Pompe disease in children and adults: natural course, disease severity and impact on daily life

Results from an international patient survey

Marloes Hagemans

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The studies described in this thesis were performed at Erasmus MC University Medical Center Rotterdam, the Netherlands and were financially supported by the Princess Beatrix Fund, the International Pompe Association and Genzyme Corp., Boston, MA. The printing of this thesis was sponsored by Genzyme Europe B.V. and the International Pompe Association.

ISBN: 90-9020644-2

Layout: Tom de Vries Lentsch
Cover photography: Peter Nicolai
Cover design: Lennart Nicolai, Tom de Vries Lentsch
Printed by: PrintPartners Ipskamp, Enschede

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De ziekte van Pompe bij kinderen en volwassenen: natuurlijk beloop, ernst van de ziekte en invloed op het dagelijks leven

Resultaten van een internationale patiëntensurvey

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr. S.W.J. Lamberts
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 21 juni 2006 om 9.45 uur

door

Maria Louise Catharina Hagemans
geboren te Terneuzen

Promotiecommissie

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Copromotoren:

Dr. A.T. van der Ploeg

Dr. A.J.J. Reuser

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Objectives and scope

Pompe disease is a lysosomal storage disorder caused by deficiency of the enzyme acid α-glucosidase and mainly characterized by progressive skeletal muscle weakness. Research on this so far untreatable disease has long been directed towards unraveling the pathophysiological mechanisms and the development of a causal treatment. At the advent of enzyme replacement therapy, the research described in this thesis was intended to include the patient's perspective in the assessment of the consequences of the disease. The aims were to map out the health status of patients with non-classic or late-onset Pompe disease, to provide more insight in the natural course and rate of progression on a group level, and to evaluate the use of specific self-report measurement scales. These studies form the basis for further follow-up of patients before and after the start of therapy, and are examples of a successful cooperation between patients, patient organizations and universities.

Chapter 1

Introduction

Pompe disease is a progressive metabolic disorder for which until recently no therapy was available. Since the promising results of the first enzyme replacement therapy trials, much progress has been made towards a registered treatment. In the meantime other treatment options such as gene therapy are being pursued as well. All these developments renewed the interest in and necessity of a comprehensive documentation of the disease severity and progression. The clinical and genetic heterogeneity of the non-classic or late-onset forms of Pompe disease have long been known, but data on the natural course are still scarce and depend on limited numbers of patients.

These considerations led us to set up a questionnaire survey among children and adults with Pompe disease, with the aim of gathering as much information as possible on current condition and medical history. A second objective of this survey was to test the value of specific measurement instruments for the assessment of (changes in) disease severity, viewed from the perspective of the patients. Before discussing the methods and results of the patient survey, in this introductory chapter some background information is given on the cause, clinical manifestations, diagnosis and treatment of Pompe disease and on the challenges in doing research on rare disorders.

1.1 CLINICAL ASPECTS OF POMPE DISEASE

Pathology

Pompe disease (OMIM #232300), also termed glycogen storage disease type II or acid maltase deficiency, is an inherited lysosomal storage disorder. The disease is characterized by a total or partial deficiency of the enzyme acid α-glucosidase. This enzyme is needed to break down glycogen that is stored within the lysosome, a cytoplasmic organelle involved in cellular recycling and tissue remodeling (figure 1).[1-3] Deficiency of acid α-glucosidase leads to accumulation of lysosomal glycogen in virtually all cells of the body, but the effects are most notable in muscle (figure 2).[4] The pathologic mechanisms by which glycogen accumulation eventually causes muscle malfunction are not fully understood. Muscle wasting in Pompe disease has been explained by increased tissue breakdown by autolytic enzymes released from ruptured lysosomes[5] and by a combination of disuse atrophy and muscle oxidative stress, reflected in the appearance of lipofuscin.[6,7] Furthermore, it is hypothesized that glycogen-filled lysosomes and clusters of non-contractile material disturb the myofibrillar morphology and the longitudinal transmission of force in the remaining muscle cells.[6,8,9]

