremely high costs of orphan drugs.[17-20]

Active and well-organized patient advocacy groups have arisen since then, pharmaceutical companies committed to the development of orphan drugs have entered the field, funding has become available for basic and clinical research on rare diseases, and academic medical institutions have implemented specialized centers to treat patients with rare diseases.

For orphan diseases like Pompe disease, relevant studies are only possible through world-wide data collection. A means to do so is the establishment of large clinical databases, also called disease registries.[21] The power of such databases lies in the number of patients included and the more or less comprehensive coverage of the patient population. Examples of such large clinical databases are the registries for rare disorders that were sponsored by pharmaceutical companies as a means to gather information on the disease, its symptoms, course and, in a later phase, also the course in treated patients. Physicians treating patients with rare disorders are encouraged to submit the results of clinical assessments to the registry. In most cases the physician enters the results of assessments performed in the routine care for their patients. Once a therapeutic product is available on the market, the registry may include data on both treated and untreated patients. In the field of the lysosomal storage disorders, such registries are active for Gaucher disease, Fabry disease, Mucopolysaccharidosis type I, II and VI and since 2004 also for Pompe disease.[22-24]

Another type of database is the population or country specific database. The Erasmus MC Center for Lysosomal and Metabolic Diseases in Rotterdam, as the national centre of reference for Pompe disease and Mucopolysaccharidosis types I, II and VI, holds such databases.[25] In other countries similar registries have been established through the collaboration of the various institutes treating these patients, such as the national database for patients with Pompe disease in France. Because these types of databases are a valuable resource for studies of population diversity, history, and disease susceptibility of rare disease, and for reimbursement, some governments even request such databases to be put in place. Because therapies for rare diseases are accompanied with high costs, most governments ask for cost efficacy studies; data derived from these national databases play an important role in these studies.

One of the largest databases in the field of Pompe disease is the IPA / Erasmus MC Pompe Survey. This database is sustained by the close collaboration between care givers and care takers, is a very valuable instrument for data collection, and is the subject of this academic thesis. It concerns a database, which collects data on an international cohort of patients from many countries including the UK, USA, Germany, France, the Netherlands, Australia and other countries. Its design and results are addressed in the subsequent paragraphs.

The IPA / Erasmus MC Pompe Survey

Study Rationale

The IPA / Erasmus MC Pompe Survey, in short 'The Pompe Survey' was initiated in 2002 with the aim to obtain more information on the natural course of Pompe disease in children and adults (non-classic Pompe disease). Specifically, it aims to assess symptoms of the disease and its impact on patients' daily life and quite uniquely gathers information directly from the patient rather than via clinicians. At the time the survey was started the prospect of ERT for Pompe disease increased the need to gather information on the natural course in order to identify endpoints for clinical trials and later judge the effects of ERT and other therapeutic interventions.

Study Design

The Pompe Survey is an ongoing international, observational longitudinal study of patients with Pompe disease. It is coordinated by the Erasmus MC in Rotterdam and run in cooperation with the International Pompe Association (IPA), the worldwide federation of patient groups for this disease.

The study is open to all patients that have been diagnosed with Pompe disease and are able to participate. Originally the survey was designed for children and adults with non-classic Pompe disease, but in 2010 a special version of the Pompe Survey was developed for all children with either classic or non-classic Pompe disease. In this child survey patients (or their parents) also complete questionnaires that are validated for their age and level of mental development. As this thesis describes the results of only adults with Pompe disease, the child survey will not be discussed further.

Patients are approached through the IPA-affiliated patient organizations in the United States, the United Kingdom, the Netherlands, Germany, France, Canada and Australia or directly through the Erasmus MC Center for Lysosomal and Metabolic diseases. Patients who have consented to participate are contacted annually and asked to complete a number of questionnaires, either on paper or via a web-interphase.

So far, data of 408 patients are available in the Pompe Survey. These patients were followed for a median of 5 years (range 0-11). Figure 1 depicts how these patients are distributed by their country of residence. The largest numbers of patients are from The European Union (n= 259) and North America (n=109). The median age of these patients was 47 years at study entry (range 2-81) compared to 37 years at diagnosis (range 0-72) (Table 1). Fourty-nine percent of the patients are women, and 65% were receiving ERT during their follow-up. Fifty four patients died during follow-up.

In 2008 and 2009, the Pompe Survey questions were reviewed and revised to also allow monitoring and evaluation of the effect of ERT. At the same time, a web based application of the Pompe Survey was developed to collect data more accurately and completely.

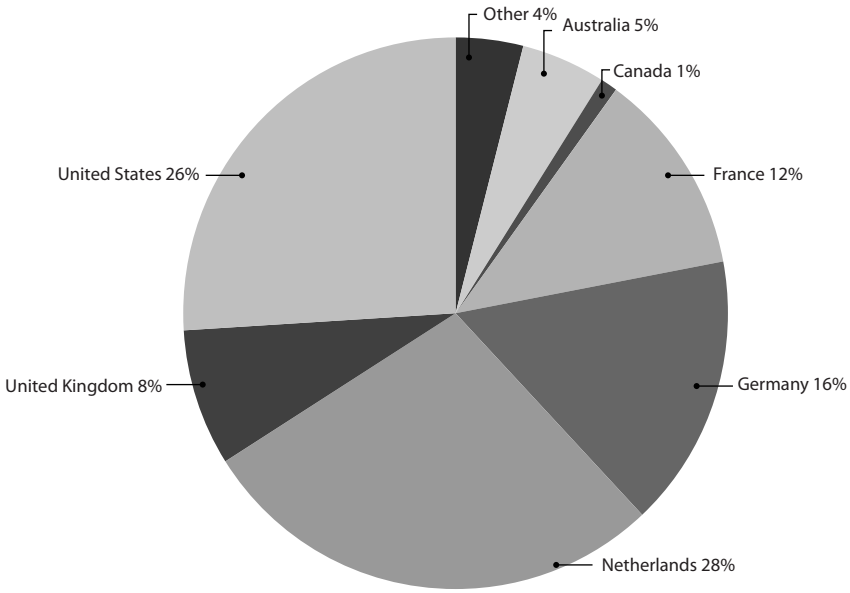

Figure 1. Patient distribution by country of residence. Distribution of the patients included in the Pompe Survey. 'Other' includes patients from Austria, Belgium, Brazil, Greece, Luxembourg, New Zealand and Switzerland

Table 1. Patient characteristics Pompe Survey.

Characteristics of the 408 patients participating in the Pompe Survey	
Female, n (%)	200 (49)
Median age at first symptoms, years (range)	29 (0-65)
Median age at diagnosis, years (range)	37 (0-72)
Median age at inclusion, years (range)	47 (2-81)
Use of walking aids at inclusion, n (%)	137 (34)
Use of a wheelchair at inclusion, n (%)	139 (34)
Use of respiratory support at inclusion, n (%)	169 (41)
Median number or hours of ventilation/ day at inclusion, n (%)	10 (2-24)
Patients receiving ERT during follow-up, n (%)	265 (65)
Deceased during follow-up, n (%)	54 (13)

N=number; %=percentages

Topics covered by the Pompe Survey

The Pompe Survey consists of a number of questionnaires including a questionnaire specifically designed for patients with Pompe disease and three generic questionnaires. The Pompe questionnaire entails questions about the patients' current situation regarding for example mobility, respiratory problems, daily activities and the patients treatment and use of care. At baseline, this questionnaire also collects information about diagnosis and disease history. In addition to the Pompe questionnaire, the Pompe Survey includes the Fatigue Severity Scale, the Rotterdam Handicap Scale, and the SF36 quality of life questionnaire. The four questionnaires are further discussed below and are available in the Appendix.

The Pompe questionnaire

At study enrolment, patients are asked to complete the Pompe questionnaire, which at baseline consists of 5 sections. Section A contains questions about onset of symptoms and diagnostic methods. Section B contains questions regarding family history. In section C the patient is asked about his/her current complaints/symptoms in the domains of mobility, movements, breathing, sleeping, eating, other complaints (e.g. muscle cramps), and daily activities. Section D inquires about the physicians that are treating the patient and whether the patient receives disease specific treatment. Finally, in section E the patient is asked to mention which questions were not clear and what questions were missed. The follow-up questionnaires only cover the sections C, D, and E.

The Rotterdam 9-item Handicap Scale

The Rotterdam 9-item Handicap Scale (RHS) assesses the level of participation in life situations, a concept formerly referred to as handicap.[26] The RHS comprises 9 topics with questions on mobility indoors, mobility outdoors, kitchen tasks, domestic tasks indoors, domestic tasks outdoors, leisure activities indoors, leisure activities outdoors, travelling and work or study. The score ranges from 9 ('unable to fulfil any task/activity') to 36 ('able to fulfil all applicable tasks or activities'). Measuring the impact of a disease on the level of participation provides insight into the functioning of a patient in his/her own environment and gives an indication of what a patient can truly gain in his/her life when further muscle damage is prevented and/or disease progression is halted. For the Pompe Survey the Rotterdam Handicap Scale was chosen for measuring the level of participation because it was specifically designed to assess handicap or participation independent of disability, and because it has good measurement properties. Most of all, its items were deemed very relevant for non-classic Pompe disease. The Rotterdam Handicap Scale was developed and validated in a Dutch population of patients with immune-mediated polyneuropathies. Data analysis showed good internal consistency and excellent test-retest reliability, also in Pompe disease, while floor and ceiling effects were absent.[27]

The Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a brief and simple self-report questionnaire with 9 statements on fatigue and its impact on daily life.[28] The answers range from 1 ('strongly disagree') to 7 ('strongly agree'). The total score is calculated as the average of the 9 items and ranges from 1 to 7; higher scores indicate more disabling fatigue. The Fatigue Severity Scale was chosen because it was short and easy to complete and had demonstrated good psychometric properties, including responsiveness to change in different patient groups. Its frequent use in various studies facilitates comparison with other study populations. In our earlier study on the prevalence of fatigue in Pompe disease the FSS showed excellent internal consistency in the international study population (Cronbach's α=0.92 for the Dutch version and 0.94 for the English and German versions) and good one-month test-retest reliability in the Dutch subgroup (intraclass correlation coefficient=0.86).[29]

The Medical Outcomes Survey Short form 36 health Survey

The Medical Outcomes Survey Short form 36 health Survey (SF-36 (version 1 and 2)) is a health-related quality of life questionnaire, consisting of 36 items.[30] The items are assigned to the domains of physical functioning, role functioning-physical, role functioning-emotional, social functioning, bodily pain, mental health, vitality, general health perception and change in health. The items are summed per subscale and transformed into scores between 0 and 100. A higher score represents better function or less pain. The SF-36 was designed for use in a wide range of populations and conditions. It is available in 40 languages and has been validated cross-culturally.[31] This was for us an important reason to use it for measuring the health-related quality of life of the patients participating in the Pompe Survey from all over the world. Other pro's were its brevity compared to other questionnaires such as for instance the Sickness Impact Profile, the availability of different norm groups, and its extensively evaluated psychometric properties. Earlier, we found good internal consistency on all domains and good test-retest reliability on all but the role functioning emotional domain.[32]

Natural course of Pompe disease: Results of the Pompe Survey

In this section I will briefly summarize the previous results from the Pompe Survey. These have taught us about the natural course of Pompe disease (Table 2). The studies described in this thesis follow on from this and investigate the effects of ERT on a range of outcome measures of the Pompe Survey.

Initially, a subgroup of 54 Dutch children and adults with Pompe disease aged 3 to 81 years old was described. Patients' first symptoms were mostly related to mobility problems and limb girdle weakness, while respiratory problems usually came second. However, the sequence of events could vary. As many as 60% of patients who were diagnosed in early and late adulthood

indicated that they had muscle related symptoms during childhood (Figure 2). These findings emphasized the importance of awareness in clinical practice so as to prevent large diagnostic delays.[33]

Table 2. Previous publications from the Pompe Survey on the natural course of Pompe Disease

Publication	Title	Subject	Patients and demographics
Hagemans, *Brain 2006*	Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients.	Clinical manifestations	N=54; mean age 49 (SD 16); female, 61%; wheelchair 48% ventilator 37%.
Hagemans, *Neurology 2005*	Disease severity in children and adults with Pompe disease related to age and disease duration.	Disease severity	N=255; age range in years (3-81) female 51%; wheelchair 44%; ventilator 45%.
Hagemans, *Neurology 2006*	Course of disability and respiratory function in untreated late-onset Pompe disease.	Disease severity	N= 52; mean age 48 years (SD 16) female 60%; wheelchair 46%; ventilator 36%.
Hagemans, *Neurology 2004*	Late-onset Pompe disease primarily affects quality of life in physical health domains.	Quality of life	N=210; mean age 48 years (SD 13.5), female 54%; wheelchair 46%; ventilator 45%.
Hagemans, *Neuromuscul Disord 2007*	Impact of late-onset Pompe disease on participation in daily life activities: evaluation of the Rotterdam Handicap Scale.	Participation in daily life	N=257; mean age 48 years (SD13) female 53%; wheelchair 42%; ventilator 46%.
Hagemans *J of Neurol 2007*	Fatigue: an important feature of late-onset Pompe disease.	Prevalence of Fatigue	N=225; mean age 47 years (SD 13) female 54%; wheelchair 43%; ventilator 46%.

N=number; SD=standard deviation

In the same subgroup of untreated Dutch patients, of whom 40 provided follow-up data, the rate of disease progression was assessed during 1 and 2 years of follow up. During this period, declines in functional activities, respiratory function, participation in daily life and survival were recorded. These observations underscored the progressive nature of Pompe disease in children and adults.[34]

Studying a much larger, international, group of patients (n=255) it was possible to study the relation between disease severity, age, and disease duration. Disease severity appeared to be more dependent on disease duration than on the patient's age. This study also showed that a subgroup of children with Pompe disease had a more severe and rapidly progressive form of the disease, requiring invasive ventilation and wheelchair support at a young age (Figure 3). All these patients had symptom onset before their 2nd birthday. Given the fast progression of

symptoms in this group, diagnostic delay can easily lead to irreversible damage in this patient group highlighting the need for regular follow-up of Pompe patients in general and these in particular.[35]

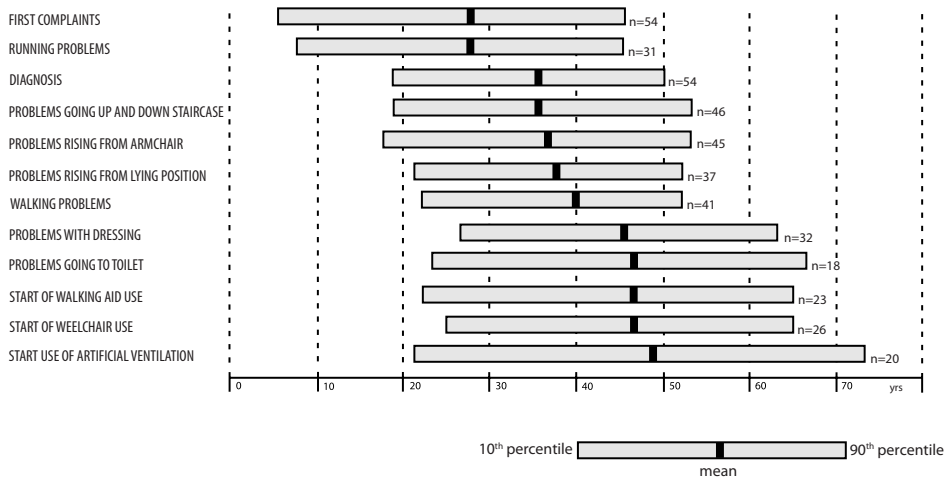

Figure 2. Age distribution for specific events in the course of the disease for 54 non-classic patients with Pompe disease. The number behind each bar indicates how many patients provided information on the time of these events. This figure was taken from Hagemans et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. *Brain* 2005;128:671-7.

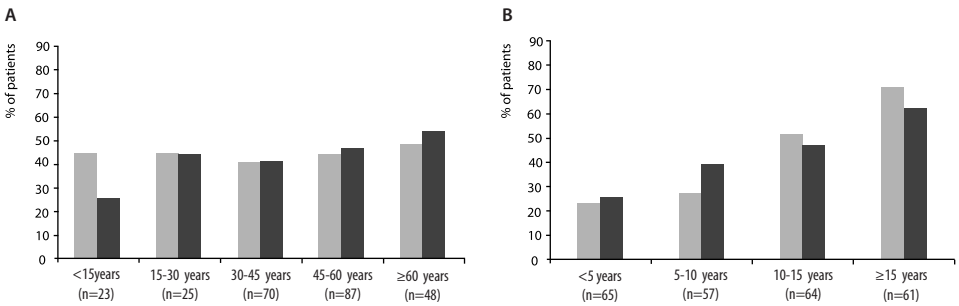

Figure 3. Wheelchair use and use of respiratory support related to age and disease duration in children and adults with Pompe disease. (**A**) Wheelchair use and use of respiratory support related to age in 253 children and adults with Pompe disease. (**B**) Wheelchair use and use of respiratory support related to disease duration in 247 children and adults with Pompe disease. Light gray represents wheelchair use; dark gray shading represents use of respiratory support. This figure was taken from Hagemans et al. Disease severity in children and adults with Pompe disease related to age and disease duration. *Neurology* 2005;64:2139-41.

Analysis of the patients' responses to the Fatigue Severity Scale showed that fatigue is a common symptom in Pompe disease and more prevalent than previously thought. Seventy-eight percent of the patients were fatigued and 67% were severely fatigued. Fatigue appeared to be a common and disabling problem of patients with both advanced as well as early stages of Pompe disease. Taken together, these results demonstrate that it is important to identify mechanisms causing fatigue and to find ways to combat it.[29]

Before the start of the Pompe Survey the level of participation in daily life activities (formerly called handicap) had not been assessed in adults with Pompe disease. The Rotterdam Handicap Scale showed good psychometric properties and seemed suitable for use in adult Pompe disease. The 257 adults with Pompe disease that were followed in the Pompe Survey scored lower on the RHS (less participation) than a cross section of healthy people. Pompe disease had particularly a large impact on patients' ability to fulfil work or study.[27]

By using the 'Short Form-36 health survey' (SF-36), data on health-related quality of life were collected among 210 adult patients from different countries. The results of this study showed that adults with Pompe disease are, on average, markedly affected in the physical health domains of quality of life, but that they score only slightly lower than the general population in the mental health domains.[32]

In short, the Pompe Survey has provided valuable information on the range of disease severity and the impact of Pompe disease on various aspects of daily life of untreated patients. These studies were based on the first years of the survey covering the period that ERT was not yet approved. Thanks to the ongoing participation of a large number of patients in the Pompe Survey we have now been able to collect several further years of data with many patients starting treatment. This provided valuable information allowing us to study the effects of ERT in adult Pompe disease. These results are described in this thesis.

Aims and outline of this thesis

During the past six decades significant scientific progress has been made in lysosomal biology from the discovery of the lysosome to the first therapeutic approaches. Pompe disease has played a pivotal role during this whole process. Despite our current ability to treat Pompe disease through enzyme replacement therapy, there is still much to be learned about this disease. This thesis comprises a number of studies aimed to gain more insight into areas where evidence is still lacking including survival, pain as a symptom of Pompe disease, and the effects of enzyme replacement therapy on patients' daily life and fatigue in adults with Pompe disease. The conclusions are mainly based on data collected as part of the Pompe Survey outlined in **Chapter 2. Chapter 3** advocates the use of a uniform nomenclature for the description of Pompe disease phenotypes; it combines old and new insights.

Chapters 4 and 5 are devoted to survival of adult Pompe patients. The survival of adult patients during their natural course is first assessed, including factors influencing survival **(Chapter 4)** followed by the effect of ERT on patients' survival **(Chapter 5**). The three chapters thereafter describe the results of a range of patient reported outcomes. The prevalence of pain in adult patients is first addressed **(Chapter 6)** after which the effects of ERT on fatigue **(Chapter 7)** and on quality of life and handicap are studied **(Chapter 8)**. Finally, the general discussion **(Chapter 9)** gives an overview of the results and outlines directions for future research.

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Chapter 3

How to describe the clinical spectrum in Pompe Disease?

Deniz Güngör and Arnold JJ Reuser

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To the Editor:

Pompe disease, which is also known as acid maltase deficiency and glycogen storage disease type II, derived its name from the Dutch pathologist Dr J.C. Pompe, who described it in a 7-month-old girl in 1932. In the same year, Dr Putschar presented an equally detailed report on a similar case. Both patients died in their first year of life due to generalized glycogen storage – later named glycogen storage disease type II – that affected mainly heart and skeletal muscle function. The underlying lysosomal a-glucosidase deficiency was discovered in 1963.

Originally, Pompe disease was thought to be a disease of early infancy leading to death in the first year of life. However, the acid a-glucosidase deficiency turned out to occur in different degrees, with the first symptoms manifesting at various ages, and the disease progressing at various speeds.[1-3]

Pompe disease is now considered to be a continuous spectrum of phenotypes, with the clinically severest, rapidly progressive phenotypes in the ultra violet, and the least severe, slowly progressive phenotypes extending into the infra red (Figure 1). Boundaries between clinical subtypes cannot be set, although this is desirable for unraveling the genotype-phenotype correlation, discovering the factors contributing to disease progression, and judging the effects of therapeutic interventions such as enzyme replacement therapy.

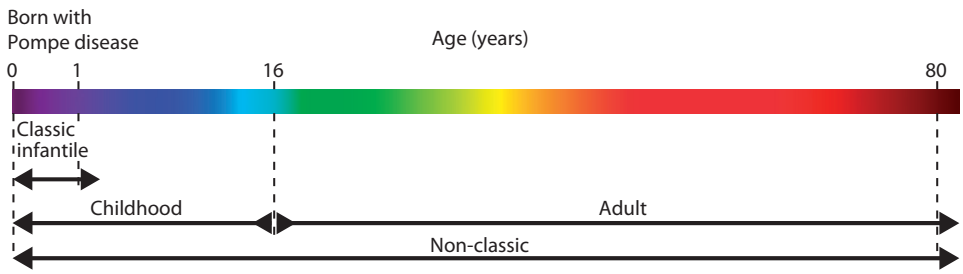

Figure 1. The spectrum of Pompe disease.

The recent series of ten articles on advancements in Pompe disease in the American Journal of Medical Genetics reflects a struggle with nomenclature.[4] Even among experts, a rich variety of nuanced terms is used to subdivide the clinical spectrum. One article distinguishes infantile onset Pompe disease (IOPD) from late onset Pompe disease (LOPD) with a caesura at the age of 1 year, while late onset Pompe disease is historically synonymous with adult onset Pompe disease – which is how it is used in the context of other articles. Terms such as classic infantile, infantile (onset), non-classic (infantile), atypical (infantile), non-infantile, muscular variant,

childhood, juvenile, adult, late(r) onset are used, sometimes to describe the same phenotypes and sometimes to describe different ones.

Though consensus on nomenclature is clearly lacking, most experts seem to agree that the term classic infantile Pompe disease represents onset of symptoms within the first year of life; it is always associated with hypertrophic cardiomyopathy, and it is always associated with virtually total lack of acid a-glucosidase activity. But late onset Pompe disease is ill defined:

- Historically, 'late onset' stood for 'adult onset' disease, but currently it is also used 1) to describe all patients with onset of symptoms above the age of one, and, alternatively 2) to distinguish between classic infantile and all other forms of Pompe disease.
- Given the average life span of Pompe disease patients and the fact that some adults living with Pompe disease were diagnosed within their first year of life, 'late' can be very early.
- Lumping a very broad spectrum of phenotypes into one 'late onset' group obscures the meaning of outcome data;'late onset' is currently used in the analyses of widely different phenotypes.

For several reasons we therefore believe that the term 'late onset' Pompe disease should better be avoided.

Given the width and continuity of the clinical spectrum, we propose to adapt a mixture of old and new terminology and to discern three broadly overlapping sections of the clinical spectrum (Figure 1): 1) 'classic infantile' Pompe disease as defined above, 2) 'childhood' Pompe disease to cover patients with onset of symptoms from birth on till adolescence, but without persisting and progressive cardiac hypertrophy; and 3) 'adult' Pompe disease for patients with onset of symptoms from adolescence to late adulthood. This crude division of the clinical spectrum into these three subtypes seems practical for many types of analysis, and will greatly improve the uniformity of data reporting. Importantly, it combines old and new insights into the clinical spectrum of Pompe disease. For certain purposes it remains practical to divide the Pompe patient population – but not the clinical spectrum – into two classes: 'classic infantile' Pompe disease and 'non-classic' Pompe disease.

Irrespective of its subdivisions, Pompe disease presents as a continuous clinical spectrum in which all patients are affected from birth onwards, but manifest their first symptoms at different ages and different severities. Effective treatment modalities are expected to shift the clinical spectrum from the severe violet into the safer red.

With this letter we intend to achieve consistent terminology in Pompe disease.

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Chapter 4

Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy

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Abstract

Background

Pompe disease is a rare lysosomal storage disorder characterized by muscle weakness and wasting. The majority of adult patients have slowly progressive disease, which gradually impairs mobility and respiratory function and may lead to wheelchair and ventilator dependency. It is as yet unknown to what extent the disease reduces the life span of these patients. Our objective was to determine the survival of adults with Pompe disease not receiving ERT and to identify prognostic factors associated with survival.

Methods

Data of 268 patients were collected in a prospective international observational study conducted between 2002 and 2009. Survival analyses from time of diagnosis and from time of study entry were performed using Kaplan-Meier curves and Cox-proportional-hazards regression.

Results

Median age at study entry was 48 years (range 19-79 years). Median survival after diagnosis was 27 years, while median age at diagnosis was 38 years. During follow-up, twenty-three patients died prior to ERT, with a median age at death of 55 (range 23-77 years). Use of wheelchair and/or respiratory support and patients' score on the Rotterdam Handicap Scale (RHS) were identified as prognostic factors for survival. Five-year survival for patients without a wheelchair or respiratory support was 95% compared to 74% in patients who were wheelchair-bound and used respiratory support. In a Dutch subgroup of 99 patients, we compared the observed number of deaths to the expected number of deaths in the age- and sex-matched general population. During a median follow-up of 2.3 years, the number of deaths among the Dutch Pompe patients was higher than the expected number of deaths in the general population.

Conclusion

Our study shows for the first time that untreated adults with Pompe disease have a higher mortality than the general population and that their levels of disability and handicap/participation are the most important factors associated with mortality. These results may be of relevance when addressing the effect of ERT or other potential treatment options on survival.

Background

Pompe disease, synonymously 'acid maltase deficiency' or 'glycogen storage disease type II', is a metabolic myopathy caused by deficiency of the enzyme acid alpha-glucosidase and resulting in intralysosomal accumulation of glycogen. This autosomal recessive disorder is mainly characterized by progressive loss of muscle strength and respiratory function due to destruction of muscle tissue.[1,2] Because of its low frequency of approximately 1 in 40,000 births and the broad ethnic spreading,[3-5] Pompe disease is a true orphan disease with the associated problem of collecting data in sufficiently large groups. Clinical heterogeneity is an additional complicating factor.[5,6] Classic infantile Pompe disease, the most severe form, presents in the first months of life with generalized muscle weakness and cardiac hypertrophy. Without treatment these infants die before age one. Later-onset forms of Pompe disease comprise childhood, juvenile, and adult cases. The majority of these patients present with symptoms in adulthood with limb- girdle weakness and respiratory problems.[5]

For a long time, supportive care such as respiratory support was the only way of managing Pompe disease, but in the course of 2006 enzyme replacement therapy (ERT) with recombinant human alpha-glucosidase became available. Clinical trials showed that ERT can ameliorate motor outcome, improve cardiomyopathy and prolong survival in classic infantile Pompe disease.[7-11] In children and adults treatment with ERT has been shown to stabilize respiratory function and to improve muscle function.[12-16]

In contrast to classic infantile Pompe disease, in which survival is a key outcome measure to describe the natural course of the disease *and* to evaluate the effects of treatment, information on mortality in adults with Pompe disease has been lacking. The present study was performed to fill the gap of knowledge on the impact of Pompe disease on survival in untreated adult patients, using data collected prospectively in an international patient survey prior to the introduction of ERT. The objective was to determine natural course survival in adult patients with Pompe disease, to compare this to the general population and to assess differences in survival between subgroups of patients.

Methods

Data

Data were collected between May 2002 and December 2009 as part of an ongoing study on the natural course of Pompe disease ('Pompe Survey') e.g.[6,17] in which patients complete a number of self-report questionnaires each year, gathering information on medical history, current disease status, use of care and quality of life.

Patients were recruited through patient organizations affiliated with the International Pompe Association (IPA) in Australia, Canada, Germany, the Netherlands, the United Kingdom

and the United States. Inclusion criteria for the Pompe Survey were a diagnosis of Pompe disease and an age above 2 years. The present analyses only include patients of 18 years and older with late-onset Pompe disease.

For the Dutch patients, more information was available as Erasmus MC was designated as the single referral center for treatment and longitudinal follow-up of Pompe patients in the Netherlands.

All research protocols were approved by the Medical Ethics Committee of Erasmus MC and/or the Central Committee on Research Involving Human Subjects. Written informed consent was obtained from all patients.

Explanation of variables

For the international participants in the Pompe Survey, the date of the last completed questionnaire before December 2009 was considered as the date of last follow-up. For the Dutch subgroup, the date of last follow-up was the last visit at our hospital in 2009 or the date of the last completed questionnaire, whichever came last.

When the date of death for the deceased was not exactly known it was estimated to be halfway between the date of the last completed questionnaire and the date at which the next questionnaire should have been completed.

The date of diagnosis was estimated as precisely as possible according to the information provided in the questionnaires.

To assess the level of participation (defined as a person's involvement in life situations; previously called 'Handicap'),[18,19] the Rotterdam Handicap Scale (RHS) was used. The RHS consists of 9 questions on the topics of mobility, kitchen tasks, domestic tasks, leisure activities, travelling and work or study. The scores per item range from 1 ('unable to fulfil the task or activity') to 4 ('complete fulfilment of the task or activity'). If an item is not applicable to a patient, a score of 0 is given. The total score is calculated as the sum of the scores per item * 9/ (9-number of non-applicable or missing items).[17,20] The RHS score thus ranges from 9 to 36 and in the present analysis the number of items necessary to calculate a score was 5 out of 9 questions.

To assess disability level at study entry patients were divided into four groups: 1) no wheelchair or respiratory support, 2) only wheelchair, 3) only respiratory support and 4) both wheelchair and respiratory support. No division was made between partial and fulltime respiratory support, or whether it was invasive or non-invasive.

According to their nationality patients were divided into the following groups: Netherlands, United Kingdom, United States, Germany, Canada, Australia and other (Denmark, Austria, Switzerland, Spain, Italy, New Zealand, Greece, Taiwan and Luxembourg).

Statistical analysis for survival from diagnosis and from study entry

Survival was calculated from the date of diagnosis or study entry until the date of last follow-up, start of ERT or death. The survival times of patients who were alive at study end or lost to

follow-up were censored. The survival times of the patients were also considered censored at the initiation of ERT.

For survival from diagnosis and from study entry, the influence on survival was tested for the following variables: gender, age at diagnosis, and nationality. The variables age at entry, disability level and RHS score were only tested for survival from study entry.

For survival from diagnosis, the PROC PHREG method in SAS was used, because most of our patients were enrolled months or years after diagnosis. This means that the data are 'left-truncated', as opposed to usual time-to-event data where all patients are followed from diagnosis. Estimates of survival from diagnosis in case not all patients enter the cohort study at the time of diagnosis require special calculations as described by Kurtzke.[21]

Univariate analysis for survival from study entry was estimated by using the Kaplan-Meier method. Factors influencing survival were identified with the log-rank test. Multivariate analysis was performed with the Cox proportional-hazards method.

Mortality of Dutch patients compared to the general population

Death probabilities from study entry were compared between the Dutch Pompe patients and the general population using death probabilities derived from the Dutch Central Bureau of Statistics (CBS).[22] For each case of our study population, the death probability per follow-up year of someone of the same age and gender from the general population was taken for comparison. Annual death probabilities per person were summed up and the sum of these cumulative death probabilities of the matched persons from the general population was used as the expected number of deaths. This was then compared to the observed number of deaths in our own cohort using the Poisson distribution.

All analyses were performed using SAS (version 9.2) or SPSS (version 15.0). Statistical significance was defined as a p-value ≤ 0.05 for all analyses.

Results

Patient characteristics

As of December 2009, 303 adult patients were enrolled in the Pompe Survey. Thirty-five of them were excluded from the analyses. These were patients who had provided too little information about their diagnosis (n=8), patients with only baseline data available (n=15), patients already receiving ERT at study entry (n=2) and patients with important data missing such as date of birth (n=10). Thus, the current analyses covering the years 2002 to 2009 comprise a total of 268 adults with Pompe disease from 15 different countries. Patient characteristics are summarized in Table 1.

At study entry patients' age varied between 19 and 79 years with a median age of 48 years. This did not differ significantly between countries. The median age at diagnosis was 38

(range 1-68) years. Median follow-up time from study entry was 3.5 years, with a maximum of 7 years. Seventy-eight percent of the patients were followed for 2 years or more and 62% of the patients for 3 years or more. Differences in disability level between countries were found, with the lowest rates of wheelchair and ventilator use in the Dutch patient group (32% and 26%, respectively). Almost all Dutch patients carried the most common c.-32-13T >G (IVS1) GAA mutation in combination with a fully deleterious mutation on the other allele. The c.-32-13T>G (IVS1) is a splice-site mutation leading to 10-20% residual activity of acid alpha-glucosidase and a broad clinical spectrum.[23]

Table 1. Patient Characteristics of 268 Untreated Adult Patients with Pompe Disease

Characteristics	n=268
Female, n (%)	141 (53)
Median age at study entry, years (range)	48 (19-79)
Median age at diagnosis, years (range)	38 (1-68)
Number of patients diagnosed in age categories of 15 years, n (%)	
<15 years	22 (8)
16-30 years	59 (22)
31-45 years	115 (43)
46-60 years	61 (23)
>61 years	11 (4)
Nationality, n (%)	
Netherlands	99 (37)
Germany	48 (18)
US	69 (26)
UK	20 (8)
Australia	13 (5)
Canada	9 (3)
Other	10 (4)
Median disease duration at entry, years (range)	9 (0-32)
Median follow up time, years (range)	3.5 (0.02-7)
Disability level at study entry, n (%)	
No wheelchair use or respiratory support[a]	127 (47)
Wheelchair use	34 (13)
Use of respiratory support	39 (15)
Both wheelchair use and respiratory support	68 (25)
Median RHS score* at study entry (range) (n=258)	27 (9-36)

Continuous variables are expressed as median (range). Categorical variables are expressed as n (%). [a]'Respiratory support' includes partial and fulltime, invasive and non-invasive respiratory support *RHS assesses the level of participation/ handicap; score varies between 9 (severe participation restrictions) and 36 (no participation restrictions).

Mortality

For 34 of the 268 patients, a death confirmation was received from the patient organization or the family. The median age at death was 56 years and did not differ significantly between countries. In 23 of the 34 cases information on cause of death was not available. For the Dutch patients (n=9), causes of death were reported as respiratory insufficiency (n=3), myocardial infarction (n=2), aortic dissection (n=1) and breast cancer (n=1). For two of them, cause of death was not known. Characteristics of the deceased patients are listed in Table 2. Data from only 23 of the deceased patients (median age at death 55 years) could be used to estimate survival prior to ERT, since the other 11 received ERT prior to their death.

Table 2. Characteristics of deceased patients (34 patients died in total, 23 of them prior to ERT)

	34 (All Deceased Patients)	23 (Died Prior to ERT)
Female, n (%)	16 (47)	12 (52)
Median age at study entry, years (range)	54 (20-75)	51 (20-75)
Median age at death, years (range)	56 (23-78)	55 (23-77)
Median age at diagnosis, years (range)	42 (13-66)	42 (13-59)
Median disease duration, years (range)	14 (2-27)	16 (2-27)
Age at diagnosis in categories of 15 years, n (%)		
0-15 years	3 (9)	3 (13)
16-30 years	6 (18)	3 (13)
31-45 years	13 (38)	10 (44)
46-60 years	10 (29)	7 (30)
>61 years	2 (6)	0
Nationality, n (%)		
Netherlands	9 (27)	5 (22)
Germany	4 (12)	4 (17)
US	13 (38)	8 (35)
UK	4 (12)	3 (13)
Australia	1 (3)	0
Canada	2 (6)	2 (9)
Other	1 (3)	1 (4)
Disability level at study entry, n (%)		
No wheelchair use or respiratory support [a]	4 (12)	4 (17)
Wheelchair use	6 (18)	4 (17)
Use of respiratory support	7 (21)	4 (17)
Both wheelchair use and respiratory support	17 (50)	11 (48)
Median RHS score* at study entry (range)	23 (9-36) (n=33)	22 (9-36)

Continuous variables are expressed as median (range). Categorical variables are expressed as n (%). [a] 'Respiratory support' includes partial and fulltime, invasive and non-invasive respiratory support. *RHS assesses the level of participation/ handicap; score varies between 9 (severe participation restrictions) and 36 (no participation restrictions).

Survival from diagnosis

The estimated median survival after diagnosis -without enzyme replacement therapy- was 27 years. The estimated 5-year survival after diagnosis was 95%. At 10, 20 and 30 years this was 83, 65 and 40%, respectively (Figure 1).

Univariate and multivariate analysis showed that none of the tested factors were related to survival after diagnosis.

Because the time between the start of ERT and death was mostly less than one year and these patients were already severely affected when they started ERT, we performed a second analysis including all patients who died within 18 months after start of ERT (n=9). To be consistent with the deceased patients, the follow-up time for all other patients on ERT was also extended by 18 months. In this analysis with 32 events, only age at diagnosis, accounting for gender and nationality, was related to survival (Hazard Ratio 1.55 per 10 years of age $p<0.01$).

Survival from study entry

The Kaplan-Meier survival curve from study entry is shown in Figure 2. After 5 years of follow-up, 88% of the patients not yet receiving ERT were still alive.

Univariate analysis revealed a statistically significant difference in survival between groups based on disability level (overall $p=0.002$ log-rank, Figure 3), RHS score (overall $p=0.002$ log-rank, Figure 4) and age at study entry (overall $p=0.03$ log-rank). After five years 95% of patients without a wheelchair or respiratory support survived, while this was only 74% for patients with both wheelchair and respiratory support at study entry. Table 3 shows the 5-year survival with respect to potential prognostic factors. Multivariate analysis of the factors age at study entry, gender, nationality and disability level showed a significant effect of disability level ($p=0.01$), i.e. less disability at study entry was associated with better survival. Analyzing RHS score instead of disability level showed that a higher RHS score at study entry was also associated with better survival ($p<0.001$). In the analysis including 32 deceased patients, the factors age at study entry ($p=0.01$) and disability level ($p=0.002$) were significantly related to survival. When RHS score was analyzed instead of disability level both age ($p=0.01$) and RHS score ($p<0.001$) were significantly associated with survival.

Mortality of Dutch Pompe patients compared to the general Dutch population

For this part of the analyses 99 Dutch patients, with median age at entry 50 (range 24-79) years, were included. The Dutch subgroup included 5 deceased patients before start and 4 after start of ERT. The median age at death was 55 (range 41-78) years. Two of the patients who died after start of ERT had died during the first year of treatment; one other had died 18 months after start of ERT and one had started and stopped ERT in the year before death. These were all severely affected patients using a wheelchair and/or respiratory support before start of ERT. To compare the probability of death in the Dutch Pompe patient group with that in the general Dutch population two analyses were performed: one taking into account only the 5 deaths

before start of ERT (median follow-up time 2.3 years) and one taking into account 9 deaths, while in the latter analysis extending the follow-up time after start of ERT with 1 year for every patient on ERT (median follow-up time 3.3 years). Table 4 shows the results.

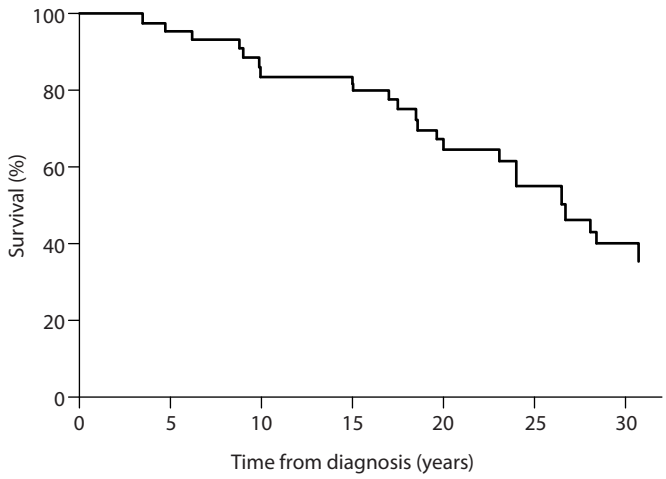

Figure 1. Survival estimates of 268 untreated adults with Pompe disease from diagnosis until end of study, start ERT or death. Twenty-three patients died during follow-up.

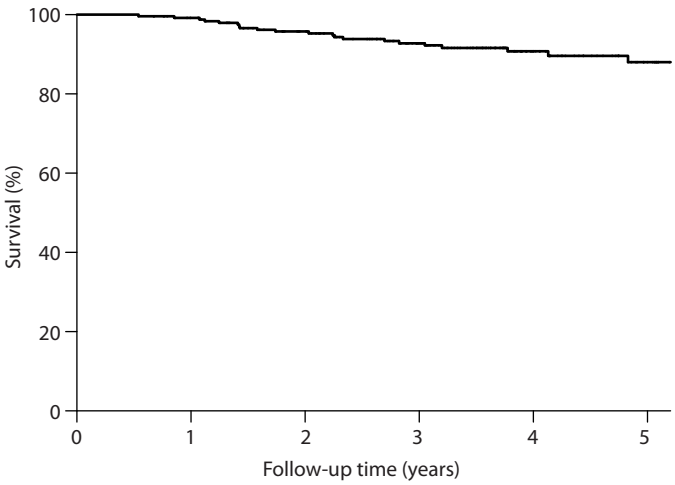

Figure 2. Kaplan Meier survival estimates of 268 untreated adults with Pompe disease from study entry until end of study, start of ERT or death. Twenty-three patients died during follow-up.

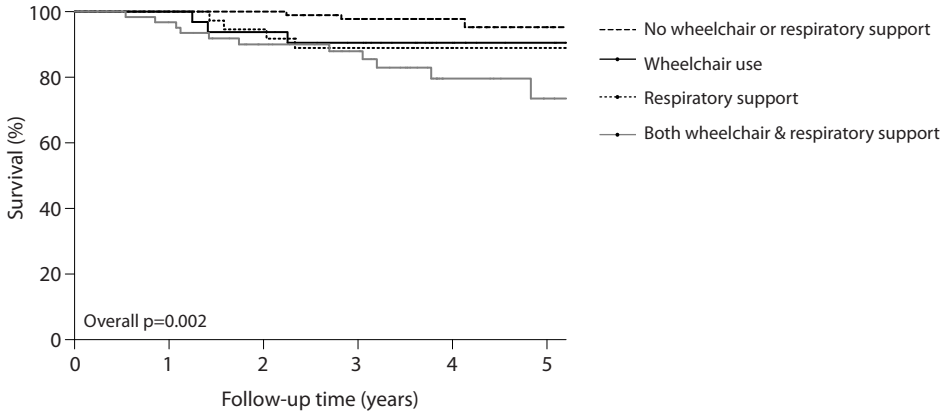

Figure 3. Kaplan Meier survival estimates of 268 untreated adults with Pompe disease from study entry until end of study, start of ERT or death by disability level. Twenty-three patients died during follow-up. 'Respiratory support' includes partial and fulltime, invasive and non-invasive respiratory support. P-value denotes result from log-rank test for trend.

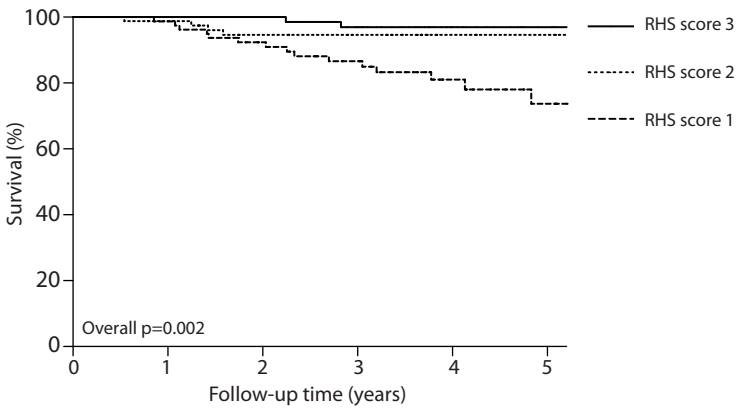

Figure 4. Kaplan Meier survival estimates of 268 untreated adults with Pompe disease from study entry until end of study, start of ERT or death by RHS score. RHS score was divided into tertiles for comparison. RHS1=score <23, RHS2= score 23-30, RHS3=score >30. Twenty-three patients died during follow-up. P-value denotes result from log-rank test for trend.

Table 3. Summaries of 5-year survival from study entry according to potential prognostic factors (23 deceased patients)

Prognostic factors	n	5-year survival percentages	P-value*
Gender			0.7
Women	141	86	
Men	127	91	
Age at diagnosis			0.4
0-15 years	22	81	
16-30 years	59	92	
31-45 years	115	89	
46-60 years	61	82	
>61 years	11	100	
Age at entry			0.03
18-30 years	32	91	
31-45 years	85	94	
46-60 years	104	89	
>61 years	47	77	
Nationality			0.7
Netherlands	99	90	
Germany	48	93	
US	69	85	
UK	20	67	
Other [o]	32	93	
Disability level at study entry			0.002
No wheelchair use or respiratory support [a]	127	95	
Wheelchair use	34	91	
Use of respiratory support	39	89	
Both wheelchair use and respiratory support	68	74	
RHS score at study entry*			0.002
1	85	74	
2	85	95	
3	88	97	

*Log rank test for the Kaplan-Meier curves, overall p-values of univariate analyses. [o]Due to small groups Canada and Australia were classified into the category "other". [a]'Respiratory support 'includes partial and fulltime, invasive and non-invasive respiratory support. *RHS score was divided into tertiles for comparison.**1)** <23, **2)** 23-30, **3)**>30.

Table 4. Mortality of 99 Dutch Pompe patients compared to general Dutch population

Analysis	Median follow-up time (range)	Observed no. deaths (O)	Expected no. deaths (E) *	Ratio (O/E)	P-Value
1	2.3 (<1 month-7 years)	5	2.3	2.2	0.09
2	3.3 (<2 months-7 years)	9	2.8	3.2	0.002

Analysis 1: 5 deceased patients before start of ERT; **Analysis 2:** including 4 patients who died after start of ERT with follow-up of every patient on ERT extended with 1 year after start of ERT. *According to death probabilities derived from Dutch Central Bureau of Statistics.

Discussion

Using data from the Pompe Survey, a long-term, disease-specific database using patient-reported outcome measures, we were able to perform the first study on survival and prognostic factors in adults with Pompe disease.

Over a prospective follow-up period of 7 years 34 of 268 patients died, 23 of them prior to ERT. Some of these patients died relatively young (23 years) and some reached very high ages despite Pompe disease (78 years). By using cumulative death probabilities of persons from the general population matched by age and gender, our study shows for the first time that mortality in adults with Pompe disease is higher than in the general population.

We also found that in our group of patients, diagnosed at a median age of 38 years, 17% died ten years after diagnosis. The median (50%) survival was estimated at 27 years after diagnosis. In an earlier study on the relation between disease severity and disease duration based on Pompe Survey data, we showed that 10-15 years after diagnosis 50% of the patients were wheelchair-bound or ventilator dependent.[24] Thus, although Pompe disease in adults generally manifests as a slowly progressive disorder, it seriously affects the lives of patients.

Several factors in our study had a significant effect on survival. For patients without a wheelchair or respiratory support the 5-year survival from entry was 95%, while for patients with a wheelchair and respiratory support this was 74%. In practice this means that patients with a wheelchair and/or respiratory support have a shorter life expectancy at any age compared to patients without wheelchair and respiratory support. RHS score at study entry, indicative of the level of handicap or participation, also was significantly associated with survival. Whether the RHS score is also useful as a prognostic tool in clinical practice is a topic for further investigation.

The strength of our study is its prospective design, the regular follow-up, the representation across countries, and the large sample size, especially for a rare disorder such as Pompe disease. In orphan diseases, it is quite unique to be able to gather information on a large group of patients over so many years, especially prior to therapeutic intervention. Our prospective data collection was achieved by relying on patient reported outcome measures through a

close collaboration with patient organizations. This approach enabled data collection without the support of a large physician's network that is -in orphan diseases- usually activated only after the introduction of a therapy. Our approach may stand model for data collection in other rare diseases. Since almost all newly diagnosed Pompe patients currently start with enzyme replacement therapy, this study might have been the very last chance to collect data on the natural course of Pompe disease.

Nevertheless, some methodological issues need further attention. Firstly, our patients were followed from 2002 onwards, which means that the majority entered the study at some cross-sectional point of their illness. The ideal method would have been to follow all patients from the time of disease onset or diagnosis until death. However, if we had applied those restrictions our study population would have been too small and the follow-up period would have been too short. Therefore, the next best thing was to also include the patients diagnosed before entering the study. This led to so-called 'left-truncated' data, with a grey area between diagnosis and study entry in which other patients may have died without entering our study, and could have caused an overestimation of the median survival. Additionally, because all data in the Pompe Survey are provided voluntarily, some deaths among enrolled patients who eventually became censored due to loss-to-follow-up (n=37) may not have been reported.

Second, differences in wheelchair and ventilator use were observed between countries, with the Dutch patients tending to be less severely affected on average. This may be explained by the fact that the Dutch group includes almost all patients known in the Netherlands, while the inclusion through patient organizations in the other countries may have led to a larger proportion of more severely affected patients. This may have affected the estimation of median survival time, but does not influence our main conclusions that mortality in adults with Pompe disease is higher compared to the general population and is associated with disease severity.

Furthermore, our patients were followed for up to 7 years, but median follow-up time was 3.5 years. Although a longer follow-up of untreated patients would offer more insight in their survival, such a study will be difficult to do as most patients currently receive ERT.

Because our aim was to investigate the natural course survival, we censored patients at the initiation of ERT. This means that 11 patients who died *after* start of ERT were not included as deceased patients in our initial analysis. Most (n=9) of these patients died within 1.5 year *after* start of ERT, or stopped ERT after a few infusions. As this treatment period is relatively short, we also performed analyses including these patients. Excluding these patients could have led to an underestimation of the number of deaths as these patients were already severely affected at the point they started ERT. All of them were wheelchair-bound and/or used respiratory support and most probably would also have died without ERT. For the same reason, in our comparison of death probabilities between the Dutch subgroup and the general population we also included the 4 patients who died shortly after start of ERT.

Unfortunately, information on cause of death was lacking for the majority of the deceased patients. However in our study, mortality was compared with the data obtained from the Dutch

Central Bureau of Statistics, which reports deaths irrespective of the cause. This comparison showed that the difference in mortality between the two groups was statistically significant. This in itself is important information, which can be used to evaluate the severity of disease and may serve as a reference when comparing the mortality of patients under treatment. With regard to the reported causes of death, it seems likely that death due to respiratory insufficiency is related to Pompe disease.[2,25] Other causes, such as aortic dissection can also (in)directly be related to Pompe disease, as it may be a consequence of glycogen accumulation in vascular smooth muscle.[26]

Whether timely start of ERT can increase survival of adults with Pompe disease is currently unknown. In a recently published randomized controlled trial of alglucosidase alfa in late-onset Pompe disease, significant differences in walking distance and pulmonary function between the alglucosidase alfa and placebo groups were found.[16] Considering these results, and given the fact that most patients die of respiratory failure, it might be expected that ERT will also positively influence life expectancy. The present study, in which we show that Pompe disease has a serious negative impact on the life span of untreated adult patients, allows for future evaluation of the effect of ERT with respect to this important parameter.

Conclusion

Our study shows for the first time that mortality of untreated adults with Pompe disease is high compared to the general population. Both the need of a wheelchair and ventilator and a low RHS score are associated with higher mortality. Our results can serve as reference for future studies addressing survival of patients treated with ERT or alternative interventions. This information will also be valuable for families, genetic counsellors, and other health-care professionals when Pompe disease is diagnosed. Future studies should focus on identifying other factors -environmental or genetic- that may determine survival or disease progression in adults with Pompe disease, with or without treatment.

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Chapter 5

Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study

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Abstract

Background

Pompe disease is a rare metabolic myopathy for which disease-specific enzyme replacement therapy (ERT) has been available since 2006. ERT has shown efficacy concerning muscle strength and pulmonary function in adult patients. However, no data on the effect of ERT on the survival of adult patients are currently available. The aim of this study was to assess the effect of ERT on survival in adult patients with Pompe disease.

Methods

Data were collected as part of an international observational study conducted between 2002 and 2011, in which patients were followed on an annual basis. Time-dependent Cox's proportional hazards models were used for univariable and multivariable analyses.