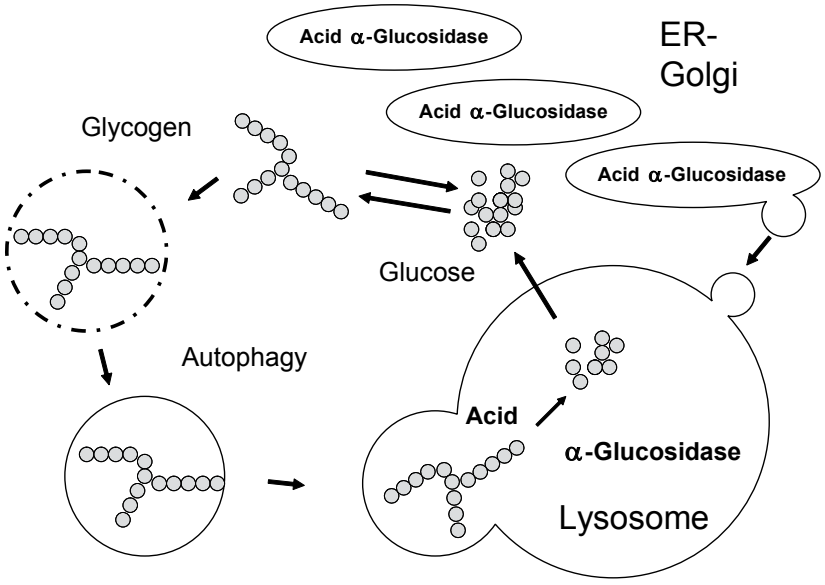

Figure 1 Degradation of glycogen in the lysosomes by acid α-glucosidase.
In the cytoplasm, glucose is converted to glycogen, a glucose polymer, as a way to store energy. When energy is needed, glycogen is again degraded to glucose. Some of the glycogen in the cytoplasm is captured in a membrane and transported to the lysosomes in a process called 'autophagy'. In the lysosomes this glycogen is degraded by the enzyme acid α-glucosidase. When α-glucosidase is deficient, lysosomal glycogen is not degraded and accumulates.

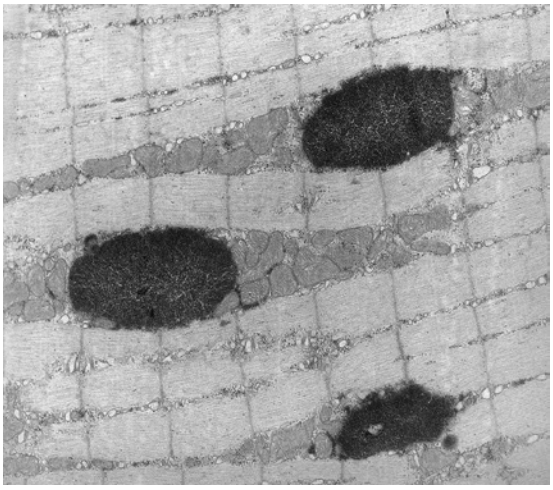

Figure 2 Lysosomal glycogen storage in Pompe disease.
This high magnification electron microscopy picture shows a piece of skeletal muscle from a mouse with Pompe disease. The three dark oval structures are lysosomes filled with glycogen. The smaller structures at the left and right of two of these lysosomes are mitochondria, cellular compartments where energy is generated. The lightly stained striated areas are unaffected.