Results

Overall, 283 adult patients with a median age of 48 years (range, 19 to 81 years) were included in the study. Seventy-two percent of patients started ERT at some time during follow-up, and 28% never received ERT. During follow-up (median, 6 years; range, 0.04 to 9 years), 46 patients died, 28 (61%) of whom had never received ERT. After adjustment for age, sex, country of residence, and disease severity (based on wheelchair and ventilator use), ERT was positively associated with survival (hazard ratio, 0.41; 95% CI, 0.19 to 0.87).

Conclusion

This prospective study was the first to demonstrate the positive effect of ERT on survival in adults with Pompe disease. Given the relatively recent registration of ERT for Pompe disease, these findings further support its beneficial impact in adult patients.

Background

Pompe disease (glycogen storage disease type II, acid maltase deficiency) is a rare metabolic myopathy caused by a deficiency of lysosomal acid α-glucosidase (GAA), resulting in the intralysosomal accumulation of glycogen. Pompe disease is characterized by a progressive loss of muscle strength and respiratory function and is inherited in an autosomal recessive manner [1]. Historically, supportive care has been the mainstay of treatment. Following decades of research, enzyme replacement therapy (ERT) for Pompe disease was approved in Europe and the United States in 2006, prompting a new era in the treatment of this disease. This was the first disease-specific treatment for an inherited muscular disorder,[2] consisting of the intravenous administration of recombinant human GAA (alglucosidase alfa).[3]

The therapeutic efficacy of alglucosidase alfa was first demonstrated in classic infantile Pompe disease.[3,4] Patients with classic infantile Pompe disease present with symptoms shortly after birth and develop significant, progressive hypertrophic cardiomyopathy and loss of skeletal muscle function within months if they remain untreated.[5] Cardiorespiratory failure is the primary cause of mortality, typically occurring within the first year of life.[5] With the introduction of ERT, survival in patients with classic infantile Pompe disease has increased significantly;[5] the oldest infants treated with ERT are now 14 years of age.[4,6]

The rapid decline in classic infantile Pompe disease is explained by the complete lack of GAA activity.[1] However, the majority of patients with Pompe disease express some residual GAA activity, leading to a spectrum of disease presentations.[7] In adults, the disease progresses more slowly, with loss of ambulation and wheelchair and respirator dependency developing in later stages of the disease at varying ages.[8] Their primary cause of death is respiratory failure.[1,7]

Trials of ERT in adults were initiated much later than those in infants. The first and only placebo-controlled randomized trial started at the end of 2005 and included 90 patients. Over a period of 78 weeks, treatment with alglucosidase alfa resulted in an improved walking distance on the six-minute walk test and stabilization of pulmonary function, meeting both primary endpoints of the trial.[9] Since 2006, more adult patients are gradually being treated,[10-15] but no studies to date have assessed the impact of ERT on survival in adults.

As an ultra-orphan drug, alglucosidase alfa is an expensive treatment; in several countries around the world, its high cost and lifelong administration have led to a debate on its reimbursement in adults. Survival is a key parameter in this discussion. Our centre has systematically collected data on patients with Pompe disease since 2002, before the approval of ERT. This activity has provided a unique set of long-term survey-based data allowing the evaluation of a large international patient population, both treated and untreated. To date, this database has the longest consistent follow-up providing information on patients with Pompe disease prior to and following ERT initiation. Findings from this survey recently revealed that untreated adults with Pompe disease have higher mortality than the general population.[16]

Age, wheelchair and ventilator dependency, and level of handicap appeared to be the main indicators of lower life expectancy.[16]

The aim of the current study was to use data collected from the same patient survey to explore the potential effect of ERT on survival in adults with Pompe disease. We report here the results of this prospective, international observational study.

Methods

The International Pompe Association /Erasmus MC Pompe Survey

The International Pompe Association (IPA)/Erasmus MC Pompe Survey, an ongoing international observational follow-up study on the clinical course of patients with Pompe disease, has continually enrolled patients since May 2002. The design of this prospective study was described elsewhere.[17,18] Patients were recruited through patient organizations affiliated with the IPA from Australia, Canada, Germany, the Netherlands, the United Kingdom, the United States, and a small number of patients from other countries. Dutch patients included in the analyses participated either directly through the Erasmus MC (the designated centre for all known patients with Pompe disease in the Netherlands) or through the Dutch patient organization. Enrolment was independent of the stage of disease and the age of disease onset. The IPA / Erasmus MC Pompe Survey covers the entire spectrum of the disease and is representative of the adult Pompe population.[19]

Information was collected through annual questionnaires, which asked patients about their medical history, current disease status, use of care, and quality of life. For Dutch patients, additional data were obtained during regular clinical evaluations at Erasmus MC, producing more frequent follow-up measurements than for other patients. The date of the last completed questionnaire before September 2011 was considered as the date of last follow-up, or – for the Dutch group – the date of the last visit if this came last. When questionnaires were not returned it was investigated whether the patient had died. The date of death was either reported, or estimated to be halfway between the date of completion of the last questionnaire and the date at which the next questionnaire should have been completed.

All research protocols were approved by the Medical Ethics Committee of Erasmus MC and/or the Central Committee on Research Involving Human Subjects. Written informed consent was obtained from all patients.

The current study included only patients 18 years of age or older at study entry and used data collected until September 2011. At that time, the database included information on 369 participants 18 years of age or older at enrolment. Patients were excluded from the analysis if only baseline data were available (n=71), if they had started receiving ERT before study enrolment (n=13), or if relevant baseline data were missing (n=2).

Statistical analysis

Data describing the patients' characteristics are presented as medians and ranges. Patient characteristics were compared using the Mann-Whitney test or the X^2 test. Survival time was assessed from the date of study entry until the date of last follow-up or until death. The association between overall survival of adult patients and treatment with ERT was estimated using time-dependent Cox proportional hazard regression models, both for univariable as well as multivariable analyses. The following covariates were considered and chosen a priori: age, sex, disease severity (based on wheelchair and ventilator use), and country of residence. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Two models were generated to describe the relationship between ERT and overall survival in adult patients with Pompe disease. In both models, ERT was included as a time-dependent covariate that took the value 0 before the start of treatment and switched to 1 at the start of treatment. As long as patients were not receiving ERT, they contributed to the untreated group and acted as controls for the treated patients during the treatment period. In the primary model (model 1a), in addition to ERT, age categories and disease severity were also modeled as time-dependent covariates and hence were updated at the start of ERT. An intent-to-treat approach was adopted in which patients who discontinued treatment were considered to have remained in the treatment group until the end of follow-up. The sensitivity of these analyses to including age and severity as time-dependent covariates was investigated using a second model with ERT as a time-dependent variable only (model 2a). Further to the intent-to-treat approach, the primary and secondary analyses were also conducted to account for the actual treatment duration. In these models, all patients who discontinued treatment were censored at the time of discontinuation (models 1b and 2b). The validity of the proportional hazards assumption was assessed by examining plots of the cumulative hazard function on a linear and logarithmic scale, stratified by categories of the covariates. Proportionality was assumed if the curves were parallel.

Statistical tests were conducted using SPSS for Windows (version 17; SPSS Inc., Chicago, IL) and SAS (version 9·2; SAS Institute Inc., Cary, NC). A P-value ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

Overall, 283 adult patients with Pompe disease (77% of those enrolled) were eligible for analysis. The baseline characteristics of these patients are shown in Table 1. Seventy-two percent of patients started ERT at some time during follow-up, and 28% never received ERT. The median age of the patients at study entry was 48 years (range, 19 to 81 years), with a median disease duration of 9 years (range, 0 to 32 years). Fifty-three percent of the patients were women.

Table 1. Patient characteristics and follow-up*

Characteristics	n = 283
Female, n (%)	149 (53)
Median age at study entry, years (range)	48 (19-81)
Median age at diagnosis, years (range)	38 (1-72)
Median disease duration at study entry, years (range)	9 (0-32)
Country of residence, n (%)	
Netherlands	109 (39)
United Kingdom	23 (8)
United States	71 (25)
Germany	48 (17)
Other†	32 (11)
Disease severity at study entry, n (%)	
No wheelchair use or respiratory support‡	134 (47)
Wheelchair use	37 (13)
Use of respiratory support	42 (15)
Both wheelchair use and respiratory support	70 (25)
Median follow-up time, years (range)	6 (0.04-9)
ERT during the course of the study, n (%)	204 (72)
Median ERT duration, years (range)	4 (0.2-8)
Median age at start of ERT, years (range)	51 (24-76)
Died during follow-up, n (%)	46 (16)
Median age at death, years (range)	59 (23-86)

*Continuous variables are expressed as median (range). Categorical variables are expressed as n (%). ERT denotes enzyme replacement therapy. †Including patients from Australia and Canada.‡Respiratory support includes partial and full-time invasive and non-invasive respiratory support.

Table 2 shows the characteristics of the ERT and the non-ERT groups at the start of ERT and at study entry. For patients who received ERT during follow-up, the median age at the start of ERT was comparable to the median age at study entry of patients who never received ERT. Differences in sex, age at diagnosis, disease duration, and disability level (based on use of wheelchair and respiratory support) between treated patients at the start of ERT and untreated patients at enrolment were not significant, whereas country of residence differed with borderline statistical significance.

Table 2. Patient Characteristics for the ERT Group at Study Entry or Start of ERT and for Untreated Patients at Study Entry*

Characteristics	ERT Group (n=204)		Non-ERT Group (n=79)	P-Value†
	At Study Entry	At Start of ERT	At Study Entry	
Female, n (%)	104 (51)	104 (51)	45 (57)	0.37
Median age at study entry/start of ERT, years (range)	47 (19-73)	51 (24-76)	51 (20-81)	0.48
Median age at diagnosis, years (range)	38 (1-72)	38 (1-72)	42 (2-67)	0.45
Median disease duration at study entry/start of ERT, years (range)	7 (0-31)	11 (0.2-33)	12 (0-32)	0.75
Country of residence, n (%)				0.05
Netherlands	86 (42)	86 (42)	23 (29)	
United Kingdom	18 (9)	18 (9)	5 (6)	
United States	44 (22)	44 (22)	27 (34)	
Germany	37 (18)	37 (18)	11 (14)	
Other‡	19 (9)	19 (9)	13 (17)	
Disease severity at study entry/start of ERT, n (%)				0.45
No wheelchair use or respiratory support§	99 (49)	70 (34)	35 (44)	
Wheelchair use	26 (13)	37 (18)	11 (14)	
Use of respiratory support	31 (15)	29 (14)	11 (14)	
Both wheelchair use and respiratory support	48 (24)	68 (33)	22 (28)	
Median follow-up time from study entry/start of ERT, years (range)	7 (1–9)	4 (0.2-8)	4 (0.04-9)	0.05
Died during follow-up, n (%)	18 (9)	18 (9)	28 (35)	<0.001

*Continuous variables are expressed as median (range). Categorical variables are expressed as n (%). ERT denotes enzyme replacement therapy. †P-value for differences between ever-treated patients at the start of ERT and never-treated patients (at study entry) as assessed with a Mann-Whitney test or the $\chi 2$ test. ‡Including patients from Australia and Canada. §Respiratory support includes partial and full-time invasive and non-invasive respiratory support.

During the 1676 person-years of follow-up (median, 6 years; range, 0.04 to 9 years), for 46 patients a death confirmation was received from the patient organization, the family or the treating physician. Twenty-eight (61%) of these patients were in the non-ERT group. The median age at death was 59 years (range, 23 to 86 years). Compared with the total patient population, the deceased patients were more severely affected by Pompe disease at study entry. Thirty-seven of the 46 deceased patients (80%) used either a wheelchair or a ventilator or both at study entry compared with 53% of the overall patient population. Causes of death in 21 of the 46 cases were (n=16) or could be (n=5) related to Pompe disease (e.g., respiratory insufficiency). In the remaining 25 cases, the cause of death was either unknown (n=20) or not

related to Pompe disease (n=5). Of the 28 patients who died without ever having received ERT, 19 died before or in the year that ERT obtained approval (2006), and 9 died later.

Nineteen of the 204 patients who received ERT stopped treatment during follow-up. The median treatment duration in these patients was 1.4 years (range, 0.2 to 4.7 years), and the median time after stopping treatment until the end of follow-up was 1.2 years (range, 0.05 to 4.0 years). Reasons for discontinuation were related to allergic type reactions/adverse events (n=10), lack of treatment effect (n=4), pregnancy (n=2), and unknown (n=3). Four of the patients who stopped treatment died, including 3 who had received ERT for less than 1.5 years. Of these 4 patients, 1 died 6 weeks after stopping treatment, and the other 3 patients died between 1 and 2.5 years after stopping treatment.

Table 3. Risk of death for 283 adults with Pompe disease applying time-dependent Cox regression*

Time-Dependent Cox Regression Model	Model 1a†		
	HR	95% CI	P-Value
ERT‡	0.41	0.19 to 0.87	0.02
Age (in quartiles)			0.14
<37 years (ref)	1		
37-48 years	1.26	0.38 to 4.12	0.71
48-57 years	1.42	0.44 to 4.61	0.56
≥57 years	2.57	0.86 to 7.72	0.09
Sex	1.01	0.55 to 1.87	0.98
Disease severity			0.001
No wheelchair use or respiratory support ᵐ (ref)	1		
Wheelchair use	2.87	0.98 to 8.36	0.05
Use of respiratory support	2.05	0.62 to 6.77	0.24
Both wheelchair use and respiratory support	5.32	2.25 to 12.56	<0.001
Country of residence			0.13
Netherlands (ref)	1		
United Kingdom	1.35	0.46 to 3.95	0.58
United States	2.14	1.01 to 4.55	0.05
Germany	0.62	0.19 to 1.95	0.41
Other§	1.23	0.42 to 3.63	0.70

*ERT denotes enzyme replacement therapy and HR hazard ratio. †Intent-to-treat approach with ERT, age categories, and disease severity as time-dependent covariates. ‡Values for ERT were derived after adjustment for age, sex, disease severity, and country of residence. ᵐRespiratory support includes partial and full-time invasive and non-invasive respiratory support. § Including patients from Australia and Canada.

Association between ERT and survival

Table 3 summarizes the results from the primary multivariable Cox proportional hazard regression model (model 1a). ERT was shown to be positively associated with survival (HR, 0.46; 95% CI, 0.22 to 0.95) in the univariable analysis. After adjustment for age, sex, country of residence, and disease severity, the HR for ERT was 0.41 (95% CI, 0.19 to 0.87). The model using only ERT as a time-dependent covariate (model 2a) produced an HR of 0.51 (95% CI, 0.24 to 1.10). The analyses in which the patients who discontinued treatment were included until discontinuation resulted in HRs of 0.33 (95% CI, 0.15 to 0.73) and 0.42 (95% CI, 0.19 to 0.93) for models 1b and 2b, respectively. The Forest plot in Figure 1 illustrates the HRs and 95% CIs of all models.

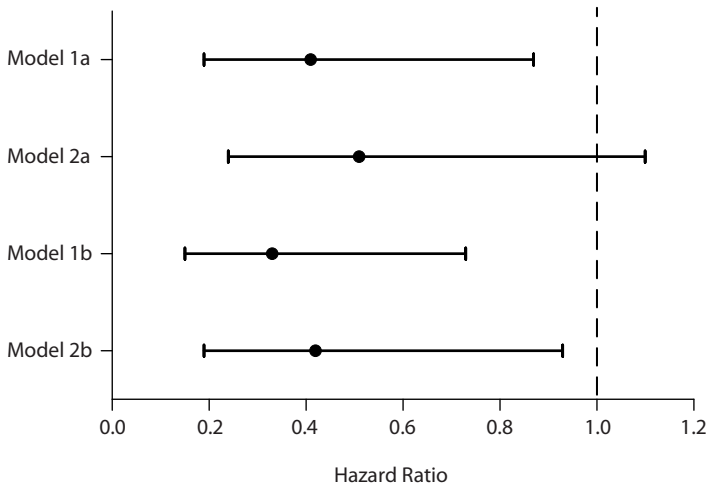

Figure 1. Adjusted hazard ratios of the different models describing the relationship between ERT and survival. Model 1a: Intent-to-treat approach with enzyme replacement therapy (ERT), age categories, and disease severity as time-dependent covariates. **Model 2a**: Intent-to-treat approach with only ERT as time-dependent covariate. **Model 1b**: Analysis excluding person-time after discontinuation of treatment with ERT, age categories, and disease severity as time-dependent covariates. **Model 2b**: Analysis excluding person-time after discontinuation of treatment with only ERT as time-dependent covariate.

Discussion

This is the first study to show the beneficial effects of ERT on the survival of adult patients with Pompe disease, a clinically meaningful finding especially given the slowly progressive disease course and relatively short treatment period. ERT in Pompe disease was initially approved for all patients in the United States and Europe on the basis of the prolonged survival of severely

affected infants with classic Pompe disease and later by the significant gain in walking distance and stabilized pulmonary function in adult patients.[8,9,20]

We observed the significant effect of ERT on survival as part of an international observational study that provided access to data from 283 adult patients with Pompe disease. Because most adult patients with Pompe disease eventually die of respiratory failure,[1,7] the beneficial effect of ERT on survival is likely to be related to its positive effect on pulmonary function. The hazard ratio of 0.41 indicates that given a specific point in time a patient on ERT has a 59% smaller chance of dying than someone not on ERT. The interpretation of this effect over the entire follow-up period is, however, not intuitive. Because of the time-dependent nature of the analysis it was not possible to estimate the additional years of life gained under ERT. However, we have made 'ad hoc' calculations assuming the adjusted HR can be interpreted as a relative risk over approximately 4 years median and 8 years maximum follow-up (from start of treatment). Using the overall raw death rate as an estimate of the raw death rate of the treated population (16%, 46/283), eight years of ERT would result in 1 year of life gained.

Our estimate should be conservative as many patients in our cohort started treatment late in their disease course and ERT was not registered until 2006. It has been hypothesized that starting treatment early in the disease course results in a better clinical outcome.[9-11,13] Indeed, all patients (with one exception) in the ERT group who subsequently died were dependent on a wheelchair and/or a ventilator and thus had a very advanced stage of disease when they first received ERT. The effect of ERT on survival may therefore be greater if treatment is initiated earlier. In addition, the positive effect of ERT observed in this analysis overall suggests that patients with advanced disease may also benefit from treatment. Further research is required to investigate the association between disease severity and treatment effect.

Collecting sufficient data to demonstrate treatment efficacy is a challenge in rare diseases. Demonstrating improved survival is particularly difficult in a slowly progressive disease such as adult Pompe disease. The opportunity to compare the natural course of Pompe disease with the disease course following ERT highlights the importance of our unique database. In this cohort, the majority of patients switched from being untreated to being treated with ERT during follow-up. Therefore, we conducted Cox regression analyses using ERT as a time-dependent variable, which was considered the most suitable method because it prevents "immortal time" bias. Immortal time bias refers to a period of follow-up or observation time during which death cannot occur,[21] which in our study would be the time until ERT became available for the patients who survived to that time point and received treatment afterward.

Our study was observational and did not have the scientific rigor of a randomized controlled trial, which is generally considered the most appropriate method for comparing the effects of (alternative) treatments. However, a placebo-controlled randomized clinical trial over as many years as in our observational study is not possible nor is it ethically acceptable to conduct; our prospective follow-up study provided a valid alternative.[22] In addition, a clinical trial requires very strict inclusion and exclusion criteria and may not be representative of the

entire adult Pompe patient population. Recruitment through a patient organization could also result in more or less severely affected patients being excluded. However, demographic and clinical characteristics of our study population show that patients were included across the entire disease spectrum and were representative of the whole patient population. A number of confounders were adjusted for in the analysis, including age, gender and disease severity, as well as country of residence to capture country specific differences such as variation in approaches to care. Selection bias was further minimized through the time dependent nature of the analysis, as the same patient could contribute to both the untreated and treated period.

Our results were robust across the different models, strengthening our conclusion that ERT positively influences patient survival. We used the equivalent of an intent-to-treat approach, because this is the standard method of analysis used to assess treatment effects in clinical trials. This cohort included 19 patients who stopped treatment during follow-up, and it may be perceived as unfair to include their time after discontinuation of ERT as "time on treatment". An additional analysis in which patients who discontinued treatment were followed only until the end of treatment provided similar results to the intent-to-treat analyses, but with greater statistical significance.

Conclusions

Enzyme replacement therapy with alglucosidase alfa is currently the only approved disease-specific therapy for Pompe disease. Although not curative, it has changed patients' perspectives through demonstrated improvements in muscle strength, pulmonary function, and other clinical parameters. Our novel findings reported here show ERT to also have a positive impact on survival of adult patients with Pompe disease. This may be considered an important and clinically meaningful observation, which is particularly relevant with respect to the recent discussion concerning the reimbursement of ultra-orphan drugs.

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Chapter 6

Pain in adult patients with pompe disease: A cross-sectional survey

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Abstract

Background

Pompe disease is a rare hereditary metabolic myopathy caused by a deficiency of acid-α-glucosidase. We investigated the presence and severity of pain and its interference with daily activities in a large group of adults with Pompe disease, who we compared with an age-matched control group.

Methods

Data were collected in a cross-sectional survey in Germany and The Netherlands. Pain was assessed using the short-form brief pain inventory (BPI). Patients also completed the Short Form-36 item (SF-36v2), the Hospital Anxiety and Depression Scale (HADS) and the Rotterdam Handicap Scale (RHS).

Results

Forty-five percent of the 124 adult Pompe patients reported having had pain in the previous 24 h, against 27% of the 111 controls ($p=0.004$). The median pain severity score in Pompe patients reporting pain was 3.1 (on a scale from 0 to 10), indicating mild pain; against 2.6 amongst controls ($p=0.06$). The median score of pain interference with daily activities in patients who reported pain was 3.3, against 1.3 in controls ($p=0.001$). Relative to patients without pain, those with pain had lower RHS scores ($p=0.02$), lower SF-36 Physical and Mental component summary scores ($p<0.001$ and $p=0.049$), and higher levels of depression and anxiety ($p=0.005$ and $p=0.003$).

Conclusions

To date, this is one of the largest studies on pain in a specific neuromuscular disorder. Nearly one in two Pompe patients had experienced pain in the previous 24 h. Although pain severity and its interference with daily life were mild, pain was related to a reduced quality of life, less participation in daily life, and greater depression and anxiety. Its management should therefore be seen as part of clinical practice involving Pompe patients.

Introduction

Pompe disease (glycogen storage disease type II) is a rare autosomal recessive metabolic myopathy caused by a deficiency of the enzyme acid α-glucosidase (GAA). The deficiency of this lysosomal enzyme results in glycogen storage, particularly in skeletal and respiratory muscles.[1,2] In 2006, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase was registered as a treatment for Pompe disease.[3-6] In adult patients, ERT has improved and/or stabilized pulmonary function, and has also improved walking distance.[7] Without treatment, the foremost features of the disease in these patients are progressive loss of muscle and deteriorating respiratory function.[8-10]

As well as effects on skeletal and respiratory muscle function, other important symptoms of Pompe disease include fatigue and scoliosis.[11,12] While patients have referred to pain as a symptom of Pompe disease, the literature has so far devoted little attention to it. Although, overall, a focus on pain in neuromuscular disorders (NMD) is rather recent, it has become clear that pain can be a prominent feature of many different NMDs,[13-17] and that it affects patients' quality of life and mental health.[14,16,18] Pain is also a highly prevalent symptom in lysosomal storage disorders such as Fabry and Gaucher disease,[19,20] in McArdle's disease (glycogen storage disease type V), myalgia is one of the dominating features.[21] In patients with Pompe disease, it may thus be an overlooked symptom.

Few studies have described pain in Pompe patients. One study in German patients with 'non-classic' Pompe disease reported myalgia as an initial symptom in 18% of the patients.[10] In a second study of Dutch 'non-classic' Pompe patients, almost half the patients experienced pain, very often in the legs.[8] In both studies, pain was not the main focus, and only assessed with a single item question. If pain in Pompe disease is to be managed appropriately, its severity and nature should be well defined, as should its effect on patients' functioning and participation in daily life.

In this cross-sectional survey, we therefore assessed the prevalence, severity and characteristics of the pain experienced by 124 adult Pompe patients, comparing these variables with those in an age-matched control group. As our second research question, we investigated whether pain was associated with lower quality of life and participation, and also with anxiety and depressive symptoms.

Methods

Patients and controls

Patients were either recruited through the German patient organization (Selbsthilfegruppe Glykogenose Deutschland e.V., n=110) or through Erasmus MC University Medical Center (n=98), which is the national referral center for Pompe disease in the Netherlands. Controls,

who had to be free of Pompe disease, were either partners, relatives or acquaintances of Pompe patients or of other neuromuscular patients. Their age was approximately the same as that of the Pompe patients who had been recruited. The study was approved by the Local Ethics Committees at Martin-Luther-University Halle (Saale) and Erasmus MC University Medical Center. All participants gave informed consent.

Questionnaires

Data were obtained through a one-time survey conducted between June 2011 and November 2012, and included general data on patient characteristics and medical history.

The Short form of the Brief Pain Inventory (BPI)[22] was used to assess the presence and severity of current pain (pain within the previous 24 h), its interference with daily activities, and other aspects of pain. The BPI was especially designed to capture pain severity and interference (i.e. interference with activities and emotions). It is a validated tool that was originally developed to assess pain in cancer patients, but has also been used in other diseases, including neuromuscular disorders.[22] It has been shown to have good reliability and validity with patients with malignant and non-malignant pain.[22,23] It measures the prevalence of pain other than everyday kinds of pain such as minor headaches, sprains and toothache.

Four items of this 9-item questionnaire are devoted to severity of pain, and ask patients to rate the worst, least, and average pain experienced in the previous 24 h, and also to rate current pain. The average of these 4 items results in a Pain Severity Score (PSS), which ranges from 0 (no pain) to 10 (pain as bad as you can imagine). A Pain Interference Score (PIS) ranging from 0 (does not interfere) to 10 (completely interferes), is calculated on the basis of the average interference of pain with the following seven activities: general activities, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. If individual items were missing, we calculated the PSS and PIS on the basis of the remaining items. Finally, the BPI assesses the sites of pain and its treatment.

As well as completing the BPI, patients with Pompe disease also completed three other measurement scales: 1) the Short Form Health Survey 36 version 2 (SF36v2),[24] which measures quality of life; 2) the Hospital Anxiety and Depression Scale (HADS),[25] in order to assess the occurrence of anxiety and depression; and 3) the Rotterdam Handicap Scale (RHS), in order to determine the level of 'participation', which is defined as a person's involvement in daily life situations (previously called 'handicap').[26] All three scales have been shown to have good reliability and validity, and have been used in patients with Pompe disease and other NMDs.[14,18,27-30]

All questionnaires were available in German and Dutch.

Statistical analysis

Descriptive statistics were used to summarize all variables for the patient and control groups. To assess differences in demographic characteristics and differences in the prevalence, severity,

interference and treatment of pain between patients and controls, we used the Chi-square (trend) test for discrete data, or the Mann Whitney U test for continuous data. Both tests were also used to assess differences in characteristics and quality of life, participation, depression and anxiety of patients with and without pain.

The internal consistency of the BPI pain-severity and interference scores was good, with a Cronbach's alpha coefficient of 0.94 for the Pain Severity Score and 0.95 for the Pain Interference Score. Test–retest reliability was moderate to good, with the intra-class correlation coefficient of the Pain Severity and Interference items and pain prevalence ranging between 0.73 and 0.87. The PSS (Spearman correlation coefficient -0.64) and the PIS (Spearman correlation coefficient -0.60) both correlated moderately with the bodily pain domain of the SF36, thereby supporting the construct validity of the BPI.

A significance level of 0.05 was used. All analyses were performed using SPSS for Windows (version 20.0, SPSS Inc., Chicago, IL).

Results

Response and patient characteristics

We invited 208 patients to participate in this survey, 124 of whom took part; 62 were Dutch and 62 were German. The overall response rate was 60%: 63% for the Dutch patients and 56% for the German patients. The demographic profiles are listed in Table 1. Patients had a median age of 53 years (range 19-74); median disease duration since onset of symptoms was 18 years (range 1-62). Fifty-six percent of patients were female. At the time of the survey, 81% of patients were receiving ERT, 12% had never received it, and 6% had received it previously but had discontinued their treatment.

A total of 111 controls responded out of 166 contacted (response rate 66%): 58 from Germany (response rate 89%) and 53 from the Netherlands (response rate 52%). The median age of the controls was 53 years (range 18-78); 59% were female (Table 1). There were no significant differences between the age and gender of patients and controls, or between the German and Dutch controls.

Prevalence, severity and interference of pain

Forty-five percent of the 124 patients reported having pain, against 27% of controls: a statistically significant difference (p=0.004). These figures, which were obtained with the BPI short-form, refer to the prevalence of pain in the last 24 h, and encompass pains other than the everyday kinds of pain such as minor headaches, sprains and toothaches.

Table 2 shows the severity of pain and its interference with daily life in patients and controls. On a scale from 0 to 10, the median Pain Severity Score (PSS) amongst patients reporting

pain in the previous 24 hours was 3.1 (range 0.75-8). For controls with pain, it was 2.6 (range 0.75-5.25), and did not significantly differ from patients (p=0.06).

Table 1. Demographic characteristics of 124 adult patients with Pompe disease and 111 controls

Characteristic	Patients (n=124)	Controls (n=111)	P-Value[a]
Median age, years (range)	53 (19-74)	53 (18-78)	0.71
Female, n (%)	69 (56)	66 (59)	0.56
Nationality, n (%)			0.73
German	62 (50)	58 (52)	
Dutch	62 (50)	53 (48)	
Median age at first symptoms, years (range)	33 (0-66)	NA	
Median disease duration, years (range)	18 (1-62)	NA	
ERT, n (%)			
Currently receiving	101 (81)	NA	
Never received	15 (12)		
Discontinued	8 (6)		
Median age at start ERT, years, (range)	49 (13-73)	NA	
Median ERT duration, years (range)	4 (0.07-12)	NA	

The percentages may not always add up to 100% due to rounding. N=number; %=percentage; NA=Not Applicable; ERT=Enzyme Replacement Therapy. [a]Difference between patients and controls assessed with the Chi-square test and the Mann Whitney U test for discrete and continuous data, respectively.

At 3.3 (range 0-8.4), patients' median Pain Interference Score (PIS) differed significantly from that of controls (PIS 1.3 (range 0-4.4); p=0.001). Pain interfered especially with patients' general activities, walking, and normal work (score of 4), followed by mild interference with mood, sleep and enjoyment of life (score of 3). Relationships with other people were the least affected (rate of 2). For each of the seven domains of daily life, interference scores were significantly worse in patients than in controls, except for interference with sleep.

Sites and type of pain, and treatment

Figure 1 shows the reported sites of pain in patients and controls. Eighty-four percent of the patients with pain reported pain in more than one site. The back (50%), the shoulders (48%), and the upper legs/thighs (46%) were the most affected by pain. In the control group the back (40%) and shoulders (33%) were also the two most affected sites, followed by the knees (30%). Controls rarely reported pain in the upper legs/thighs (3% versus 46% in patients).

Figure 2 depicts the way pain was described by patients and controls. The commonest word patients used to describe pain was "exhausting" (70%), a term that was used less frequently by controls (30%). Pulling/tearing and dull/pressing pains were frequent in both patients (57% and 55%, respectively) and controls (37% and 57%, respectively).

Table 2. Characteristics of pain as reported by 56 patients and 30 controls in the Brief Pain Inventory.

	Pompe patients reporting pain[a]	Controls reporting pain	P-Value[b]
Number (%) out of total population	56 (45%)	30 (27%)	0.004
Pain severity (0-10)			
Median Pain Severity Score (range)	3.1 (0.75-8.0)	2.6 (0.75-5.25)	0.06
Pain Severity Subgroups			0.04[c]
No pain (rating of 0), n (%)	-	-	
Mild pain (1-3), n (%)	31 (55)	23 (77)	
Moderate pain (4-6), n (%)	22 (39)	7 (23)	
Severe pain (7-10), n (%)	3 (5)	-	
Pain related interference with daily activities (0-10)			
Median Pain Interference Score (range)	3.3 (0-8.4)	1.3 (0-4.4)	0.001
General activity, median, (range)	4.0 (0-9.0)	3.0 (0-6.0)	0.02
Mood, median, (range)	3.0 (0-9.0)	1.0 (0-5.0)	0.004
Walking ability, median, (range)	4.0 (0-10.0)	2.0 (0-8.0)	0.001
Normal work, median, (range)	4.0 (0-10.0)	2.0 (0-8.0)	0.003
Relations with other people, median, (range)	2.0 (0-9.0)	0 (0-3.0)	0.001
Sleep, median, (range)	3.0 (0-10.0)	2.0 (0-9.0)	0.10
Enjoyment of life, median, (range)	3.0 (0-9.0)	1.0 (0-7.0)	0.01
Treatment for pain			
Patients receiving treatment for pain, n (%)	39 (70)	12 (40)	0.01

The percentages may not always add up to 100% due to rounding. N=number; %=percentage. [a]Patients who reported to have had pain the last 24 h. [b]Difference between patients and controls assessed with the Chi-square test and the Mann Whitney U test for discrete and continuous data, respectively. [c]Chi-square trend test.

Thirty-nine of the 56 patients with pain (70%) reported receiving trea tment for it. Twenty of them used medication only (mainly non-steroidal anti-inflammatory drugs (NSAIDS), and paracetamol (acetaminophen), but also opiates, etc). Eight received physical therapy alone, and 11 received a combination of physiotherapy and medication. Fifty-five percent of the patients with mild pain used some kind of pain therapy, against 88% of the patients with moderate to severe pain. On average, patients stated that these treatments/medications relieved their pain by 50% (range 0-100). Only 40% of the controls with pain used treatments for it, which was significantly different from patients (p=0.01). Seven controls used medication only, two physical therapy, and three a combination of the two.

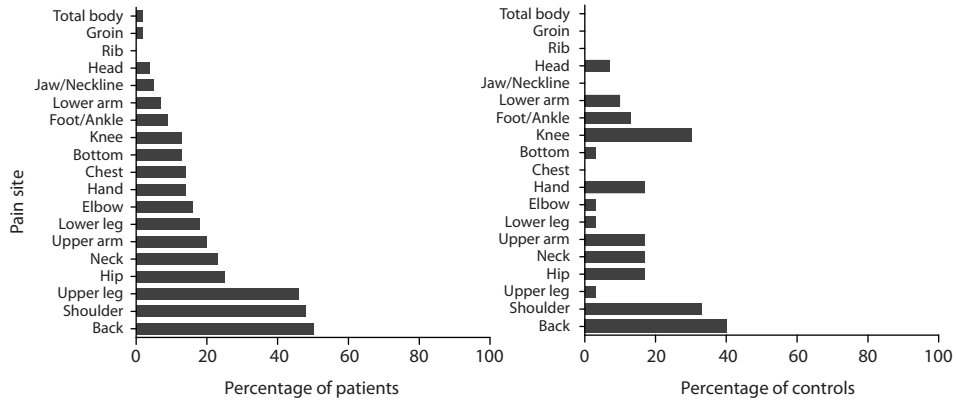

Figure 1. Sites of pain (in/across different areas of the body) in 56 Pompe patients and 30 controls reporting pain in the last 24 h.

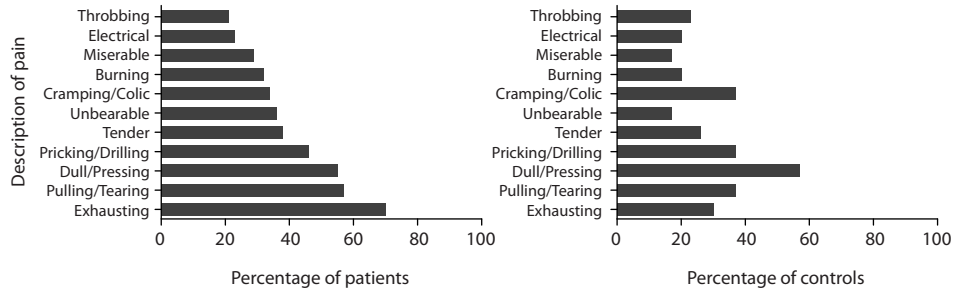

Figure 2. Description of the type of pain by 56 Pompe patients and 30 controls reporting pain in the last 24 h.

Association of pain with patients' demographic characteristics, clinical characteristics and health status

In terms of age, sex, disease duration, and the use of ERT, Pompe patients reporting pain were similar to patients who did not report pain (Table 3). Amongst patients receiving ERT, the median treatment duration was longer amongst patients not reporting pain (p=0.02).

Relative to patients without pain those reporting pain had significantly lower (i.e. worse) Physical (p<0.001), and Mental (p=0.049) Component Summary Scores on the SF-36v2 (Table 3). Similarly, the HADS depression score (p=0.005) and anxiety scores (p=0.003) were higher (i.e. worse) in patients with pain, and the RHS scores were lower in patients with pain (p=0.02).

Table 3. Differences in characteristics and health status between patients with Pompe disease reporting pain and not reporting pain.

Characteristic	Pain (n=56)	No pain (n=68)	P-Value [a]
Median age, years (range)	55 (25-74)	49 (19-74)	0.12
Female, n (%)	35 (63)	34 (50)	0.16
Median age at first symptoms, years (range)	34 (2-66)	32 (0-57)	0.35
Median disease duration, years (range)	18 (1-62)	19 (3-59)	0.91
Nationality, n (%)			0.43
German	29 (52)	33 (49)	
Dutch	27 (48)	35 (51)	
ERT, n (%)			0.63 [b]
Currently receiving	44 (79)	57 (84)	
Never received	7 (13)	8 (12)	
Discontinued	5 (9)	3 (4)	
Median age at start ERT, years, (range)	50 (24-73)	48 (13-70)	0.57
Median ERT duration, years (range)	4 (0.07-9)	5 (0.27-12)	0.02
Measurement scales			
Median SF36v2 PCS score (range)	30 (11-45)	35 (17-58)	<0.001
Median SF36v2 MCS score (range)	54 (29-74)	58 (29-71)	0.049
Median HADS depression score (range)	5 (0-13)	2 (0-14)	0.005
Median HADS anxiety score (range)	5 (0-15)	3 (0-12)	0.003
Median RHS score (range)	26 (15-36)	28 (16-36)	0.02

Percentages may not always add up to 100% due to rounding. N=number; %=percentage, ERT=Enzyme Replacement Therapy; SF-36v2=Short Form Health Survey 36 version 2; PCS=Physical Component Summary; MCS=Mental Component Summary; HADS=Hospital Anxiety and Depression Scale; RHS=Rotterdam Handicap Scale. [a]Difference between patients with and those without pain assessed with the Chi-square test and the Mann Whitney U test for discrete and continuous data, respectively. [b]Chi-square trend test.

Discussion

This is the first study to describe the prevalence and characteristics of pain in a large number of adult patients with Pompe disease. It is also one of the largest studies on pain in a specific neuromuscular disorder. We show that the prevalence of pain was significantly higher in patients with Pompe disease (45%) than in controls (27%). Nearly one Pompe patient in two had experienced pain in the previous 24 h, against just over 1 in 4 controls.

While the Pain Severity and Pain Interference Scores in our patient group might be seen as mild,[31] and while few patients reported severe pain, some of the mildness may be attributable to the fact that two-thirds (70%) of patients with pain used pain medication – a much higher

proportion than in controls (40%). Similarly, the interference of pain in patients' daily lives was higher than in controls, and Pompe patients with pain had significantly lower participation and quality of life scores and higher levels of depression and anxiety than those without. Overall, this indicates that, despite the mild severity and interference scores, pain is an important debilitating symptom in Pompe disease, and thus warrants further attention.

The estimated prevalence of pain in this study was similar to an earlier study amongst a subset of Dutch Pompe patients (46%)[8] and higher than its occurrence as the first symptom in German patients (18%).[10] These two studies were based on non-validated single-item questions to assess pain and did not use a specific pain questionnaire like the BPI. In another study of 51 Dutch patients, we could not detect significant differences in pain with the general population.[27] In this study we used the SF36, which focuses on general bodily pain and hence does not measure exactly the same construct of pain. Both the different estimates and the lack of use of specific pain questionnaires were reasons for us to perform more detailed investigations into pain in Pompe disease. Recent studies of other neuromuscular disorders reported a prevalence of pain between 51% and 100%.[13-18] In addition to differences between diseases, these higher pain estimates may also have been due to the different questionnaires used, in which also the time-frame to assess pain differed. A study that did use the BPI-short form assessed pain in patients with Rheumatoid Arthritis, in which pain is the dominant symptom, and reported that all patients had pain.[32]

The use of different scales in different studies clearly indicates a lack of consensus on which type of pain measure should be used. Due to the growing awareness of pain as an important aspect of various neuromuscular diseases, we therefore suggest that the various stakeholders invest in reaching consensus on this matter. Our own decision to use the BPI short form to assess pain in this study lay in the fact that it has been validated, is short and easy to complete. One potential disadvantage is that it assesses current pain (i.e. pain in the previous 24 h) rather than pain over a longer period, and may thus underestimate the presence of chronic pain. On the other hand, recall bias is minimized.

Distinct features of pain described by patients with Pompe disease were its location in the upper legs – which was seldom reported by controls – and its description as exhausting. The pain experienced in Pompe disease may have various causes. Postural problems resulting from mechanical stress imposed on the musculoskeletal system by muscle weakness may lead directly or indirectly to local pain.[33] Another possible form of pain is muscle pain, which is likely to explain the pain in the upper legs/thighs, and also the type of exhausting pain described by patients. In McArdle's disease, where myalgia is a dominating symptom, the upper legs and thighs are also the sites most affected.[21,34] A comparable pain pattern is also seen in Myotonic Dystrophy type 2.[16,35]

While the exact mechanisms that cause pain in Pompe disease require further investigation, each mechanism may require a different therapeutic approach. Most patients in our study used some kind of treatment for pain, mainly over-the-counter drugs, but they also used other

drugs and physical therapy. Without these measures, the prevalence of pain might have been even higher. Patients reported a subjective average pain relief of about 50%, indicating that their current pain management did not suffice.

Whether ERT can itself help to reduce pain requires further research. In our study the use of ERT was similar between patients who reported pain and those who did not, while ERT duration was related to pain in those patients who did receive ERT. We were prevented from drawing any conclusions on this by the cross-sectional design and the small percentage of patients who were not on ERT.

Our study is the first to focus specifically on pain in Pompe disease, and has a relatively large sample of patients from two Western European countries. It also benefits from its comparison with a control group, which other pain studies often lack. In our view, the response rate of 60% is very reasonable. The design of the study, with recruitment partly through patient organizations without access to diagnostic data, means that the diagnosis could not be confirmed in all included patients. However, 90% of patients were known to us to be confirmed by mutation analysis, while most of the remaining patients had been started on ERT, which makes it reasonable to assume that the diagnosis was confirmed.

Conclusions

Although pain is not the dominant symptom of Pompe disease, this sample of Pompe patients clearly showed it to be a prevalent and debilitating symptom. As pain is generally a well-defined symptom for which many treatment options are possible, extra efforts should be made to manage it properly in this population. We suggest that research and clinical practice involving Pompe patients should identify and classify pain better, and should also adopt a mechanism-based treatment strategy.

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Chapter 7

Enzyme replacement therapy and fatigue in adults with Pompe Disease

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Abstract

Background

Pompe disease is a hereditary metabolic myopathy, for which enzyme replacement therapy (ERT) has been available since 2006. We investigated whether ERT reduces fatigue in adult patients with Pompe disease.

Methods

In this prospective international observational survey, we used the Fatigue Severity Scale (FSS) to measure fatigue. Repeated measures ANOVA was used to analyze the data over time. In a subgroup of patients, we also evaluated muscle strength using the Medical Research Council scale, measured pulmonary function as Forced Vital Capacity, and assessed depression using the Hospital Anxiety and Depression scale

Results

We followed 163 patients for a median period of 4 years before ERT and for 3 years during ERT. Before ERT, the mean FSS score remained stable at around 5.3 score points; during ERT, scores improved significantly by 0.13 score points per year ($p<0.001$). Fatigue decreased mainly in women, in older patients and in those with shorter disease duration. Patients' improvements in fatigue were moderately correlated with the effect of ERT on depression (r 0.55; CI 95% 0.07 to 0.70) but not with the effect of ERT on muscle strength or pulmonary function.

Conclusions

Fatigue is a common and disabling problem in patients with early and advanced stages of Pompe disease. Our finding that ERT helps to reduce fatigue is therefore important for this patient population, irrespective of the mechanisms underlying this effect.

Introduction

Fatigue accompanies many chronic neuromuscular and neurological disorders,[1,2] and is often reported by patients with Pompe disease,[3-5] an inherited metabolic myopathy caused by deficiency of acid alpha-glucosidase, a lysosomal enzyme. Pompe disease presents as a wide clinical spectrum, the most prominent symptoms in adults being muscle weakness and respiratory distress.[6,7] As well as these main symptoms, many adults – however badly affected – complain of fatigue.[5]

The pathophysiology of fatigue in neurological disorders is not fully understood. As well as physiological changes in the muscle or the Central Nervous System (CNS), it may involve respiratory dysfunction and/or inadequate energy expenditure or energy production. Psychological fatigue ('weariness') may also be involved.[1,2,8]

At present there are no proven therapeutic strategies to combat fatigue. Its general management involves identifying and treating contributory factors such as psycho-sociological factors, sleep disturbances, and comorbidities.[1]

Since 2006, enzyme replacement therapy (ERT) has become available for Pompe disease. Though this has been shown to positively affect respiratory and muscle functions in adults,[9-13] very little is known about its effect on fatigue. While three studies suggested that ERT reduces fatigue in adult patients,[14-16] we do not know of any study that has investigated this subject in detail.

To establish whether ERT reduces fatigue, we therefore investigated a large international cohort of adult Pompe patients. We also investigated whether the potential effect of ERT on fatigue differed between subgroups of patients, and whether it was related to improvements or changes in muscle strength, pulmonary function, and/or depression.

Material and methods

Patients and settings

Data were collected between May 2002 and February 2011 as part of an ongoing observational follow-up study on the clinical course of Pompe disease in patients in Australia, Canada, Germany, the Netherlands, United States, United Kingdom, and in a small number of patients from other countries. Patients were recruited through national patient organizations or directly through our expertise center, the Center for Lysosomal and Metabolic Diseases at Erasmus MC University Medical Center, as described previously.[3,5] The study was approved by the Erasmus MC Ethical Committee, and all participants provided written informed consent.

Beyond a diagnosis of Pompe disease, there were no strict inclusion or exclusion criteria for participation in the study. For the analyses described in this paper, we included only patients

aged 18 years and older who were receiving ERT, and who had had at least 6 months of follow-up before and after ERT.

Measurements

Each year, participants were asked to complete several questionnaires, including one on fatigue. Demographic and clinical data were collected on country of residence, age, year of diagnosis, gender, disease duration, and use of wheelchair and/or ventilator.

For patients seen at the Dutch center, more frequent measurements and additional data were available from clinical assessments and further questionnaires. As well as fatigue, these included pulmonary function and muscle strength (assessed between January 2005 and August 2009) and depression (assessed between January 2005 and February 2011) measured as described below.

Fatigue assessment

The severity and impact of fatigue were assessed using the Fatigue Severity Scale (FSS).[17] This self-report questionnaire focuses on the physical symptoms of fatigue, and measures the severity of fatigue and its impact on an individual's daily functioning. A mean score is calculated from the nine items, which range from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'). Scores ≥4 indicate the presence of fatigue, and scores ≥5 severe fatigue.[17,18] As described previously,[5] we used the English, Dutch and German translations. The FSS has demonstrated good internal consistency, reliability and validity in studies involving patients with several neurological disorders.[5,17,19,20] When individual item scores were missing, the mean FSS score was calculated from the remaining items.[5] The maximum number of missing items per questionnaire was 2, and missing items were found in only 2% of the 1199 questionnaires completed.

Pulmonary function (Dutch patients)

Forced Vital Capacity (FVC) in sitting and supine positions was measured using spirometry as described previously.[21] Results were expressed as a percentage of the predicted normal value.

Muscle strength (Dutch patients)

Skeletal muscle strength was measured manually in scores from 0 to 5 using the Medical Research Council (MRC) grading scale.[22] A sumscore was calculated by adding the grades of 26 muscle groups as described earlier.[23] This sumscore could range from 0 (total paralysis) to 130 (normal strength), and was expressed as a percentage of the maximum possible score of 130. When 3 or more muscle groups were missing the score was not calculated.[23]

Depression (Dutch patients)

Symptoms of depression were assessed using the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D),[24] which ranges from 0 to 21. The HADS has been widely used in different disorders (including neuromuscular disorders), and has demonstrated good reliability and validity.[25]

Statistical analysis

Analyses of the longitudinally assessed fatigue scores were performed using repeated measures ANOVA (random coefficient models), which allows for irregular measurement times. To assess the effect of ERT on the mean FSS scores, the model included linear effects of time before ERT and time after ERT. Per individual, the two segments connect at the time ERT started, a method generally known as the "broken-stick" method or "piece-wise linear regression". The two regression coefficients provide estimates of the mean annual change (slope) of the scores before and after the start of ERT. The difference between these two provides an estimate of the effect of ERT on the outcome measure.

For subgroup analyses, patients were divided into strata based on gender, age, disease duration, wheelchair use, and use of respiratory support, all at start of ERT.

For the Dutch patients we also analyzed the correlation between the effect of ERT on the FSS and its effect on the MRC sumscore, on FVC in upright and supine positions, and on the HADS depression score. After performing univariate analysis by using linear mixed-effects models with broken-stick evolutions for the FSS and the three other outcomes, we estimated random effects for each model using Empirical Bayes estimates (EB). Afterwards the correlation between the EB estimates for FSS and the other outcomes was calculated. The significance of the correlation coefficients was tested using 95% confidence intervals obtained from 1000 bootstrap samples.

Data were analyzed using SPSS for Windows (version 17, SPSS Inc., Chicago, IL) and SAS (version 9.2, SAS Institute Inc., Cary, NC). Bootstrap sampling was implemented in R (version 2.14). A p-value of ≤ 0.05 was considered statistically significant.

Results

General characteristics

The eligibility criteria were met by 163 adults (55% female) out of a total of 383 patients participating in the survey. Thirty patients were excluded as they were younger than 18 years of age, 67 were excluded for not receiving ERT, 85 had no follow-up measurements (yet), and 38 had less than 6 months follow-up before and/or after the start of ERT.

The 163 patients in our study (see Table 1) had a median disease duration of 13 years. The patients' median age at start of ERT was 50 years (range 24-76 years); 52% used a wheelchair

and 50% respiratory support. The median follow-up time before ERT was 4 years (range 0.5-8); after start of ERT, this was 3 years (range 0.5-8). Per patient, a median of seven questionnaires were completed (range 2-18).

At start of ERT, 85% of the patients with an available FSS score were fatigued (FSS ≥4) and 68% severely fatigued (FSS ≥5); at the last measurement, 79% were fatigued and 55% severely fatigued.

Table 1. Patient Characteristics at start of ERT.

Characteristic	All (n=163)
Median age at start of ERT, years (range)	50 (24-76)
Median age at diagnosis, years (range)	37 (1-66)
Median disease duration, years (range)	13 (1-33)
Gender, no. (%)	
Female	90 (55)
Country of residence, no. (%)	
Netherlands	59 (36)
Germany	36 (22)
US	37 (23)
Other *	31 (19)
Use of wheelchair at start of ERT, no. (%)	
Yes	85 (52)
Respiratory support at start of ERT **, no. (%)	
Yes	81 (50)

Continuous variables are expressed as median (range). Categorical variables are expressed as numbers (%). *Includes patients from Australia, Canada, United Kingdom and a small number of patients from other countries. **Respiratory support includes partial and fulltime, invasive and non-invasive support.

Change in fatigue scores before and during ERT

Before ERT, the mean FSS score remained stable (annual change of 0.01 score points; CI 95% -0.05 to 0.06; p=0.84). In contrast, the mean fatigue score declined significantly during ERT by 0.13 score points per year (CI 95% -0.19 to -0.07; p<0.001). Comparison of the trends in fatigue over time in the periods before and after the start of ERT showed that fatigue significantly improved during ERT (mean difference in slopes 0.14 FSS score points per year, 95% CI -0.23 to -0.04; p<0.01, Figure 1).

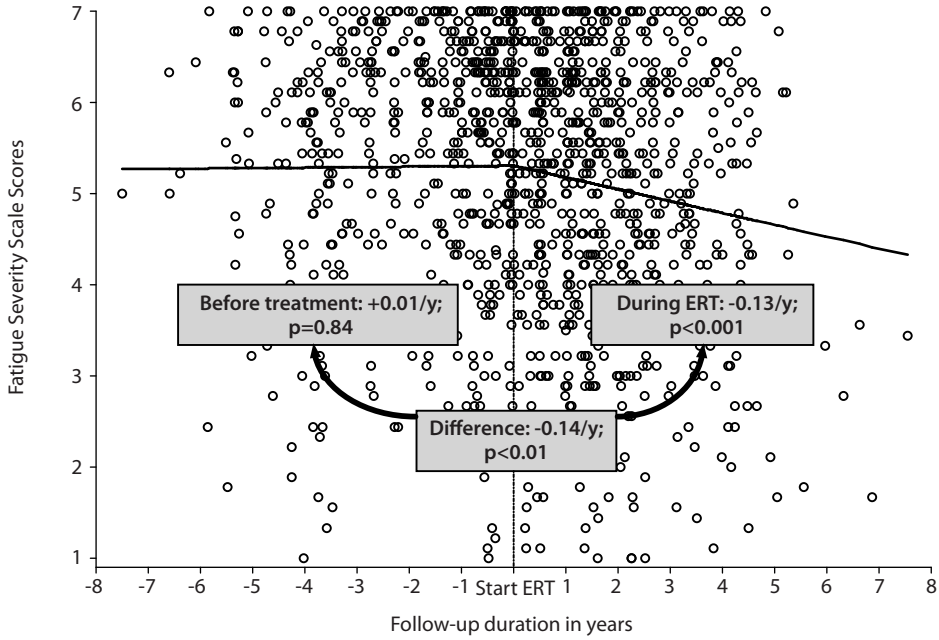

Figure 1. The figure shows the change in Fatigue Severity Scale scores (FSS) before and after the start of enzyme replacement therapy (ERT). The dots represent individual measurements and the lines represent the mean slopes calculated by the 'broken stick' repeated measures ANOVA for the group of 163 patients. The median follow-up during the natural course of Pompe disease was 4 years and the median follow-up during treatment was 3 years. The mean FSS score did not change significantly in the period before ERT, but declined significantly during ERT. The difference between the period before and during ERT was 0.14 FSS score points per year ($p<0.01$).

Relative to fatigue in the pre-treatment period, fatigue during ERT improved significantly in women, in older patients and in those whose disease duration was <15 years. This improvement was not statistically significant in men, younger patients, and those with longer disease duration (Table 2). Fatigue improved significantly in patients who used a wheelchair and in those who were not on respiratory support. It also tended to improve in wheelchair-independent patients ($p=0.06$) and in those who received any kind of respiratory support ($p=0.08$). Statistical testing of the differences between these subgroups showed that these differences were not significant for any of the aforementioned subgroups.

Table 2. Subgroup analyses for the effect of ERT on the Fatigue Severity Scale scores.

Subgroups	Difference in FSS score before and during ERT (Comparison between change over time in FSS before and during ERT) Score points/year (95% CI)	P-Value *
All	-0.14 (-0.23 to -0.04)	<0.01
Gender		
Female (n=90)	-0.18 (-0.31 to -0.05)	<0.01
Male (n=73)	-0.08 (-0.23 to 0.07)	0.30
Age at ERT, years		
< 45 (n=66)	-0.10 (-0.27 to 0.07)	0.26
≥ 45 (n=97)	-0.15 (-0.27 to -0.03)	0.01
Disease duration, years		
< 15 (n=94)	-0.19 (-0.32 to -0.05)	<0.01
≥ 15 (n=68)	-0.07 (-0.22 to 0.07)	0.33
Wheelchair use		
Yes (n=85)	-0.13 (-0.24 to -0.01)	0.04
No (n=78)	-0.15 (-0.32 to 0.01)	0.06
Respiratory support **		
Yes (n=81)	-0.13 (-0.27 to 0.02)	0.08
No (n=82)	-0.14 (-0.27 to -0.004)	0.04

Data show the mean changes in score points per year (sp/y) as calculated by stratified analysis using repeated measures ANOVA; CI=Confidence Interval; FSS=Fatigue Severity Scale. *P-value for the difference in FSS score before and during ERT per subgroup. Statistical testing of the differences between these subgroups showed that these differences were not significant. **Respiratory support includes partial and fulltime, invasive and non-invasive support.

Correlation between the effect of ERT on fatigue and its effect on muscle strength, pulmonary function and depression

For this part of the analysis, only the 59 Dutch patients were included. At start of ERT, their median age was 52 years (range 26-76), 59% were women and 46% used a wheelchair. Relative to the total study population, fewer patients used respiratory support (32% versus 50%) and more were fatigued at start of ERT (92% versus 85% of the total patient population). Median MRC sumscore (in percentage) at start of ERT was 78% (range 48-92). Median FVC percentages were 70% in sitting position (range 11-107) and 49% in supine position (range 23-99). Only 13 patients (22%) scored ≥8 on the HADS depression subscale, indicating clinical signs of (borderline) depression. Median HADS depression score was 4 (range 0-15).

As in the total study population, FSS scores significantly decreased during ERT. The difference with the pre-treatment period was borderline significant (Table 3), and was moderately correlated with a decrease in the level of depression (r 0.55; CI 95% 0.07 to 0.70). No

significant correlations were found between the improvement in fatigue and muscle strength in response to ERT and in pulmonary function in upright and supine positions.

Table 3. Change in fatigue as a result of ERT and its correlation with the change over time in muscle strength, pulmonary function and level of depression.

	Change over time			
	Before ERT (95% CI)	**During ERT (95% CI)**	**Difference before and after ERT (95% CI)**	**Correlation to FSS * r (95% CI)**
Main outcome measure				
FSS (n=59)	-0.04 (-0.13 to 0.04)	-0.21 (-0.33 to -0.09) **	-0.17 (-0.35 to 0.01)	Reference
Covariates				
MRC sumscore (n=55***)	-1.28 (-1.80 to -0.49) **	2.01 (1.20 to 2.81) **	3.29 (2.04 to 4.53) **	-0.36 (-0.61 to 0.08)
FVC upright position (n=52***)	-1.95 (-3.09 to -0.83) **	0.06 (-1.09 to 1.21)	2.02 (0.26 to 3.77) **	-0.26 (-0.49 to 0.08)
FVC supine position (n=45***)	-1.71 (-2.76 to -0.67) **	-0.67 (-1.79 to 0.45)	1.04 (-0.50 to 2.57)	-0.31 (-0.56 to 0.17)
HADS depression (n=59***)	0.08 -0.40 to 0.48)	-0.48 (-0.85 to -0.11) **	-0.57 (-1.23 to 0.09)	0.55 (0.07 to 0.70) **

Data show the mean changes in score points per year (sp/y) as calculated by univariate analysis using linear mixed-effects models CI=Confidence Interval; FSS=Fatigue Severity Scale; MRC=Medical Research Council; FVC=Forced Vital Capacity; HADS=Hospital Anxiety Depression Scale. *Correlation between the differences in FSS scores and the difference in the other outcome measures following ERT. **Represents statistical significance. ***Only patients with sufficient data were included.

Discussion

This is the first prospective follow-up study to assess the effect of ERT on fatigue in a large number of adult Pompe patients. We found that ERT significantly reduces self-reported fatigue, the mean decrease in FSS score being 0.14 per year relative to the pre-treatment period. The decrease in fatigue during ERT was correlated with improvements in depression, but not significantly with changes in muscle strength or pulmonary function. The effect of ERT on fatigue was not consistent across patient subgroups: fatigue decreased mainly in women, older patients and those with shorter disease duration.

Our study mirrors previous findings in this cohort, providing a reminder that fatigue is a highly prevalent symptom among adults with Pompe disease. Therapies that can reduce fatigue in this population are therefore of great importance, and our finding that ERT positively affects fatigue is a significant finding. While the annual improvement might seem small (0.14

points per year), it resulted in a substantial drop in the proportion of patients who were fatigued or severely fatigued at the end of our follow-up.

Subgroup analyses suggest that fatigue may be more responsive to ERT in women, older patients and those with shorter disease duration. A better response in women might be explained by the more pronounced effect of ERT on muscle strength in females that was identified recently by our group.[23] It is unknown whether hormonal influences are involved in this. The better effect in patients with shorter disease duration might be due to less severe muscle damage. The absence of an effect in younger patients may seem at odds with this, but it is possible that younger patients have more demanding lifestyles, resulting in more fatigue. Since glycogen degradation occurs mainly in the cytoplasm, we doubt that lower levels of fatigue can be attributed to the increased release of glucose from the lysosome (by ERT mediated lysosomal glycogen degradation).[26]

Muscle strength, pulmonary function and depression, have been shown to be related to fatigue in other neurological disorders.[1,2,8] Against our expectations, we found no significant correlation between the improvement in fatigue and in muscle strength or pulmonary function. This might be due to the smaller sample size available for this sub-analysis. Alternatively, it may be that the level of fatigue is determined by the degree of muscle endurance rather than of muscle strength.[27] Because patients with impaired pulmonary function often use mechanical ventilation, their oxygen levels will be normal, which could explain the absence of a correlation between the response to ERT in fatigue and pulmonary function.

We found that as fatigue decreased during ERT, the scores on the depression scale also decreased. Several studies have described a relationship between depression and fatigue in neurological disorders.[2,28-31] Depression may predispose for fatigue,[2,28] but fatigue secondary to an underlying illness can also cause depression, with one sometimes influencing the other.[29] Since the majority of patients (78%) were not depressed, ERT has presumably contributed to a decrease in fatigue by affecting the underlying pathophysiology.

As fatigue is a multifactorial entity, it is likely that other factors – including changing patient's perspectives and perceptions, intensified medical care and altered muscle metabolism –contribute to its improvement after ERT. Although, as a treatment of the underlying disease, ERT seemed to reduce fatigue, it is hard to define the extent to which it acts directly (by reversing disease-related pathophysiology) or indirectly (through psycho-sociological factors). Further research is needed to unravel the underlying mechanisms.

This study benefits from the relatively large number of patients who participated, and from the fact that patients were included irrespective of their disease severity; the study thereby represents the entire spectrum of adult Pompe disease. Despite the large sample, it was not possible to build multivariate models, and multiple testing might limit the results of the subgroup analysis. Our correlation analysis was based on a subset of patients and was limited by a smaller sample size.

Fatigue is a subjective and complex concept that is difficult to define and measure. The FSS is a uni-dimensional scale that measures fatigue as a single construct. Because of its brevity and simplicity, we preferred the FSS to a multi-dimensional scale in which different forms of fatigue – such as physical, cognitive and psychosocial fatigue – are assessed separately. Uni-dimensional and multi-dimensional scales have been found to produce similar measurements of fatigue.[32]

Conclusions

Fatigue is a common problem in patients with Pompe disease. Our finding that ERT helps to reduce it is therefore important for this patient population, irrespective of the mechanisms underlying this effect. Fatigue decreased mainly in women, in older patients and in patients with short disease duration.

To manage fatigue successfully, treatment options such as rehabilitation and exercise [33] should be considered in addition to ERT. Further investigations should be devoted to the roles of pharmacotherapeutics and cognitive therapy in treating fatigue, and to the exact role of muscle cell changes, pulmonary function, and psychological and other factors that may be associated with it.

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Chapter 8

Quality of life and participation in the daily life activities of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up

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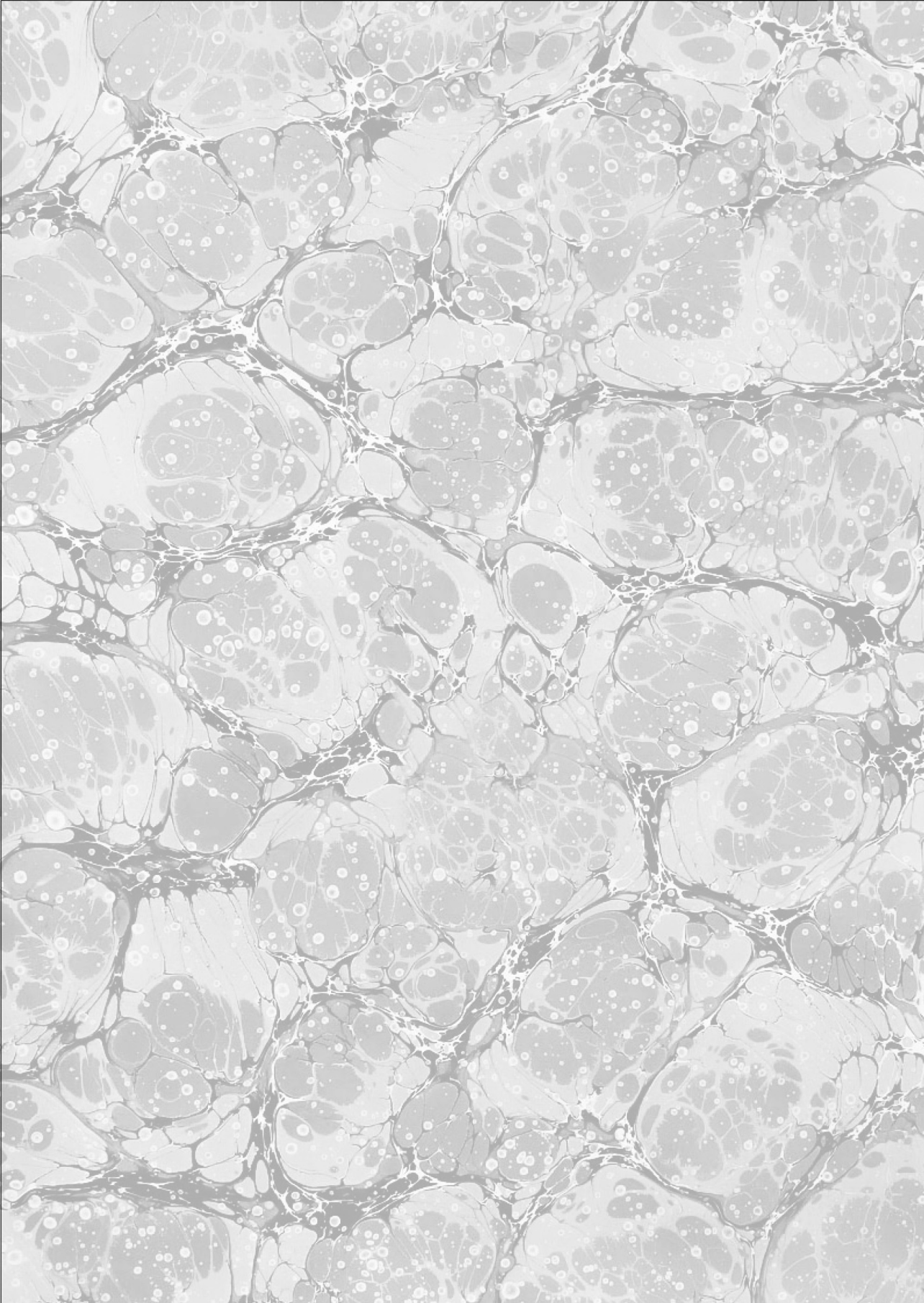
Submitted



Chapter 9

General Discussion

According to the French Surgeon and biologist Alex Carrel (1873-1944) the quality of life is more important than life itself: in those days a quite revolutionary statement. Nowadays one generally agrees that therapies should not solely aim at survival but also at improving quality of life.[1,2] Life is a keyword in this thesis. Although the availability of enzyme replacement therapy for Pompe disease has changed patients' perspectives in terms of increased life expectancy in infants and improved muscle strength and pulmonary function in adults, information on the effects of ERT on survival and quality of life were either lacking or limited for adult patients. These were therefore important subjects of research in this thesis.

Based primarily on data from the IPA / Erasmus MC Pompe Survey, an on-going international open cohort study among patients with Pompe disease, we aimed to gain insight in the survival of adults with Pompe disease, the contribution of pain to the Pompe disease symptomatology, and the effects of enzyme replacement therapy on patient reported outcome measures. Thanks to the participation of many patients for more than 10 years the Pompe Survey has provided a detailed overview of the spectrum of disease severity and the impact of Pompe disease on daily life.

This chapter reviews and evaluates the main findings in the context of present day knowledge about Pompe disease. The second part of this chapter discusses study related methodological issues, while the third part addresses recommendations for future research.

MAIN FINDINGS

- *Pompe disease presents as a continuum of clinical phenotypes; "the clinical spectrum". (Chapter 3)*
- *Pompe disease is life threatening for infants, children, and adults alike. (Chapter 4)*
- *Pompe disease in adults is experienced as being associated with more than normal pain. (Chapter 6)*
- *Pain affects quality of life, participation in daily life and depression and anxiety in adults. (Chapter 6)*
- *Enzyme replacement therapy improves the survival of adult patients. (Chapter 5)*
- *Enzyme replacement therapy lowers the level of fatigue that is experienced by adult patients. (Chapter 7)*
- *Enzyme replacement therapy positively affects the quality of life and participation in daily life activities of adult patients. (Chapter 8)*

Review and evaluation

Nomenclature

Approximately fifty years have passed since Henri-Géry Hers reported the first Pompe patient with a non-classic infantile phenotype.[3] A decade later Andrew G. Engel described Pompe disease as a clinical spectrum.[4] While the idea of a continuous clinical spectrum has not changed since then, the distinction and naming of subgroups within the disease entity has grown in divergent directions. A plethora of terms can be found in the medical literature describing both the same, as well as different clinical sub-classes.[5-16] The example that we discuss in Chapter 3 is the use of the term "late-onset". This term was originally used to refer to Pompe patients with onset of symptoms in adulthood.[17] In later articles, however, it was also applied to all patients with onset of symptoms above the age of one year, while according to several recent publications even patients diagnosed within their first year of life can have late-onset Pompe disease as opposed to classic infantile Pompe disease.[16,18] In Chapter 3 we advocate the use of consistent terminology in both scientific as well as clinical reporting. There should be no doubt about what type of patients clinicians, researchers and health authorities are speaking of while counseling their patients and making vital decisions. In Chapter 3 we therefore propose to adhere to the traditional interpretation of Pompe disease as a clinical spectrum, whereby a distinction is made between classic infantile and non-classic Pompe disease for prognostic purposes. Based on the presence or absence of cardiac hypertrophy presenting in the first 3 months after birth a valid distinction can be made between classic infantile Pompe disease and non-classic Pompe disease, whereby patients with classic infantile Pompe disease have virtually no acid alpha-glucosidase activity in cultured skin fibroblasts whereas most patients with non-classic Pompe disease do have some residual activity.[19] Even these criteria do not always hold since physicians may use different definitions describing the extent of cardiomyopathy or the time of symptom onset (e.g. <3 months or <12 months). All this, once again, underscores the fact that, above all, Pompe disease should be seen as a clinical spectrum.

While all further sub-classifications are arbitrary they can be useful for the purpose of data interpretation, especially in non-classic Pompe disease which includes a very broad group of patients both in terms of age, disease severity and clinical aspects. In Chapter 3 we propose to use the age of onset (e.g. childhood *versus* adulthood) as a further means of subdividing this group of patients.

Survival in adult Pompe Disease

From the moment that Drs Pompe, Putschar and Bisschop presented their first case reports it was clear that patients with classic infantile Pompe disease die very early in life.[20-23] These patients rarely survive beyond their first year. Consequently, mortality was used as the main outcome measure in clinical trials assessing the therapeutic efficacy of enzyme therapy in

infants.[24,25] Survival is not a suitable trial endpoint for measuring an effect in less affected children and adults with Pompe disease since their natural disease progression is too slow to measure a significant improvement within the context of a 1 to 2 years long clinical trial. Survival analyses require long term follow-up of a large number of patients, which is only achievable through following an international cohort of patients for many years.

The IPA / Erasmus MC Pompe Survey thus offered a unique opportunity to study survival in adult Pompe patients. In this international survey a large number of patients had been followed systematically since 2002 providing sufficient follow-up time and patient numbers to study survival. We first investigated survival of untreated patients, showing for the first time that adult Pompe patients have a higher mortality rate than the general population (Chapter 4). Age and disease severity (and handicap) were the most important factors associated with mortality.

Next, we estimated the effect of ERT on survival using data of 283 treated and untreated adult Pompe patients that were followed for up to 9 years (Chapter 5). Enzyme replacement therapy had a significant effect on survival and decreased the risk of death by 59% at any one point in time. This translates approximately to a gain of 1 additional year for 8 years of treatment. Since disease awareness has grown, diagnostic methods have improved, and treatment is started earlier than nine years ago – when the Pompe Survey data collection started- we expect that the effect of ERT in terms of survival will improve even further.

Pain, fatigue and quality of life in adults with Pompe Disease

The first reports coming out of the Pompe Survey were focused on describing the common diagnostic symptoms as well as the most debilitating symptoms of untreated patients.[6,26,27] Furthermore, they specifically assessed patient reported outcome measures such as fatigue and quality of life during the natural course.[28,29] Patient reported outcome measures have contributed important information on the natural course alongside clinical data. Continued follow-up of patients in the survey before and from the moment they started to receive ERT allowed us to address the question whether ERT improves fatigue and quality of life. Also the impact of pain, a symptom that so far received little attention, was assessed in an international group of both treated and untreated adult Pompe patients by means of a survey in the Netherlands and Germany.

Pain in adults with Pompe disease

Using the Brief Pain Inventory we assessed the frequency, the severity and the characteristics of pain in a cross-sectional design (Chapter 6). We found that 45% of the study population experienced pain whereas the comparable figure for our control population was only 27%. This makes pain a relatively frequent symptom of Pompe disease. The severity of pain and its interference with daily life in patients were scored as mild. While interpreting this it should nevertheless be noted that a large proportion of patients used pain medication, and that

patients did report pain to affect their quality of life, participation in daily life and mental health status. These results suggest that pain warrants further attention in clinical practice, both in terms of its recognition as well as its treatment.

A number of options are available to treat pain in general, from analgesics and other drugs to physical therapy and massage.[30-33] The ideal approach to pain control begins with the identification and then the elimination or treatment of the underlying etiologic factors.[30,34] Whether treating the disease using ERT reduces pain requires further study using a longitudinal design.

Effect of ERT on fatigue, quality of life and participation

Using follow-up data on nearly 200 patients that were queried via the IPA / Erasmus MC Pompe Survey, both before and after their start of ERT, ERT was shown to positively affect fatigue (Chapter 7), quality of life and handicap (Chapter 8).

Fatigue is a frequently reported symptom in Pompe disease,[29] which we also saw reflected in the high proportion of patients reporting fatigue at the start of ERT. The observation that fatigue scores decreased during treatment with ERT is hence important for patients. The mechanisms by which ERT reduces fatigue and the causes of fatigue in Pompe disease remain to be determined. Our research did not detect a direct link between the effect of ERT on fatigue and its effect on muscle strength and pulmonary function. We did observe a correlation between fatigue levels and depression levels reducing under treatment. However, depression can both cause fatique as well as result from fatigue. Given the relatively few depressed Pompe patients it is unlikely that the effect of ERT on fatigue is achieved through relieve of depression. Fatigue is a multifactorial entity and further research is needed to determine its causes in Pompe disease.[35,36]

ERT also positively affected quality of life and participation in daily life of adult Pompe patients. This is an important finding, since it means that ERT allows the patient to increase or maintain his/her level of (social) functioning. Compared to the progressive decline observed prior to treatment, physical health summary scores improved and participation stabilized after starting ERT. It is important to note that in the context of a progressive disease, a stabilization should be seen as an improvement of the patient's situation. The effect on the physical health summary scores seemed to be largest in the first two years of ERT. These improvements might reflect the positive effect that ERT has on muscle function and strength, however, this was not investigated and cannot be confirmed. Mental health summary scores remained stable over time, also prior to ERT, which corroborates previous studies describing that mental health of Pompe patients is not affected.[28]

Clinical implications

Pompe disease is a chronic progressive disorder characterized by gradual decline and loss of vital functions like walking and unsupported breathing, which for some patients come sooner

in life than for others. Since 2006, many studies devoted to the effect of ERT have shown that treatment improves a range of clinical outcome measures including prolonged survival of infants, and improved muscle strength, distance walked and pulmonary function in adults.[7,15,25] Our current studies, using information collected via the Pompe Survey, support the positive effects that ERT can have on the patients' well-being and importantly show that the reported clinical effects expand to the patient's perspective as well as their survival.

Many of the outcomes reported in this thesis come directly from the patient, without interpretation by a clinician or anyone else. Reports of the status of a patient's health condition by the patient him/herself are referred to as patient reported outcomes (PRO).[37] PRO's use the patient's experience in a direct way that goes beyond the outcomes that are measured by the clinician. They are increasingly used in clinical research and medical practice, especially since 2006, the year in which the US Food and Drug Administration (FDA) released a draft guidance document discussing the importance of PROs in clinical trials and patient-centred healthcare. Similarly, the European Agency for the Evaluation of Medicinal Products (EMA) has released a reflection paper on the use of measures of health-related quality of life in the evaluation of drug applications.[1,2,37]

Although now frequently used in chronic diseases, PROs are not yet common use in rare metabolic disorders such as Pompe disease. As the ultimate goal of any treatment is that the patient feels better and is able to resume or maintain his or her previous activities, the patients' point of view is crucial. PROs furthermore allow measuring additional domains of functioning that go beyond the measurement of separate organ functions like the measurement of muscle strength and pulmonary function. The measures used in the Pompe Survey such as FSS, RHS and SF-36 complement the evidence of clinical measures assessing the functioning of the patient as a whole as well as in a social context (the International Classification of Functioning, Disability and Health.[38,39] Patient reported outcomes are thus important for two reasons: they provide the patients' perspective and measure additional domains of functioning.

In the discussion on reimbursement of ERT in the Netherlands,[40] health authorities have highlighted the importance of survival data. While improvements in clinical outcome measures like distance walked and pulmonary function had been demonstrated, it was felt that these were insufficient to justify such an expensive treatment. Our survival results therefore provide key information to this debate. Generally, when reimbursement of medication for non-rare diseases is discussed, both quantity and quality of life are taken into consideration. For example, in oncology research quality of life has been identified as the second most important outcome, with survival being the most important. The studies in this thesis provide both these outcomes regarding the effect of ERT in Pompe disease.

As it stands, the currently available clinical as well as Pompe Survey outcome measures indicate that adults with Pompe disease benefit in several ways from ERT; not the least that ERT lengthens their life.

Methodological considerations

In the following sections general methodological considerations related to the design of the Pompe Survey will be addressed, including the choice of measurement scales.

The IPA / Erasmus MC Pompe Survey

The IPA / Erasmus MC Pompe Survey was designed as a longitudinal study with structured questionnaires and centralized data collection. The continuous data collection allowed us to describe the natural course of non-classic Pompe disease as well as the alterations brought about by ERT. The international character of the survey allows access to a large cohort of patients, which makes it possible to draw conclusions on a group level. The Pompe Survey probably presents the longest standardized follow-up of a large group of Pompe patients. It is an example of a very successful international collaboration between patients, patient organizations and academic institutions that was supported by commercial parties interested to develop therapeutic strategies. The initiative for the Pompe survey was taken at a time that it was virtually impossible to reach out to the very many specialists around the world that had possibly seen a Pompe patient in their clinic: neurologists, pediatricians, internists, cardiologists, and physical therapists. Getting in touch with the Dutch Patient Association for muscular diseases (Vereniging Spierziekten Nederland), the Association of Glycogen Storage Diseases (AGSD, UK), the Acid Maltase Deficiency Association (AMD, USA), L' Association Francophone des Glycogénoses (A.F.G., France), and the Selbsthilfegruppe Glykogenose Deutschland e.V. (Germany) that later combined forces to expand their activities worldwide and started the International Pompe Association (IPA) to combat Pompe disease, made it possible to reach out to many Pompe patients worldwide.

Sources of bias and other limitations

The downside of including patients via patient organizations is that information regarding the diagnosis relies on information provided by the patients themselves. It may be that a certain percentage of participants in the Pompe Survey was not appropriately diagnosed. We tested this hypothesis by contacting in our pain prevalence study the physicians of a German subgroup. In 78% of the German patients we could contact the physician and the diagnosis could be confirmed in all these cases. Thus, the percentage of falls-positive diagnoses is probably very low. Albeit, we have heard of incidental cases that were wrongly diagnosed, and some of these patients even received ERT before their diagnosis was revised. We estimate the number of misdiagnosed patients receiving ERT to be so low that it cannot have influenced the outcome of our survival studies one way or the other. Improvement of the diagnostic routine will minimize these uncertainties.

Recruitment through patient organizations could furthermore result in the selection of a particularly motivated and perhaps more severely affected group of patients. However, our

study included all stages of disease severity, ranging from almost asymptomatic patients to those who were both wheelchair and ventilator dependent, and the age of participants ranged from childhood to late adulthood. Thus, patients in the Pompe Survey represent the entire clinical spectrum of (non-classic) Pompe disease. This is different in most clinical trial situations in which there are stringent inclusion and exclusion criteria. Thus, our analyses reflect the real-life situation in a better way.

Studies lasting many years are often troubled by missing data in at least one questionnaire or missing answers to one specific question. Traditionally, statistical models would remove all subjects with a single missing value from the analysis. This 'complete case analysis' can lead to considerable bias by selection of the study population. In our study, the risk of bias is reduced by using statistical models that make it possible to also include in the analyses those subjects with some missing data. Finally, information bias may have occurred in our long-term follow-up studies on survival due to (selective) loss to follow-up.

The measurement scales

The Fatigue Severity Scale (FSS) was chosen because it is short, easy to complete and had demonstrated good psychometric properties including responsiveness to change in other patient groups such as neuromuscular diseases.[41] In our study on the effects of ERT the FSS also showed significant responsiveness to change; the decrease in FSS scores was 0.13 score points per year. Recently a shorter 7-item FSS was built using Rasch analysis and was presented for assessment of fatigue in patients with immune-mediated neuropathies.[42] Perhaps in future studies on fatigue in Pompe disease a Rasch analysis might be useful to perform in order to develop a tailor-made fatigue scale for Pompe patients. Such a scale may be more responsive to change in Pompe patients. On the other hand, the gain in measurement properties has to be weighed against the efforts involved in performing a Rasch analysis, as well as the fact that such disease-specific outcomes cannot be compared to other diseases. This discussion point also applies to the Rotterdam Handicap scale.

Earlier, we found that the ability of the SF-36 to capture changes over time was questionable in Pompe disease assessed in 38 patients over a one year period.[28] In our study with a longer follow-up and larger numbers of patients, the SF-36 did show significant changes on various quality of life domains before and after start of ERT.

Although the BPI-short form was mainly chosen for its brevity and frequent use in many disorders and countries, limitations of the questionnaire are the fact that the types of pain are limited to subjective descriptions of pain (exhaustive, unbearable) rather than a more concrete description of the character of pain (muscle pain, joint pain and so on). Furthermore, the BPI–short form assesses pain experienced during the last 24 hours instead of pain over a longer period of time and it could be argued that this might underestimate the prevalence of pain in a chronic disorder such as Pompe disease. The BPI also has a long form assessing pain in the last 4 weeks,[43] however, this questionnaire is much longer and was not validated in the languages

we needed. Another option would have been to use a pain diary, or performing follow-up assessments to give insight into the chronic and possibly temporal character of pain in Pompe disease. However for an inventory study like the current one we decided it was one of the most practical scales to use.

Conclusions and future directives

Pompe disease is an orphan disease. Consequently, large numbers of patients can only be accrued through national and international collaboration. The IPA / Erasmus MC Pompe Survey, which is currently one of the largest databases in the field of Pompe disease, is an excellent example of a fruitful international collaboration. It has provided a wealth of information on both the natural course of Pompe disease as well as the effects of ERT. While much of the information collected in the survey has been exploited there are still a number of topics that could be explored including the long term effects of ERT on mobility and respiratory status, the role of prognostic factors for a response to treatment (age of onset and disease severity), the difference in diagnostic delay prior to and after the introduction of ERT, and an analysis of patient reported data compared to physician driven data. Given the current search for improved and alternative treatments it is paramount to continue running the survey so as to ensure that future therapies can be evaluated against the natural course and the effect of ERT.

While the survey includes a wide range of topics based on review and expert opinion, the identification of pain as an important problem in Pompe patients suggests that inclusion of a validated pain assessment tool in the Pompe Survey should be considered. Though inherent to the collection of patient reported outcome data, the absence of clinical data is a drawback. Linking the patient reported outcome data to the clinical data, as we did in our study on fatigue for the Dutch patient population, can result in further insights in the mechanisms behind pathophysiological changes. In addition, collecting clinical data in an international context would result in much stronger clinical evidence than national or local databases can provide. This is in fact the purpose of the Pompe Registry that was set up by Genzyme Corp in 2004.[18] It collects world-wide clinical data of patients with Pompe disease through physicians. The Pompe Registry has already provided valuable information about less well known clinical features of Pompe disease. The difficult part of registries like the Pompe Registry is to keep the data entry consistent and complete, and to secure regular follow-up.[44,45] In the Pompe Survey we contacted patients directly on an individual basis, which together with the strong motivation of patients, resulted in a consistent long-term follow-up for a large number of patients.

Based on the experience with the Pompe Survey the following suggestions might be valuable for setting up registries and develop detailed knowledge about orphan diseases, particularly those that may become treatable in the near future. First, standardized data collection needs to

be set up with a structured follow-up throughout childhood and adulthood, even when there is not yet (the prospect of) therapy. Standardization of variables is important to ensure that the data collected in different centres and different countries can be compared and be pooled. Second, a close collaboration with patient associations should be sought to learn what lacks in text books and to keep all parties updated on recent developments. Patient associations can quickly reach out to patients if breakthroughs and therapeutic opportunities emerge. Patient associations are invaluable for disseminating information and raising awareness. Multi-institutional and international collaborations are equally important to reach sufficient patient numbers. The design of patient reported outcome surveys and clinical registries should be longitudinal and preferably allowing the combination of clinical and patient reported data sets at different levels.

To conclude, this thesis poses the example of the Pompe Survey illustrating the power of combining the efforts of patients, patient associations, academia and supportive pharmaceutical parties to gather information on an orphan disease that would have been hard to obtain otherwise. The studies reported and discussed in this thesis illustrate that patient reported surveys next to clinical registries and fundamental research are a valuable tool to delineate the natural course of a disease and to evaluate the effects of existing and upcoming new therapies.

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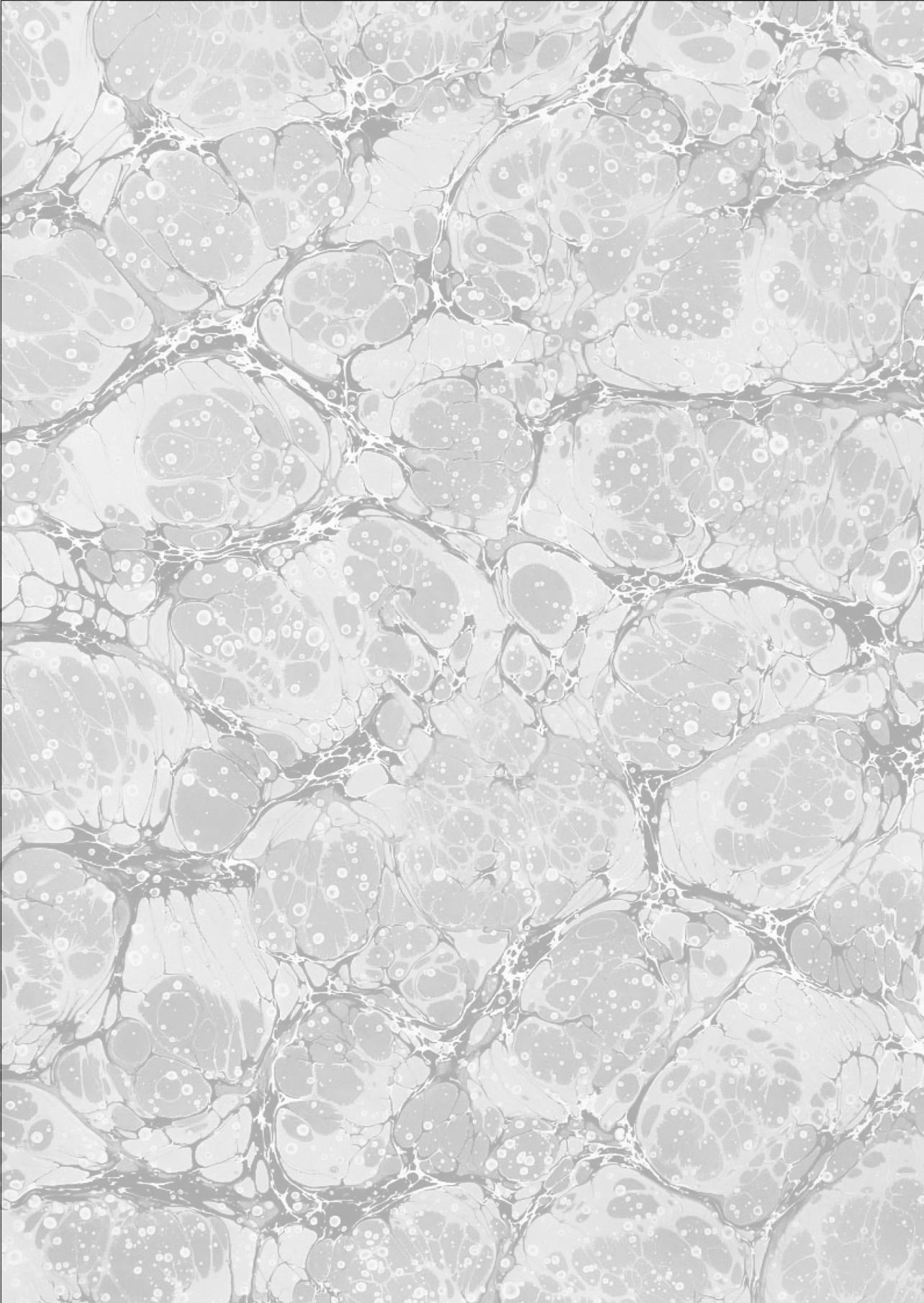


Summary
Samenvatting
Őzet

Summary

Pompe disease is an autosomal recessive lysosomal storage disorder caused by deficiency of acid α-glucosidase, which leads to storage of glycogen in mainly muscle cells and consequently to muscle dysfunction. The majority of affected adults eventually become wheelchair and ventilator dependent.

Enzyme replacement therapy (ERT) is currently the only treatment available for patients with Pompe disease. Registration in 2006 was supported by the outcome of trials performed in patients with classic infantile Pompe disease. Since then, evidence for therapeutic efficacy has also been presented in less severe phenotypes. However, some of the most important outcome measures such as the effect of enzyme replacement therapy on survival and quality of life were still lacking at the time that the studies described in this thesis were started.

The studies in this thesis are focused on the burden of Pompe disease in adulthood and are primarily based on data collected via the IPA / Erasmus MC Pompe Survey; an on-going international open cohort study. We aimed to gain insight in the survival of adults with Pompe disease, the contribution of pain to the Pompe disease symptomatology, and the effects of enzyme replacement therapy on patient reported outcome measures.

Chapter 1 serves as general introduction to Pompe disease. It provides background information about clinical features, pathogenesis, and treatment of Pompe disease.

Chapter 2 describes the design of the IPA / Erasmus MC Pompe Survey, an ongoing international study on Pompe disease in children and adults, in which information is gathered via questionnaires distributed to the patients at regular time intervals. This chapter also includes a brief outline of the questionnaires that were used and concludes with the outline of the thesis and the rationale for the studies that were done.

International consensus about the nomenclature used for describing the Pompe disease phenotypes is currently lacking. In **Chapter 3** we therefore propose to adhere to the traditional interpretation of Pompe disease as a clinical spectrum, whereby a distinction is made between classic infantile and non-classic forms of Pompe disease for diagnostic and prognostic purposes. Classic Pompe disease is a well circumscribed clinical entity. Non-classic Pompe disease covers a very wide age-range, which for practical reason can be roughly subdivided in childhood and adult phenotypes.

Chapter 4 reports the world-wide first study investigating to what extent Pompe disease shortens the life expectancy of untreated adults. Given the small number of patients seen in individual clinics such study had not been possible before the Pompe Survey was established. A total of 268 untreated patients participating in the Survey were followed for a median of 3.5 years. The estimated 5-year survival rate from diagnosis was 95%. The 10, 20, and 30 year survival rates were estimated at 83, 65, and 40%, respectively. Factors associated with patients' survival were age, disease severity -based on wheelchair and/or respiratory support-, and

patients' score on the Rotterdam Handicap Scale (RHS). In a Dutch subgroup of 99 patients, the observed number of deaths was compared with the expected number of deaths in the age- and sex-matched general population. We concluded that mortality among the Dutch Pompe patients was higher than in the general population.

The effect of enzyme replacement therapy on the survival of adult patients is described in **Chapter 5.** A total of 283 adult patients were included in this study. Seventy two percent of these patients started enzyme replacement therapy at some time during their follow-up. During a median follow-up period of 6 years, 46 patients died, of whom 61% had never received ERT. After adjustment for age, sex, country of residence, and disease severity -based on wheelchair and ventilator use-, enzyme replacement therapy was positively associated with survival (HR 0.41). This first study on the effect of enzyme replacement therapy on the survival of adults and its results support the beneficial impact that enzyme replacement has in this age category.

The focus of **Chapter 6** is pain; its severity and interference with daily-life activities as measured with the short-form brief pain inventory (BPI). A large group of adults with Pompe disease (n=124) from Germany and the Netherlands were included in this cross-sectional study and compared to an age-matched control group (n=111). Compared to the control group, the prevalence of pain was almost twice as high in Pompe patients (27% versus 45%). Pain severity and pain interference scores were also higher in patients than in controls. Furthermore, pain seemed to negatively affect patients' quality of life, participation in daily life and mental status. Based on this study we concluded that pain deserves more attention: its management should be included in the clinical management of patients with Pompe disease. The effect of enzyme replacement therapy on pain could not be assessed with this cross-sectional study design.

Fatigue is a frequently experienced symptom in patients with Pompe disease, both in mildly and severely affected patients. In **Chapter 7** we therefore investigated whether enzyme replacement therapy reduces fatigue. In this prospective international observational survey, we used the Fatigue Severity Scale (FSS) to measure fatigue. We followed 163 adult patients for a median of 4 years before, and 3 years during enzyme replacement therapy. Before the start of therapy, the mean FSS score remained stable; during therapy fatigue improved significantly. Fatigue decreased mainly in women, older patients, and in those with shorter disease duration. Sub-analyses -in the Dutch cohort- furthermore showed the improvements to be correlated with the effect of enzyme replacement therapy on depression, but not on muscle strength or pulmonary function. Although we were not able to elucidate the mechanisms by which enzyme replacement therapy reduces fatigue, our finding that it helps to reduce fatigue is important for this patient population in which fatigue is a common and disabling problem.

Chapter 8 investigates whether enzyme replacement therapy improves quality of life and participation in daily-life in 174 adult patients. The SF-36 Physical Component Summary measure (PCS) deteriorated before enzyme replacement therapy, while it improved significantly in the first 2 years of therapy and remained stable thereafter. The Mental Component Summary

measure (MCS) remained stable in all three periods. The Rotterdam Handicap Scale score (RHS) stabilized under enzyme replacement therapy, after a significant decline prior to the start of therapy. The conclusion is that enzyme replacement therapy positively affects quality of life and participation in daily-life of adults with Pompe disease.

The clinical implications of the studies described in this thesis are discussed in **Chapter 9**, and suggestions for follow-up research are provided. The studies have improved the knowledge on clinical symptoms of Pompe disease, its natural course and they support existing evidence that adult patients benefit from enzyme replacement therapy. They also illustrate that patient reported outcome measures based on surveys are a valuable tool in addition to data collected in clinical registries and by fundamental research. This holds particularly for rare diseases. Surveys are not only useful for delineating the natural course of a disease, but are equally useful for evaluating the effects of existing and upcoming therapies. The recruitment of patients through international patient associations -united in the IPA- facilitates the inclusion of large numbers of patients, while the broad scope of the Pompe Survey secures that a wide range of questions can be addressed. The Pompe Survey can be used as a template for doing research in other rare diseases.

Samenvatting

De ziekte van Pompe is een autosomaal recessieve overerfelijke ziekte veroorzaakt door een deficiëntie van het lysosomale enzym zure α-glucosidase. Deze deficiëntie leidt tot stapeling van glycogeen in met name spiercellen wat vervolgens weer leidt tot spierdysfunctie. De meerderheid van aangedane volwassen patiënten wordt uiteindelijk rolstoel afhankelijk en beademingsbehoeftig.

Enzymtherapie is momenteel de enige behandeling beschikbaar voor patiënten met de ziekte van Pompe. Op basis van resultaten van klinische studies onder heel jonge kinderen met de meest ernstige "klassieke" vorm van de ziekte werd dit geneesmiddel in 2006 op de markt toegelaten. Later werd de therapeutische effectiviteit van enzymtherapie ook aangetoond bij patiënten met de niet-klassieke vorm van de ziekte van Pompe, die zich meestal pas op later leeftijd manifesteert. Desondanks, ontbrak informatie ten aanzien van het effect op een aantal van de meest belangrijke uitkomstmaten zoals overleving en kwaliteit van leven ten tijde van de start van de studies beschreven in dit proefschrift.

De studies in dit proefschrift focussen op de ziektelast van volwassen patiënten met de ziekte van Pompe, die wel en niet behandeld worden met enzymtherapie en zijn primair gebaseerd op data verzameld als onderdeel van de IPA / Erasmus MC Pompe Survey; een doorlopend internationaal cohortonderzoek. De studies in dit proefschrift hadden tot doel meer inzicht te krijgen in de overleving van volwassen patiënten met de ziekte van Pompe, de bijdrage van pijn aan de symptomatologie, en de effecten van enzymvervangingstherapie op patiënt gerapporteerde uitkomstmaten en overleving.

In Hoofdstuk 1 wordt de ziekte van Pompe geïntroduceerd met aandacht voor de genetische en biochemische achtergronden, de klinische kenmerken, de pathogenese, en de behandeling.

Hoofdstuk 2 beschrijft de opzet van de IPA / Erasmus MC Pompe Survey. Dit is een doorlopend internationaal vragenlijstonderzoek bij kinderen en volwassenen met de ziekte van Pompe, waarin informatie wordt verzameld via vragenlijsten die jaarlijks uitgestuurd worden naar patiënten. Aan deze activiteit werd de naam IPA / Erasmus MC Pompe Survey gegeven omdat het initiatief ertoe genomen werd door de 'International Pompe (Patient) Association' (IPA) en het Erasmus MC. Het is een doorlopend onderzoek dat in 2002 van start ging en waar patiënten van over de hele wereld aan deelnemen. Er wordt informatie verzameld over symptomen en problemen bij de ziekte van Pompe, kwaliteit van leven, participatie in het dagelijks leven en vermoeidheid. De vragenlijsten zelf waarmee deze informatie wordt verzameld worden in dit hoofdstuk ook beschreven. Dit hoofdstuk eindigt met de hoofdlijnen van dit proefschrift en de rationale voor het uitvoeren van de studies beschreven in het proefschrift.

Er is momenteel geen overeenstemming over hoe de verschillende vormen van de ziekte van Pompe het best benoemd kunnen worden (de "nomenclatuur"). In **hoofdstuk 3** stellen wij voor vast te houden aan de traditionele interpretatie van de ziekte van Pompe als zijnde een klinisch spectrum, waarbij we een onderscheid maken tussen de meest ernstige "klassieke" vorm en andere niet-klassieke vormen, dit om eenduidigheid te creëren als het gaat om het beschrijven van diagnostiek, prognose en effecten van therapie. De klassieke vorm van de ziekte van Pompe is een duidelijk omschreven ziekte entiteit. De eerste symptomen dienen zich vrijwel altijd kort na geboorte aan, waarbij hart- en ademhalingsfuncties dusdanig gecompromitteerd raken dat deze patiënten meestal al voor het eerste jaar overlijden. De niet-klassiek vormen van de ziekte van Pompe daarentegen kunnen zich op elke leeftijd manifesteren en sterk verschillen in mate van progressie. Spierzwakte is een prominent verschijnsel terwijl problemen van het hart zich zelden tot nooit voordoen. Om praktische redenen bevelen wij in **hoofdstuk 3** aan deze patiënten aan te duiden als kinderen of volwassenen met de ziekte van Pompe.

Hoofdstuk 4 beschrijft de eerste studie ooit waarin wordt onderzocht in hoeverre de ziekte van Pompe de levensverwachting verkort van onbehandelde volwassenen. Een dergelijke studie was niet mogelijk voordat de Pompe Survey werd opgezet, omdat door individuele artsen in de verschillende ziekenhuizen wereld maar een klein aantal patiënten worden gevolgd. In het totaal werden 268 onbehandelde patiënten die deelnamen aan de Pompe Survey prospectief gevolgd voor een (mediane) periode van 3.5 jaar. De geschatte 5-jaarsoverleving van onbehandelde volwassen Pompe patiënten vanaf diagnose bleek 95% te zijn. De overlevingspercentages na 10, 20, en 30 waren respectievelijk 83, 65, en 40%. Ziekte ernst, uitgedrukt in rolstoelgebondenheid en beademingsbehoefte, bleek van invloed op de overleving. Daarnaast werd overleving ook beïnvloed door de mate van handicap gemeten met de Rotterdam Handcap Scale (RHS). Voor patiënten die slechter scoorden op de Rotterdam Handicap Scale (RHS) en dus meer handicaps hadden, waren de overlevingspercentages lager dan voor patiënten met goede scores en weinig handicaps. Bij vergelijking van het aantal overleden patiënten in een subgroep van 99 Nederlandse patiënten en het verwachte aantal overledenen in de algemene bevolking -gestandaardiseerd naar leeftijd en geslacht- bleek de sterftekans onder onbehandelde Nederlandse Pompe patiënten hoger dan in de algemene bevolking.

De resultaten ten aanzien van het effect van enzymtherapie op de overleving van volwassen patiënten met de ziekte van Pompe zijn te lezen in **Hoofdstuk 5.** Een totaal aantal van 283 volwassen patiënten werd geïncludeerd in deze studie. Tweeënzeventig procent van deze patiënten bleek te zijn gestart met enzymtherapie op een bepaald moment tijdens follow-up vanaf het moment dat zij besloten hadden mee te doen met de studie. De mediane follow-up van patiënten in deze studie was 6 jaar. Gedurende deze periode, overleden 46 patiënten; 61% van deze patiënten had nooit enzymtherapie gehad. Op basis van de studiegegevens konden we berekenen dat enzymtherapie een positief effect had overleving (Hazard Ratio (HR) 0.41), ook nadat gecorrigeerd was voor leeftijd, geslacht, land van herkomst en ziekte ernst van patiënten. Deze allereerste studie die de effecten van enzymtherapie op de overleving

van volwassen patiënten met de ziekte van Pompe bestudeert, ondersteunt de resultaten van eerdere studies die positieve effecten van enzymtherapie aantoonden bij volwassenen.

De focus van **Hoofdstuk 6** ligt op pijn. Het viel ons op dat veel volwassen Pompe patiënten klagen over pijn. De rapportage daarover in de literatuur was tot dusverre beperkt. Dit was reden om de ernst en de invloed van pijn op het dagelijks leven van volwassen Pompe patiënten te meten met een specifieke vragenlijst: de Brief Pain Inventory. Een grote groep volwassen patiënten (n=124) uit Duitsland en Nederland deden mee aan deze cross-sectionele studie. Een groep van 111 qua leeftijd overeenkomende gezonde personen diende daarbij als controle groep. Vergeleken met de controle groep was de prevalentie van pijn bijna twee keer zo hoog in de groep Pompe patiënten (27% versus 45%). De ernst van pijn en de invloed van pijn op dagelijkse activiteiten waren bij patiënten ook hoger dan in de controle groep. Daarnaast had pijn een negatieve invloed op de kwaliteit van leven, participatie in het dagelijks leven (de mate van handicap) en het optreden van angst en depressiviteit. Op basis van de resultaten van dit onderzoek hebben we geconcludeerd dat pijn een belangrijk symptoom is van de ziekte van Pompe bij volwassenen, dat op dit moment te weinig aandacht krijgt. Pijnklachten en de behandeling ervan moeten daarom een prominentere plaats krijgen in het klinisch management van patiënten met de ziekte van Pompe. Het effect van enzymtherapie op pijn kon niet worden bestudeerd vanwege het "cross-sectionele" studie design.

Eerder onderzoek waarbij gegevens werden gebruikt uit de IPA / Erasmus MC Pompe Survey had aangetoond dat vermoeidheid een vaak voorkomend symptoom is bij volwassen patiënten met de ziekte van Pompe, onafhankelijk van het feit of ze nu mild of ernstig aangedaan zijn. In **Hoofdstuk 7** hebben derhalve onderzocht of enzymtherapie deze vermoeidheid bij patiënten vermindert. In dit prospectief internationaal vragenlijst onderzoek, hebben we de "Fatigue Severity Scale" (FSS) gebruikt om vermoeidheid te meten. Tijdens deze studie hebben we 163 volwassen patiënten gevolgd tijdens een mediane follow-up tijd van 4 jaar voor en 3 jaar na het start van enzymtherapie. Voor start van enzymtherapie bleef de gemiddelde FSS score stabiel. Na start verbeterde de FSS score significant. Met name vrouwen, oudere patiënten en patiënten met een kortere ziekteduur lieten een goed effect op hun vermoeidsscore zien, dat wil zeggen dat zij door enzymtherapie minder vermoeid werden. Subanalyse – in de Nederlandse groep – liet verder zien dat verbeteringen in vermoeidheid na enzymtherapie gecorreleerd waren met het effect van enzymtherapie op depressie. Omdat maar een klein aantal patiënten met de ziekte van Pompe depressieve klachten vertoonde kon dit niet het volledig effect van enzymtherapie op vermoeidheid verklaren. Het effect op vermoeidheid correleerde in de Nederlandse subgroep niet met het effect van enzymtherapie op spierkracht en longfunctie. We kunnen de achterliggende mechanismen die ten grondslag liggen aan het effect van enzymtherapie op vermoeidheid niet volledig verklaren. Toch concluderen we dat het effect van enzymtherapie op vermoeidheid een belangrijke bevinding is, omdat ernstige vermoeidheid bij veel Pompe patiënten voorkomt onafhankelijk van de ernst van de ziekte en een belangrijk invaliderend effect heeft op leven van patiënten.

Hoofdstuk 8 bestudeert of enzymtherapie de kwaliteit van leven en mate van handicap van volwassen Pompe patiënten verbetert. Deze studie werd uitgevoerd bij 174 volwassen patiënten. De totale mediane follow-up periode waarover patiënten werden gevold was 7 jaar. De SF -36 bestaat uit twee onderdelen. Eén onderdeel meet het fysiek functioneren van de patiënt (Physical Component Summary Measure, (PCS); het andere onderdeel het mentaal functioneren (Mental Component Summary Measure (MCS)). Aangetoond werd, dat de score van de PCS significant verslechterde voor de start van enzymtherapie, terwijl de score in de eerste 2 jaar na start van therapie significant verbeterde en daarna stabiliseerde. De MCS bleef stabiel gedurende alle perioden zowel voor als na therapie. De mate van handicap gemeten met de 'Rotterdam Handicap Scale score (RHS') bleef gelijk na start van enzymtherapie. Ook dit vonden wij een belangrijke bevinding, omdat onze studie liet zien dat de score en dus de mate handicap significant verslechterde in de jaren voor start van behandeling. De behandeling bleek een halt toe te brengen aan de verslechtering. De algehele conclusie van deze studie is dat enzymtherapie een positief effect heeft op kwaliteit van leven en de mate van handicap van volwassen patiënten met de ziekte van Pompe en daarmee een belangrijke invloed heeft op het dagelijks leven van patiënten.

De klinische implicaties van de studies beschreven in dit proefschrift en implicaties voor het dagelijks leven van patiënten worden bediscussieerd in **Hoofdstuk 9.** Tevens worden er suggesties gedaan voor toekomstig (vervolg) onderzoek. Al met al kunnen we concluderen dat de IPA / Erasmus MC Pompe Survey tot dusverre in belangrijke mate heeft bijgedragen aan het verkrijgen van nieuwe kennis ten aanzien van het natuurlijk beloop van de ziekte van Pompe en effecten van enzymtherapie. De resultaten van de Pompe Survey ondersteunen positieve resultaten uit klinische studies, ten aanzien van het effect van enzymtherapie. Daarnaast laten de studies ook zien dat informatie verzameld direct van de patiënt zelf, door middel van jaarlijkse surveys, waarbij onder andere gebruik gemaakt wordt van gestandaardiseerde en gevalideerde vragenlijsten een waardevol instrument is. Dit naast dataverzameling uit klinische studies en arts gestuurde registries, die klinische informatie vaak op niet gestandaardiseerde en geprotocolleerde wijze verzamelen. Ons Pompe onderzoek toont aan dat patiënten surveys met name in het geval van zeldzame ziekten een belangrijke rol kunnen spelen bij de data verzameling. Het laat zien dat vragenlijstonderzoeken niet alleen nuttig zijn voor het in kaart brengen van het natuurlijk beloop van een ziekte, maar tevens voor het evalueren van bestaande en eventueel toekomstige therapieën. De werving van patiënten via internationale patiënten verenigingen, die zoals voor de ziekte van Pompe verenigd zijn in een internationale patiënten organisatie, de "International Pompe Association (IPA)"- vergemakkelijkt de inclusie van een groot aantal patiënten. Door te focusseren op een breed aantal aspecten van de ziekte en gebruik te maken van toepasselijke gestandaardiseerde vragenlijsten en patiënten te betrekken bij de ontwikkeling van de survey, zodat ook de meest relevante beperkingen door de ziekte worden meegenomen, heeft ervoor gezorgd dat de Pompe Survey een groot aantal vragen over een breed aandachtsgebied heeft kunnen beantwoorden. De Pompe Survey kan daarom als voorbeeld dienen voor het onderzoek bij andere zeldzame ziekten.

Özet

Pompe hastalığı, glikojenin temel olarak kaslarda birikmesi ve sonuçta kas disfonksiyonuna yol açmasıyla sonuçlanan, asit α-glukozidaz eksikliğinden kaynaklanan bir otozomal resesif lizozomal depo hastalığıdır. Etkilenmiş olan erişkin hastaların büyük kısmı tekerlekli sandalye ve ventilatör ile yaşamlarını sürdürür.

Enzim replasman tedavisi (ERT) günümüzde Pompe hastalığı için tek tedavi seçeneğidir. 2006 yılında düzenlenen kayıt sistemi, klasik infantil Pompe hastalığına sahip hastalarda yürütülen araştırmaların sonuçları ile desteklenmiştir. O günden bu yana, daha az ağır hastalığı olanlarda da, terapötik etkiye dair kanıtlar gösterilmiştir. Ancak, bu tezde sözü edilen çalışmaların başladığı dönemde, enzim replasman tedavisinin sağ kalım ve yaşam kalitesi gibi önemli sonuç değişkenleri üzerine etkisini inceleyen çalışmalar yetersizdi.

Bu tezdeki çalışmalarda, erişkin yaşamda Pompe hastalığının yarattığı hastalık yükü incelenmiştir ve temel olarak, halen devam eden uluslararası bir açık kohort çalışması olan IPA / Erasmus MC Pompe Surveyi verileri kullanılmıştır. Hastalarca rapor edilen sonuç değişkenleriyle, Pompe hastalığı olan erişkinlerde sağ kalımı, ağrının Pompe hastalığı semptomlarına olan katkısını ve enzim replasman tedavisinin etkisini anlamayı amaçladık.

1. Bölümde Pompe hastalığına dair genel bilgiler sunulmuştur. Hastalığın klinik özellikleri, patogenezi ve tedavisine dair temel bilgiler verilmiştir.

2. Bölümde erişkin ve çocuklarda Pompe hastalığıyla ilgili olan ve hastalara düzenli aralarla gönderilen ölçeklerle verinin toplandığı, sürmekte olan bir uluslararası çalışma olan IPA / Erasmus MC Pompe Surveyinin tasarımı açıklanmaktadır. Ayrıca, bu bölümde, kullanılmış olan ölçeklerin ana hatları sunulmuştur. Bu bölüm tezin ana hatlarını ve bu tezde yer alan çalışmaların dayandığı bilimsel temelleri de açıklamaktadır.

Pompe hastalığının fenotiplerini açıklayan terminoloji ile ilgili uluslararası bir ortak görüş halen mevcut değildir. Bu nedenle **3. Bölümde** bir klinik yelpaze olarak Pompe hastalığının geleneksel tanımlanmasına (burada tanı ve hastalığın gidişi ile ilgili olarak klasik-infantil ve non-klasik form ayrımı yapılmıştır) bağlı kalmayı öneriyoruz. Klasik Pompe hastalığı sınırları net çizilmiş bir klinik antitedir. Non-klasik Pompe hastalığı ise geniş bir yaş aralığını kapsar ve kabaca çocukluk ve erişkinlik döneminde ortaya çıkan fenotipler olarak alt gruplara ayrılabilir.

Bölüm 4 tedavi edilmemiş erişkin Pompe hastalarında, hastalığın yaşam süresini ne kadar kısalttığını inceleyen dünya çapındaki ilk çalışmanın sonuçlarını vermektedir. Çok az sayıda Pompe hastası görüldüğünden, klinik pratikte, bunun gibi bir çalışmayı yapmak daha önce mümkün olmamıştır. Araştırmaya katılan toplam 268 tedavisiz hasta, ortanca 3.5 yıl süreyle izlenmiştir. Tanıdan sonraki 5 yıllık sağ kalım hızı %95'ti. Sırasıyla 10, 20 ve 30 yıllık sağ kalım hızları % 83, 65 ve 40'ti. Hastaların sağ kalımını etkileyen faktörler, yaş, hastalık şiddeti (tekerlekli sandalye ve/veya solunum desteği temel alınarak) ve hastaların Rotterdam Handikap Ölçeği (RHO) puanıydı. 99 Hollandalı hastadan oluşan bir alt grupta gözlenen ölüm sayısı, genel

popülasyondan yaş ve cinsiyet açısından eşleştirilmiş bir başka grupla karşılaştırılmıştır. Hollandalı Pompe hastalarında mortalitenin genel toplum örnekleminden yüksek olduğu sonucuna vardık.

Enzim replasman tedavisinin erişkin hastalardaki sağ kalıma etkisi **5. Bölümde** ele alınmıştır. Çalışmaya toplam 283 erişkin hasta dâhil edilmiştir. Bu hastaların %72'si izlem dönemlerinin herhangi bir aşamasında tedaviye başlamışlardır. Ortanca 6 yıllık izlem süresince, ölen 46 hastanın %61'i hiç ERT almamıştır. Yaş, cinsiyet, yaşanılan ülke ve hastalık şiddeti (tekerlekli sandalye ve/veya solunum desteği temel alınarak), ile ilgili değerlendirmelerden sonra enzim replasman tedavisi sağ kalım süresi ile pozitif ilişkiliydi (HR 0.41). Enzim replasman tedavisinin erişkin hastalarda sağ kalım üzerine etkilerini araştıran bu ilk çalışma, tedavinin, bu yaş grubunda faydalı etkileri olduğunu desteklemektedir.

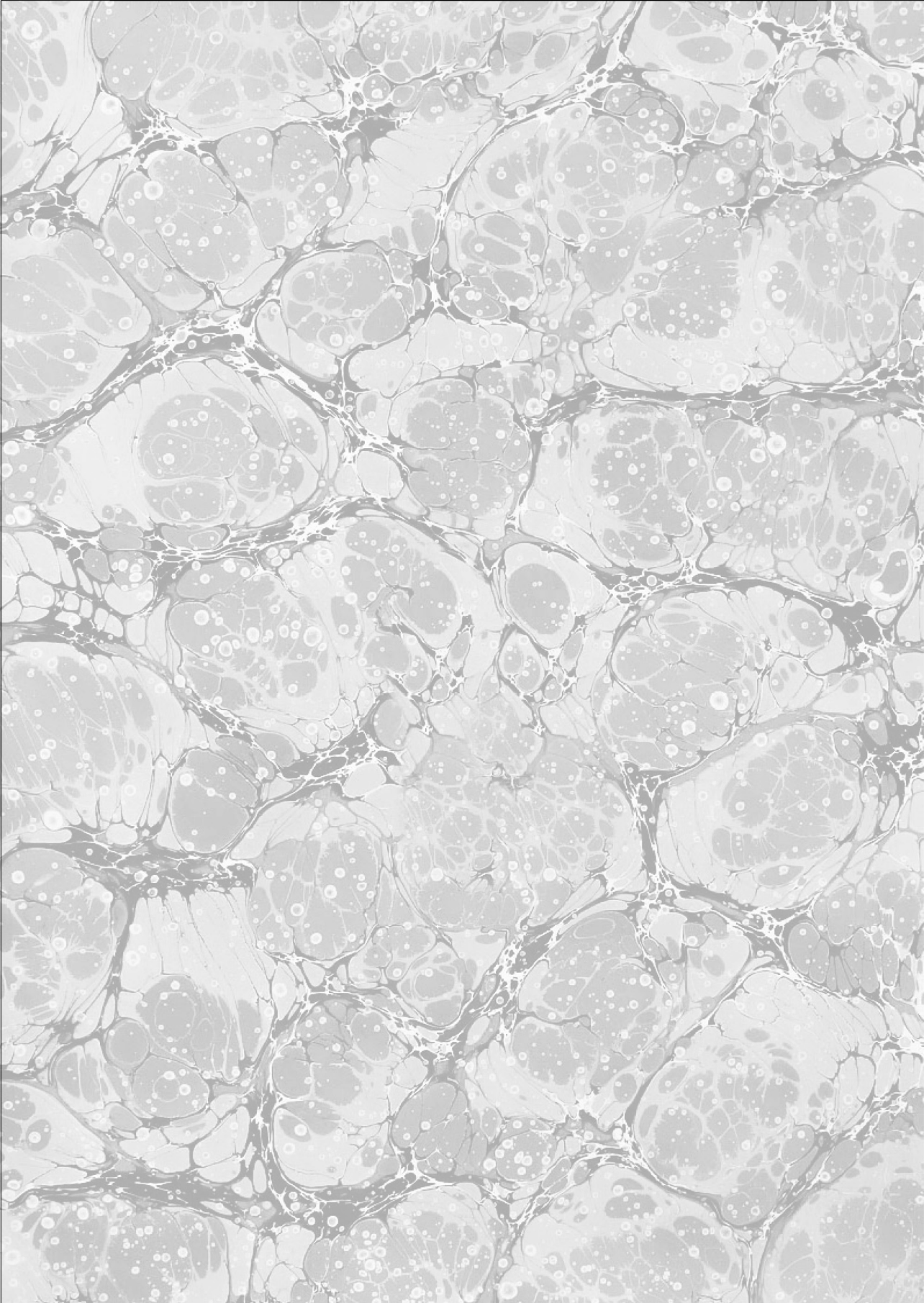
6. Bölümün odak noktaları, ağrı, ağrının şiddeti ve kısa ağrı envanteri-kısa form- ile ölçülen günlük yaşam aktiviteleri arasındaki etkileşimdir. Almanya ve Hollanda'dan Pompe hastalığı olan büyük bir erişkin grubu (n=124) bu kesitsel çalışmaya dahil edilmiştir ve yaş açısından eşleştirilmiş bir grupla (n=111) karşılaştırılmıştır. Kontrol grubuyla karşılaştırıldığında, ağrı prevalansı Pompe hastalarında yaklaşık 2 kat daha yüksekti (%27'ye karşılık %45). Ağrı şiddeti ve ağrı etkileşimi puanları da hasta grubunda kontrollere göre daha yüksekti. Ayrıca, ağrı hastaların yaşam kalitesini, günlük yaşama katılımlarını ve ruh sağlığını negatif yönde etkiliyor gibi görünmektedir. Bu çalışmanın sonuçlarına göre, ağrı üzerine daha fazla düşünülmesi gerektiği sonucuna vardık. Ağrı değerlendirmesi, Pompe hastalarının klinik değerlendirmelerinde yer almalıdır. Bu kesitsel çalışmada enzim replasman tedavisinin ağrı üzerine etkisi incelenememiştir.

Yorgunluk, hem hafif hem de şiddetli derecelerde etkilenmiş Pompe hastalarında sıklıkla gözlenen bir belirtidir. **7. Bölümde** enzim replasman tedavisinin yorgunluğu azaltıp azaltmadığını inceledik. Bu uzunlamasına uluslararası gözlemsel çalışmada, yorgunluğu ölçmek için Yorgunluk Şiddeti Ölçeği (YŞÖ) kullandık. 163 erişkin hasta enzim replasman tedavisinden ortanca 4 yıl önce ve tedavi boyunca ortanca 3 yıl süreyle izlenmiştir. Tedavi başlamadan önce ortalama YŞÖ puanı sabit kaldı ve tedavi boyunca yorgunluk anlamlı olarak azaldi. Yorgunluk öncelikle kadınlarda, yaşlı hastalarda ve hastalık süresi kısa olanlarda azaldı. Alt analizler- Hollanda kohortu- bu düzelmenin enzim replasman tedavisinin kas ve pulmoner fonksiyonlardan ziyade depresyondaki düzelmeyle korele olduğunu göstermiştir. Enzim replasman tedavisinin yorgunluğu nasıl azalttığına dair mekanizmaları araştıramamış olsak da, tedavinin yorgunluğu azalttığını gösteren bulgumuz, yorgunluğun yaygın ve yaşamı etkileyen bir sorun olduğu hastalar için önemlidir.

8. Bölümde 174 erişkin hastada, enzim replasman tedavisinin, yaşam kalitesini ve günlük yaşama katılımı artırıp artırmadığı araştırılmıştır. SF-36 Fiziksel Komponent Sonuç (FKS) ölçümü tedavi öncesinde kötüyken, tedavinin özellikle ilk iki yılında anlamlı olarak düzelmiş ve sabit kalmıştır. Mental Komponent Sonuç (MKS) ölçümü her üç dönemde de sabit kaldı. Rotterdam Handikap Ölçeği (RHO) puanı, tedavinin başlangıcındaki ani düşüşten sonra tedavi boyunca

sabitti. Bu bölümün sonucu olarak, erişkin Pompe hastalarında enzim replasman tedavisinin yaşam kalitesini ve gündelik yaşama katılımı artırdığını söylemek mümkündür.

Bu tezde yer alan çalışmaların klinikteki uygulamaları ve bundan sonra yapılacak çalışmalar için öneriler **9. Bölümde** verilmiştir. Çalışmalar Pompe hastalığının klinik semptomları, doğal gidişi ile ilgili bilgilerimizi artırmış ve erişkin hastaların enzim replasman tedavisinden fayda gördüğünü gösteren verileri desteklemiştir. Tezdeki çalışmalar ayrıca surveylerde hastalarca bildirilen sonuç değişkenlerinin, klinik kayıtlar ve klasik araştırmalarda toplanan verilere ek olarak değerli birer araç olduğunu da ortaya koymuştur. Surveyler sadece hastalığın doğal gidişini göstermekle kalmayıp, süregiden veya ileride başlanacak olan tedavilerin etkinliklerini de göstermektedir. Hastaların uluslararası hasta dernekleri - IPA altında birleşmiş- aracılığıyla çalışmaya alınması, özellikle de amacı çok sayıda farklı ölçeği uygulamak olan Pompe Surveyinde çok sayıda hastaya ulaşmayı kolaylaştırmıştır. Pompe Surveyi diğer nadir görülen hastalıkları araştırmak için bir model olarak kullanılabilir.



Appendix

Abbreviations

Authors and Affiliations

Dankwoord/Acknowledgements

About the author

List of Publications

PhD portfolio

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

Baseline IPA/ Erasmus MC Pompe Survey
(For patients 16 years and older)

General introduction

Thank you for participating in the IPA/ Erasmus MC Pompe Survey. The goal of this survey is to obtain better insight into the natural course of Pompe disease, the impact of the disease on patients' lives, and the changes that occur with treatment.

For patients 16 years of age and older, the baseline survey consists of the following questionnaires:

- Baseline Pompe Questionnaire
- Fatigue Severity Scale
- Rotterdam Handicap Scale
- SF-36v2™ Health Survey

Questions will be asked about subjects of a very different nature. Also, symptoms that rarely occur in Pompe disease, and symptoms about whose relationship to Pompe disease we are still unsure, will be mentioned in the questionnaires. Some questions or subjects therefore will apply more specifically to you than other questions or subjects.

We are aware of the fact that we are asking you many questions. Please take all the time that you need to answer them. You may complete the questionnaires in the order that you prefer and at the time that is most convenient for you.

We thank you in advance for your cooperation; it is much appreciated.

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

Baseline Pompe Questionnaire

Date of Completion: |____||_____||_____|
DD MM YYYY

Your Initials: _____/_____/_____
F M L

Date of Birth: |____||_____||_____| **Gender:** ☐ **Male** ☐ **Female**
DDMM YYYY

EXPLANATION

- This baseline Pompe questionnaire consists of five sections. Section A asks how and when you became aware that you have Pompe disease. Section B inquires about the occurrence of the disease among your blood relatives. Section C discusses your current situation. Section D asks about the physicians / medical specialists who are treating you and whether you are currently receiving any specific therapy for Pompe disease. Finally, Section E asks you to indicate which questions were not clear to you and which questions you skipped in this questionnaire, so that we can take such questions into account in future studies.
- In this questionnaire, questions are often asked about the year in which certain complaints occurred for the first time. If you do not remember the exact year, you may also indicate how many years ago (for example <5 years ago, 5-10 years ago, 11-15 years ago, etc.).

A. DIAGNOSIS

The following questions concern how and when you became aware of the nature of your disease.

1. What were your first complaints that had to do with Pompe disease? (check a maximum of four complaints)
   1. ☐ Difficulty walking
   2. ☐ Difficulty running
   3. ☐ Difficulty playing sports
   4. ☐ Difficulty going up and down stairs
   5. ☐ Difficulty rising from a sitting position
   6. ☐ Difficulty rising from a lying position
   7. ☐ Difficulty lifting my head
   8. ☐ Difficulty bending over
   9. ☐ Difficulty swimming
   10. ☐ Difficulty maintaining balance
   11. ☐ General muscle weakness
   12. ☐ Breathing problems
   13. ☐ Sleep problems
   14. ☐ Fatigue
   15. ☐ Muscle spasms / cramps (check all that apply):

☐ Neck	☐ Shoulders	☐ Back
☐ Chest	☐ Upper arms	☐ Lower arms
☐ Abdomen	☐ Hands	☐ Upper legs
☐ Lower legs	☐ Feet	

   16. ☐ Muscle pain (check all that apply):

☐ Neck	☐ Shoulders	☐ Back
☐ Chest	☐ Upper arms	☐ Lower arms
☐ Abdomen	☐ Hands	☐ Upper legs
☐ Lower legs	☐ Feet	

   17. ☐ Other, specify: _____
   18. ☐ Don't know

Case Number: ☐☐☐☐☐☐

Baseline
IPA/ Erasmus MC Pompe Survey

2. When did these <u>first</u> complaints (from question 1 above) occur for the first time?

A. Complaint number B. Please fill in **year** <u>or</u> indicate **how many years ago**.

No. ☐☐ **Year** ☐☐☐☐ **Years ago (select one)**

○ <5 years ago ○ 5-10 years ago ○ 11-15 years ago
○ 16-20 years ago ○ 21-25 years ago ○ 26-30 years ago
○ 31-35 years ago ○ 36-40 years ago ○ 41-45 years ago
○ 46-50 years ago ○ >50 years ago

No. ☐☐ **Year** ☐☐☐☐ **Years ago (select one)**

○ <5 years ago ○ 5-10 years ago ○ 11-15 years ago
○ 16-20 years ago ○ 21-25 years ago ○ 26-30 years ago
○ 31-35 years ago ○ 36-40 years ago ○ 41-45 years ago
○ 46-50 years ago ○ >50 years ago

No. ☐☐ **Year** ☐☐☐☐ **Years ago (select one)**

○ <5 years ago ○ 5-10 years ago ○ 11-15 years ago
○ 16-20 years ago ○ 21-25 years ago ○ 26-30 years ago
○ 31-35 years ago ○ 36-40 years ago ○ 41-45 years ago
○ 46-50 years ago ○ >50 years ago

No. ☐☐ **Year** ☐☐☐☐ **Years ago (select one)**

○ <5 years ago ○ 5-10 years ago ○ 11-15 years ago
○ 16-20 years ago ○ 21-25 years ago ○ 26-30 years ago
○ 31-35 years ago ○ 36-40 years ago ○ 41-45 years ago
○ 46-50 years ago ○ >50 years ago

3. Which complaints (from question 1 above) made you go to a doctor to find out what was wrong with you?

1. ☐ **2.** ☐ **3.** ☐ **4.** ☐ **5.** ☐ **6.** ☐ **7.** ☐
8. ☐ **9.** ☐ **10.** ☐ **11.** ☐ **12.** ☐ **13.** ☐ **14.** ☐
15. ☐ **16.** ☐ **17.** ☐ ☐ None ☐ Don't know

NOTE: numbering of the complaints is the same as under question 1.

4. When were you diagnosed with "Pompe disease" (also called: "glycogen storage disease type 2" or "acid maltase deficiency" or "alpha glucosidase deficiency")?

Please fill in **year** <u>or</u> indicate **how many years ago**.

Year ☐☐☐☐ **Years ago (select one)**

○ <5 years ago ○ 5-10 years ago ○ 11-15 years ago
○ 16-20 years ago ○ 21-25 years ago ○ 26-30 years ago
○ 31-35 years ago ○ 36-40 years ago ○ 41-45 years ago
○ 46-50 years ago ○ >50 years ago

5. Which of the following diagnostic tests have you had?

Muscle biopsy	○ Yes	○ No	○ Don't know
Fibroblasts (skin biopsy)	○ Yes	○ No	○ Don't know
Leukocytes (blood)	○ Yes	○ No	○ Don't know
DNA analysis	○ Yes	○ No	○ Don't know
Dried blood spot	○ Yes	○ No	○ Don't know

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

6. Do you currently play any sports or do any physical exercise? (select one)
   - ○ Yes, specify: _____
   - ○ No

Movements

7. Are you currently able to go up and down stairs? (select one)
   - ○ Don't know, I never have to deal with stairs
   - ○ Without any problems
   - ○ With the support of banisters
   - ○ With the assistance of other people
   - ○ With the support of banisters and assistance of other people
   - ○ I am no longer able to go up and down stairs

   7a. When did you first have any problems going up and down stairs?
   Please fill in **year** or indicate **how many years ago**.

   Year | | | | |

   Years ago (select one)

○ <5 years ago	○ 5-10 years ago	○ 11-15 years ago
○ 16-20 years ago	○ 21-25 years ago	○ 26-30 years ago
○ 31-35 years ago	○ 36-40 years ago	○ 41-45 years ago
○ 46-50 years ago	○ >50 years ago	

8. Are you currently able to rise by yourself from a sitting position (chair, armchair)? (select one)
   - ○ Yes, without any problems
   - ○ Yes, but with difficulty
   - ○ No

   8a. When did you first have any problems rising from a sitting position (chair, armchair)?
   Please fill in **year** or indicate **how many years ago**.

   Year | | | | |

   Years ago (select one)

○ <5 years ago	○ 5-10 years ago	○ 11-15 years ago
○ 16-20 years ago	○ 21-25 years ago	○ 26-30 years ago
○ 31-35 years ago	○ 36-40 years ago	○ 41-45 years ago
○ 46-50 years ago	○ >50 years ago	

9. Are you currently able to rise by yourself from a lying position? (select one)
   - ○ Yes, without any problems
   - ○ Yes, but with difficulty
   - ○ No

   9a. When did you first have any problems rising from a lying position?
   Please fill in **year** or indicate **how many years ago**.

   Year | | | | |

   Years ago (select one)

○ <5 years ago	○ 5-10 years ago	○ 11-15 years ago
○ 16-20 years ago	○ 21-25 years ago	○ 26-30 years ago
○ 31-35 years ago	○ 36-40 years ago	○ 41-45 years ago
○ 46-50 years ago	○ >50 years ago	

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

10. Are you currently able, when lying on your back, to raise your legs from the surface you are lying on? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

11. Are you currently able to raise your arms above your head? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

    11a. When did the first problems with moving in this way occur?
    Please fill in **year** or indicate **how many years ago**.

    Year | | | | |

    Years ago (select one)

○ <5 years ago	○ 5-10 years ago	○ 11-15 years ago
○ 16-20 years ago	○ 21-25 years ago	○ 26-30 years ago
○ 31-35 years ago	○ 36-40 years ago	○ 41-45 years ago
○ 46-50 years ago	○ >50 years ago	

12. Are you currently able to rise by yourself from a squatting position? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

13. Are you currently able to jump? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

14. Are you currently able to return to an upright position by yourself after bending over? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

Breathing

15. Please indicate whether you are currently experiencing, or have experienced in the past year, any of the following breathing problems. (check all that apply)
    - ☐ Shortness of breath after heavy exercise
    - ☐ Shortness of breath after a small amount of exercise
    - ☐ Shortness of breath while not moving
    - ☐ Shortness of breath when lying down
    - ☐ Pneumonia or airway infection
    - ☐ Other, specify: _____
    - ☐ None

Case Number: ☐☐☐☐☐☐

Baseline
IPA/ Erasmus MC Pompe Survey

16. Do you currently use any help for breathing? (select one)
    - ○ No
    - ○ Yes

    16a. Do you use any of the following to help with breathing? (check all that apply)
    - ☐ Air stacking
    - ☐ BiPAP
    - ☐ CPAP
    - ☐ Supplemental oxygen
    - ☐ Invasive ventilation
    - ☐ Other, specify: _____

    16b. When do you use help for breathing? (check all that apply)
    - ☐ After exercise
    - ☐ During the daytime
    - ☐ During the night time (sleeping)

    16c. How many hours per day in total (add time during the day and night) do you use help for breathing?
    Total number of hours: _____ per day

    16d. Since when have you been using help for breathing?
    Please fill in **year** or indicate **how many years ago**.

    Year ☐☐☐☐

    Years ago (select one)
    - ○ <5 years ago
    - ○ 5-10 years ago
    - ○ 11-15 years ago
    - ○ 16-20 years ago
    - ○ 21-25 years ago
    - ○ 26-30 years ago
    - ○ 31-35 years ago
    - ○ 36-40 years ago
    - ○ 41-45 years ago
    - ○ 46-50 years ago
    - ○ >50 years ago

Sleeping

17. Do you currently have any sleeping problems? (select one)
    - ○ Never / hardly ever
    - ○ Occasionally
    - ○ Often

18. When rising in the morning, do you currently have a headache or feel light-headed? (select one)
    - ○ Never / hardly ever
    - ○ Occasionally
    - ○ Often

19. Do you currently experience nausea in the morning? (select one)
    - ○ Never / hardly ever
    - ○ Occasionally
    - ○ Often

20. Are you currently able to lie flat on your back while sleeping? (select one)
    - ○ Yes
    - ○ No

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

Eating

21. Do you currently have any problems with chewing while eating? (select one)
    - ○ Not applicable, I use a tube to eat
    - ○ Never / hardly ever
    - ○ Occasionally
    - ○ Often
    - ○ Always

22. Do you currently have any problems with swallowing while eating? (select one)
    - ○ Not applicable, I use a tube to eat
    - ○ Never / hardly ever
    - ○ Occasionally
    - ○ Often
    - ○ Always

23. Are you currently able to eat by yourself? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

24. Are you currently on a special diet? (select one)
    - ○ No
    - ○ Yes

    24a. Are you on any of the following special diets? (check all that apply)
    - ☐ High-protein, low-carbohydrate
    - ☐ High-protein, high-fat
    - ☐ Low-carbohydrate, high-fat
    - ☐ Other, specify: _____

    24b. Do you currently take any food supplements? (check all that apply)
    - ☐ Alanine
    - ☐ Carnitine
    - ☐ Ephedrine
    - ☐ Glutamine
    - ☐ Other, specify: _____

25. Do you currently use a PEG tube to take in food? (select one)
    - ○ No
    - ○ Yes

    25a. Since when have you been using a PEG tube?
    Please fill in **year** or indicate **how many years ago**.

    Year | | | | |

    Years ago (select one)
    - ○ <5 years ago
    - ○ 5-10 years ago
    - ○ 11-15 years ago
    - ○ 16-20 years ago
    - ○ 21-25 years ago
    - ○ 26-30 years ago
    - ○ 31-35 years ago
    - ○ 36-40 years ago
    - ○ 41-45 years ago
    - ○ 46-50 years ago
    - ○ >50 years ago

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

26. Do you currently use a nasogastric (NG) tube to take in food? (select one)
    - ○ No
    - ○ Yes

    26a. Since when have you been using a NG tube?
    Please fill in **year** or indicate **how many years ago**.

    Year | | | | |

    Years ago (select one)

○ <5 years ago	○ 5-10 years ago	○ 11-15 years ago
○ 16-20 years ago	○ 21-25 years ago	○ 26-30 years ago
○ 31-35 years ago	○ 36-40 years ago	○ 41-45 years ago
○ 46-50 years ago	○ >50 years ago	

Other Complaints

27. Are you currently suffering from restricted movement in one or more joints (contractures)? (select one)
    - ○ No
    - ○ Yes

    27a. In what part of your body are you suffering from restricted movement in joints (contractures)? (check all that apply)

☐ Neck	☐ Shoulders
☐ Elbows	☐ Hands
☐ Hips	☐ Knees
☐ Ankles	☐ Other, specify: _____

28. Are you currently suffering from muscle cramps? (select one)
    - ○ Never / hardly ever
    - ○ Occasionally
    - ○ Often
    - ○ Always

    28a. In what part of your body are you suffering from muscle cramps? (check all that apply)

☐ Neck	☐ Shoulders
☐ Back	☐ Chest
☐ Upper arms	☐ Lower arms
☐ Hands	☐ Abdomen
☐ Upper legs	☐ Lower legs
☐ Feet	☐ Other, specify: _____

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

29. Are you currently suffering from muscle pains? (select one)
- ○ Never / hardly ever
- ○ Occasionally
- ○ Often
- ○ Always

29a. In what part of your body are you suffering from muscle pains? (check all that apply)

☐ Neck	☐ Shoulders
☐ Back	☐ Chest
☐ Upper arms	☐ Lower arms
☐ Hands	☐ Abdomen
☐ Upper legs	☐ Lower legs
☐ Feet	☐ Other, specify: _____

30. Are you currently suffering from pain in your back? (select one)
- ○ Never / hardly ever
- ○ Occasionally
- ○ Often
- ○ Always

31. Are you currently suffering from pain in your neck? (select one)
- ○ Never / hardly ever
- ○ Occasionally
- ○ Often
- ○ Always

32. Are you currently suffering from pain in your legs? (select one)
- ○ Never / hardly ever
- ○ Occasionally
- ○ Often
- ○ Always

33. Do you currently have any problems with raising your head? (select one)
- ○ No
- ○ Yes, a little bit
- ○ Yes, a lot

34. Do you currently have any problems in keeping your head upright (head balance)? (select one)
- ○ No
- ○ Yes, a little bit
- ○ Yes, a lot

35. Do you currently have any problems with hearing? (select one)
- ○ No
- ○ Yes

36. Do you currently have any problems with speaking? (select one)
- ○ No
- ○ Yes

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

37. Please indicate from the following list which complaints you are currently suffering from, or have suffered from in the past year. (check all that apply)

- ☐ Cerebral haemorrhage
- ☐ Constipation
- ☐ Difficulty with holding your faeces
- ☐ Heart complaints
- ☐ Quickly tired / fatigued
- ☐ Sleepiness
- ☐ Urinary tract infection
- ☐ Other, specify: _____
- ☐ Concave back (lordosis)
- ☐ Diarrhoea
- ☐ Difficulty with holding your water
- ☐ Osteoporosis
- ☐ Scoliosis (sideways curvature of the spine)
- ☐ Suspended eyelid
- ☐ Widened blood vessel (aneurysm)
- ☐ None

Daily Activities

38. Are you currently able to do your shopping yourself? (select one)
    - ○ Not applicable, I never go shopping
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

39. Do you currently have any problems with carrying out certain household chores? (select one)
    - ○ Not applicable, I don't carry out any household chores
    - ○ No
    - ○ Yes

40. Are you currently able to drive a car? (select one)
    - ○ Yes
    - ○ Yes, but only with adjustments to my car
    - ○ No, I have not yet / never obtained my driver's license
    - ○ No, I learned to drive at one point, but am no longer able to

41. Are you currently able to comb your hair yourself? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

42. Are you currently able to wash yourself? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

43. Are you currently able to dress and undress yourself? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

44. Are you currently able to go to the toilet by yourself (possibly with a raised lavatory bowl or aids)? (select one)
    - ○ Yes, without any problems
    - ○ Yes, but with difficulty
    - ○ No

D. TREATMENTS

1a. Please indicate which specialists have ever treated you in relation to Pompe disease. (check all that apply)
- ☐ Cardiologist
- ☐ Dermatologist
- ☐ Gastroenterologist
- ☐ Lung specialist
- ☐ Ophthalmologist
- ☐ Paediatrician
- ☐ Rehabilitation specialist
- ☐ Surgeon
- ☐ Other specialists, specify: _____
- ☐ Clinical geneticist / genetic counsellor
- ☐ E.N.T. specialist
- ☐ Internist
- ☐ Neurologist
- ☐ Orthopaedist
- ☐ Psychiatrist
- ☐ Rheumatologist
- ☐ Urologist

1b. Please indicate which specialists are currently treating you, or have treated you in the past year, in relation to Pompe disease. (check all that apply)
- ☐ Cardiologist
- ☐ Dermatologist
- ☐ Gastroenterologist
- ☐ Lung specialist
- ☐ Ophthalmologist
- ☐ Paediatrician
- ☐ Rehabilitation specialist
- ☐ Surgeon
- ☐ None
- ☐ Clinical geneticist / genetic counsellor
- ☐ E.N.T. specialist
- ☐ Internist
- ☐ Neurologist
- ☐ Orthopaedist
- ☐ Psychiatrist
- ☐ Rheumatologist
- ☐ Urologist
- ☐ Other specialists, specify: _____

2a. Please indicate which health care professionals have ever treated you in relation to Pompe disease. (check all that apply)
- ☐ Dietician
- ☐ Occupational therapist
- ☐ Psychologist
- ☐ None
- ☐ Exercise therapist
- ☐ Physical therapist
- ☐ Speech therapist
- ☐ Other health care professional, specify: _____

2b. Please indicate which health care professionals are currently treating you, or have treated you in the past year, in relation to Pompe disease. (check all that apply)
- ☐ Dietician
- ☐ Occupational therapist
- ☐ Psychologist
- ☐ None
- ☐ Exercise therapist
- ☐ Physical therapist
- ☐ Speech therapist
- ☐ Other health care professional, specify: _____

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

3. Do you currently receive a Pompe disease specific treatment? (select one)
   - ○ No, I have never received treatment
   - ○ No, I have received treatment in the past but discontinued this treatment (answer questions 3a, 3b, 3c, 3e and 3f)
   - ○ Yes, I am currently receiving treatment (answer questions 3a, 3b, 3c and 3d)

3a. What is the name of the drug you have received/are receiving for treatment of Pompe disease?
- ○ Alglucosidase alfa
- ○ Other drug, specify: _____

3b. Date you first received treatment with this drug: |____| |_____| |_____|
DD MM YYYY
If you do not know the exact date, if possible please provide at least the year.

3c. In what setting did you first receive treatment with this drug? (select one)
- ○ Commercially available drug
- ○ International Charitable Access Program
- ○ Expanded Access Program
- ○ Compassionate Use/Autorisation Temporaire d'Utilisation
- ○ Clinical trial, specify: _____
- ○ Other, specify: _____

3d. In what setting do you currently receive treatment with this drug? (select one)
- ○ Commercially available drug
- ○ International Charitable Access Program
- ○ Clinical trial, specify: _____
- ○ Other, specify: _____

3e. Date you discontinued treatment with this drug: |____| |_____| |_____|
DD MM YYYY
If you do not know the exact date, if possible please provide at least the year.

3f. What was the reason for discontinuation of treatment with this drug?
- ○ Reimbursement issues
- ○ Pregnancy
- ○ Personal
- ○ Other, specify: _____

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

E. CONCLUSION

1. Do (cid) you have any other complaints or disorders that have not been discussed in this questionnaire? Please indicate since when. Both complaints that are related to Pompe disease and disorders you may suffer from (have been suffering from) apart from Pompe disease should be mentioned here.

2. Please indicate the domain in which you have complaints that are the most uncomfortable to you and/or most restricting for you. (check one)
   - ☐ Activities of daily living
   - ☐ Fatigue
   - ☐ Mobility
   - ☐ Pain
   - ☐ Psychosocial
   - ☐ Strength
   - ☐ Other, specify: _____

3. Are there any matters that have not been discussed in this questionnaire, but that are of importance in your opinion?

4. By way of concluding this questionnaire we would like to know whether you still have any remarks about the questions. Were there questions that were not clear? Were any questions upsetting for you?

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

Fatigue Severity Scale

We are interested in the role of fatigue on your everyday life. Please read the following statements, then thick the figure that corresponds best with your current situation.

1 = strongly disagree, 2 = mainly disagree, 3= partially disagree, 4 =do not agree/disagree, 5 = partially agree, 6 = mainly agree, 7 = strongly agree.

My motivation is lower when I am fatigued	1	2	3	4	5	6	7
Exercise brings on my fatigue	1	2	3	4	5	6	7
I am easily fatigued	1	2	3	4	5	6	7
Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
Fatigue causes frequent problems for me	1	2	3	4	5	6	7
My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
Fatigue is among my three most disabling symptoms	1	2	3	4	5	6	7
Fatigue interferes with my work, family, or social life	1	2	3	4	5	6	7

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

Rotterdam 9-items handicap scale

For each question, please tick the answer that describes your current situation best.

Regarding items 1 and 2: moving from room to room or outdoors does not necessarily mean that you have the ability to walk. For example, you can also move from room to room in a wheelchair.

1. Mobility indoors
Are you able to move from room to room, negotiating doors, carpets and polished surfaces?
0 = not applicable
1 = unable to move between rooms
2 = move between rooms mostly with help of another person
3 = move between rooms most of the time independent; sometimes needing help of another person
4 = move between rooms totally independent

2. Mobility outdoors
Are you able to move outdoors from one place to another, negotiating kerbs and uneven grounds?
0 = not applicable
1 = unable to move outdoors
2 = move outdoors mostly with help of another person
3 = move outdoors most of the time independent; sometimes needing help of another person
4 = move outdoors totally independent

3. Kitchen tasks
Are you able to fulfil tasks like making a pot of tea/ coffee, and serving it; are you able to collect items from a high and low cupboard, refrigerator, etcetera? (other kitchen tasks are also applicable)
0 = not applicable
1 = unable to fulfil any kitchen task
2 = able to fulfil only a minimum of these tasks; mostly needing help of another person
3 = able to fulfil the vast majority of these tasks independently; sometimes needing help of another person
4 = able to fulfil all kitchen tasks independently

4. Domestic tasks (indoors)
Are you able to fulfil house-cleaning tasks, such as vacuum cleaning, dishwashing, doing the laundry, dusting, etcetera?
0 = not applicable
1 = unable to fulfil any domestic tasks indoors
2 = able to fulfil only a minimum of these tasks; mostly needing help of another person
3 = able to fulfil the vast majority of these tasks independently; sometimes needing help of another person
4 = able to fulfil all domestic tasks indoors independently

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

5. Domestic tasks (outdoors)
Are you able to do the shopping, managing the garden, cleaning the car, etcetera?
0 = not applicable
1 = unable to fulfil any domestic tasks outdoors
2 = able to fulfil only a minimum of these tasks; mostly needing help of another person
3 = able to fulfil the vast majority of these tasks independently; sometimes needing help of another person
4 = able to fulfil all domestic tasks outdoors independently

6. Leisure activities (indoors)
Are you able to read a newspaper/magazine or a book, use the telephone, fulfil a hobby (other than sporting)?
0 = not applicable
1 = unable to fulfil these activities
2 = able to fulfil only a minimum of these activities; mostly needing help of another person
3 = able to fulfil the vast majority of these activities independently; sometimes needing help of another person
4 = able to fulfil all these activities independently

7. Leisure activities (outdoors)
Are you able to go to a party, theatre, movies, concerts, museums, meetings, participate in sport?
0 = not applicable
1 = unable to fulfil these activities
2 = able to fulfil only a minimum of these activities; mostly needing help of another person
3 = able to fulfil the vast majority of these activities independently; sometimes needing help of another person
4 = able to fulfil all these activities independently

Regarding item 8: For example, if you don't have a driving license, you can consider this part of the question as 'being fulfilled', unless it is clear that driving would be absolutely impossible due to your illness.

8. Drive a car/ go by bus/ ride a bicycle
Are you able to drive a car, go on a bus/ subway, or ride a bicycle?
0 = not applicable
1 = unable to fulfil any of these tasks
2 = able to fulfil only one of these tasks (if needed with help of another person)
3 = able to fulfil two of these tasks (if needed with help of another person)
4 = able to fulfil all these tasks independently

9. Work/ study
Are you able to fulfil your prior (before becoming ill) job/ study?
0 = not applicable
1 = unable to fulfil prior job/ study
2 = able to fulfil (partly) adapted job/ study
3 = able to fulfil partly the prior job/ study
4 = able to fulfil completely prior job/ study

Case Number: ☐☐☐☐☐☐

Baseline
IPA/ Erasmus MC Pompe Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

Case Number: | | | | | | |

Baseline
IPA/ Erasmus MC Pompe Survey

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several hundred yards	☐ 1	☐ 2	☐ 3
i	Walking one hundred yards	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Case Number: ☐☐☐☐☐☐

Baseline
IPA/ Erasmus MC Pompe Survey

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

Case Number: ☐☐☐☐☐☐

Baseline
IPA/ Erasmus MC Pompe Survey

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

Case Number: ☐☐☐☐☐☐

Baseline
IPA/ Erasmus MC Pompe Survey

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Abbreviations

AFG	L' Association Francophone des Glycogénoses
AGSD	Association of Glycogen Storage Diseases
AMDA	Acid Maltase Deficiency Association
BPI	Brief Pain Inventory
CBS	Dutch Central Bureau of Statistics
CHO	Chinese Hamster Ovary
CI	Confidence Intervals
CNS	Central Nervous System
CRIM	Cross Reactive Immunogenic Material
EMA	European Drug Agency
ERT	Enzyme replacement therapy
FDA	USA Federal Drug Administration
FSS	Fatigue Severity Scale
FVC	Forced Vital Capacity
GAA	the gene coding for acid alpha-glucosidase
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratios
IPA	International Pompe Association
LVMI	left ventricular mass index
LSD	Lysosomal Storage Disorders
MCS	Mental Component Summary
MRC	Medical Research Council
NMD	neuromuscular disorders
NSAIDS	Non-steroidal anti-inflammatory drugs
PCS	Physical Component Summary
PIS	Pain Interferences Score
PSS	Pain Severity Score
QoL	Quality of life
RHS	Rotterdam Handicap Scale
SF-36	Medical Outcome Study 36-item Short Form Health Survey
SF36v2	Medical Outcome Study 36-item Short Form Health Survey version 2
VSN	Vereniging Spierziekten Nederland

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Benedikt Schoser

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Deniz Güngör, 2013

About the author

Deniz Güngör was born on January 8th, 1982 in Rotterdam, the Netherlands. She is the daughter of Seyit Ali and Sare Seher Güngör; and sister of Seyit Çağrı and Nazife Nergiz Güngör. After a happy childhood she attended the Caland Lyceum in Rotterdam and graduated in 2000. In the same year she started studying Medicine at the Erasmus University in Rotterdam and obtained her medical degree in February 2007. During her medical training she performed a research project on Vitamin D deficiency in infants in a rural hospital in Samarkand, Uzbekistan. Shortly after graduating, she started working as a resident at the department of Neurology of the Erasmus MC University Medical Center and Sint Franciscus Gasthuis in Rotterdam until the summer of 2008. That same summer she started working on her PhD thesis lying before you, again at the Erasmus MC University Medical Center. But this time at the Center for Lysosomal and Metabolic Disease as part of the team of Prof.dr. Ans van der Ploeg and Dr. Arnold Reuser. Meanwhile, due to her eagerness to learn, Deniz Güngör was admitted to the Master of Science programme in Clinical Epidemiology at the Institute for Health Sciences (NIHES) in Rotterdam and obtained her degree in 2011. Yet, throughout the years, her interest in the discipline of Neurology has always remained. Therefore, in July 2013, she began working as a Neurology resident again at the Erasmus MC University Medical Center, while finishing her PhD thesis. Fortunately, alongside her busy career over the past years, Deniz has always made time to attend parties, concerts and films festivals, take painting courses and even walk the Great Wall in China.

Nazife Nergiz Güngör
Rotterdam, September 2013

List of Publications

Güngör D, Bicer I, Rodrigues Pereira R, Rasulov A, Rachimov A, Mavlyanov S, Ponjee G, Brabin BJ. Prevalence of vitamin D deficiency among infants in Samarkand, Uzbekistan. *J Nutr Environ Med. 2008 Dec; 17(4): 223 – 231.*

Güngör D, De Vries J, Hop W, Van Doorn PA, Reuser A, Van der Ploeg A, Hagemans M. Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy. *Orphanet J Rare Dis 2011, 6:34.*

Güngör D, Reuser AJ.J. How to Describe the Clinical Spectrum in Pompe Disease? *Am J Med Genet A. 2013 Feb;161A(2):399-400.*

Rigter T, Weinreich SS, van El CG, de Vries JM, van Gelder CM, **Güngör D**, Reuser AJ, Hagemans ML, Cornel MC, van der Ploeg AT. Severely impaired health status at diagnosis of Pompe disease: a cross-sectional analysis to explore the potential utility of neonatal screening. *Mol Genet Metab. 2012 Nov;107(3):448-55.*

Güngör D, Kruijshaar ME, Plug I, D'Agostino Sr RB , Hagemans MLC, Reuser AJJ, van der Ploeg AT. Impact of enzyme replacement therapy on survival in adults with Pompe's disease: results from a prospective international observational study. *Orphanet J Rare Dis. 2013 Mar 27;8(1):49.*

Güngör D, de Vries JM, Brusse E , Kruijshaar ME, Hop WCJ, Murawska M, van den Berg LEM, Reuser AJJ, van Doorn PA, Hagemans MLC, Plug I, van der Ploeg AT. Enzyme replacement therapy and fatigue in adults with Pompe disease. *Mol Genet Metab. 2013 Jun;109(2):174-8.*

Güngör D, Schober AK, Kruijshaar ME, Plug I, Karabul N, Deschauer M, van Doorn PA, van der Ploeg AT, Schoser B, Hanisch F. Pain in adult patients with Pompe disease: a cross-sectional Survey *Mol Genet Metab. 2013 Aug;109(4):371-6.*

Güngör D, Kruijshaar ME, Plug I, Rizopoulos D, Kanters TA, Wens SCA, Reuser AJJ, van Doorn PA, van der Ploeg AT. Quality of life and participation in daily life activities of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up. *Submitted.*

Brands MM, **Güngör D**, Van der Hout JM, Karstens FP, Oussoren E, Plug I, Boelens JJ, Van Hasselt P, Hollak CE, Mulder MF, Rubio Gozalbo E, Smeitink JA, Smit GA, Wijburg FA, Meutgeert H, Van der Ploeg AT. Pain: a prevalent feature in patients with Mucopolysaccharidosis. Results of a cross-sectional national survey. *Submitted*.

PhD portfolio

Summary of PhD training		Year	Workload (ECTS)
Name PhD student:	D. Güngör		
Erasmus MC Department:	The Department of Pediatrics, Center for Lysosomal and Metabolic Diseases		
Research School:	NIHES: Erasmus University Rotterdam		
	MSc in Clinical Epidemiology: 2009 – 2011		
Advisor:	Prof.dr. A.T van der Ploeg		
Co-advisors:	Dr. M.E. Kruijshaar, Dr. A.J.J. Reuser		
General Academic Skills			
– Basiscursus regelgeving en management (BROK)		2010	0.9
– Biomedical English writing and communication		2010	3.0
Research skills			
– Biostatistics for Clinicians		2009	0.7
– Prognosis Research		2009	0.7
– Principles of Research in Medicine		2009	0.7
– Clinical Decision Analysis		2009	0.7
– Methods of Clinical Research		2009	0.7
– Clinical Trials		2009	0.7
– Pharmaco-epidemiology		2009	0.7
– Introduction to Decision-making in Medicine		2009	0.7
– Study Design		2010	4.3
– Classical Methods for Data Analysis		2009	5.7
– Clinical Epidemiology		2010	5.7
– Modern Statistical Methods		2009	4.3
– Methodologic Topics in Epidemiologic Research		2010	1.4
– Bayesian Statistics		2011	1.1
– Missing Values in Clinical Research		2011	0.7
– Courses for the Quantative Researcher		2009	1.4
– Repeated Measurements in Clinical Studies		2010	1.9
– Quality of Life Measurement		2011	0.9
– Topics in meta-analysis		2011	0.7
– Genome wide association analysis		2011	1.4
– Case Control studies		2011	0.7

– Introduction to global Public Health	2011	0.7
– Markers and Prognostic Research	2011	0.7
– English Language	2009	1.4
– A first glance at SPSS for Windows	2009	0.15
– Development Research Proposal (Master Clinical Epidemiology)	2011	2.5
– Research Period (Master Clinical Epidemiology)	2011	30.3
– Oral research presentation	2011	1.4

Presentations and (Inter)national conferences

– AGSD Conference, Leicester, UK (oral presentation)	2009	1.0
– 3d Symposium Steps Forward in Pompe disease, Münich, Germany (poster presentation)	2009	0.5
– 4th Symposium Steps Forward in Pompe Disease, London, UK (oral and poster presentation, both awarded)	2010	1.5
– 10th International Postgraduate course on Lysosomal Storage Diseases, Nierstein, Germany (oral presentation)	2011	1.0
– SSIEM 2011 Annual Symposium, Geneva, Switzerland (poster presentation)	2011	0.5
– AMDA Scientific conference, San Antonio, United States (oral presentation)	2011	1.0
– 16th symposium of the World Muscle Society, Almancil, Portugal (poster presentation)	2011	0.5
– 5th Symposium Steps Forward in Pompe Disease, Budapest, Hungary (oral and poster presentation)	2011	1.5
– 3rd International Conference on Lysosomal Storage disorders, Northern Cyprus (oral presentation)	2012	1.0
– 10th Pompe disease Expert day, Rotterdam, the Netherlands (oral presentation)	2012	1.0
– 12th International symposium on MPS and related diseases, Noordwijkerhout, the Netherlands (poster presentation)	2012	0.5
– 6th Symposium Steps Forward in Pompe Disease, Berlin, Germany (2x poster presentation)	2012	1.0
– SSIEM, 2012 Annual Symposium, Birmingham, UK (poster presentation)	2012	0.5

In depth courses

– Pompe disease expert day, Rotterdam	2008	0.5
– Nierstein postgraduate course on lysosomal and metabolic diseases	2010	1.9

Other

– Peer Review of articles for Scientific Journals	2012	0.5