Clinical features

The classic infantile form of Pompe disease presents shortly after birth, at a median age of 1.6 months.[10] Affected neonates have virtually no residual acid α-glucosidase activity and show generalized muscle weakness, hypotonia, a rapidly progressive cardiac hypertrophy, poor motor development and failure to thrive.[4,10-12] Their growth deviates from the normal curve, even despite naso-gastric tube feeding. Hepatomegaly and macroglossia are characteristically present. Important motor milestones like turning over, sitting and standing are not achieved. The median age of death is 6 to 8 months; patients rarely survive beyond the first year.[10] The first description of the infantile form of Pompe disease was made by the Dutch pathologist Dr. J.C. Pompe in 1932.[13]

Patients with non-classic or late-onset Pompe disease do have some residual acid α-glucosidase activity. In these patients the disease presents as a slowly progressive proximal myopathy without cardiac involvement, eventually leading to wheelchair dependency and use of respiratory support. The main cause of death is respiratory failure, sometimes associated with pulmonary infections.[4,14,15] The course of the disease is very heterogeneous: onset of symptoms may range from the first to the sixth decade. This has led to a further sub-typing, based on age at onset and rate of progression, in non-classic infantile, childhood, juvenile and adult forms.[4] However, this division is rather arbitrary, as there may be patients with an early onset of (mild) symptoms but a very slow disease progression and vice versa. In fact, Pompe disease comprises a continuous spectrum of phenotypes, with the generalized, rapidly progressive classic infantile form on one extreme, and adult patients presenting only with muscular symptoms on the other.[4,14,15] In this thesis all phenotypes with a slower progressive course, compared to the classic infantile form, are referred to with the terms non-classic or late-onset.

Genetic heterogeneity

The enzyme deficiency in Pompe disease is caused by pathogenic mutations in the acid α-glucosidase gene (GAA) located on the distal part of the long arm of chromosome 17 (region 17q25.2-q25.3).[16] The mode of inheritance is autosomal recessive. A patient has two pathogenic mutations in the acid α-glucosidase gene, one on each chromosome. These mutations are either similar (homozygous affected patient) or different (compound heterozygote). At present more than 200 different mutations in the acid α-glucosidase gene are known, including missense and splice-site mutations as well as insertions and deletions.[17] The most common mutation is c.-32-13T>G (IVS1-13T>G). This mutation was found in over two thirds of patients with late-onset disease. It leads to aberrantly spliced non-functional mRNA, but also to a small proportion of normal transcript that is responsible for the residual acid α-glucosidase activity in these patients.[18-20] Other frequently occurring mutations are the deletion of exon 18 and the delT525 mutation in

exon 2 among Caucasian patients,[19,21] Asp645Glu in Chinese patients,[22,23] and Arg854X among African and African American patients.[24]

Basically, the nature of the mutations in the acid α-glucosidase gene and the combination of mutant alleles determine the level of residual lysosomal acid α-glucosidase activity and primarily the clinical phenotype of Pompe disease.[15,25-28] A combination of two alleles with fully deleterious mutations leads to virtual absence of acid α-glucosidase activity and to the severe classic infantile phenotype. However, exceptional cases have been described such as a patient with two deleterious mutations and undetectable acid α-glucosidase activity in fibroblasts, who would have been classified as a classic infantile case of Pompe disease based on enzymatic and molecular findings but was already 6 years old at the time of description. It was concluded that secondary genetic or environmental factors must play a role in determining the disease phenotype when the residual acid α-glucosidase activity is extremely low.[29]

A severe mutation in one allele and a milder mutation such as c.-32-13T>G in the other result in a slower progressive non-classic or late-onset phenotype with residual activity up to 23% of average control activity.[15] In most cases patients with onset of symptoms in childhood or adolescence show a lower acid α-glucosidase activity compared to patients with onset of symptoms in adulthood, but the ranges overlap considerably (figure 3). Nevertheless, young children with a non-classic, but still relatively severe disease course are consistently described as having a very low residual activity.[30-34]

It should be noted that genotype and enzyme activity are not always predictive of the age at onset and the progression of the disease in patients with the non-classic or late-onset form of Pompe disease. For example, patients with the common c.-32-13T>G mutation, combined with a fully deleterious mutation on the other allele, all show significant residual enzyme activity and a protracted course of disease, but onset of symptoms varied from the first year of life to late adulthood.[35]

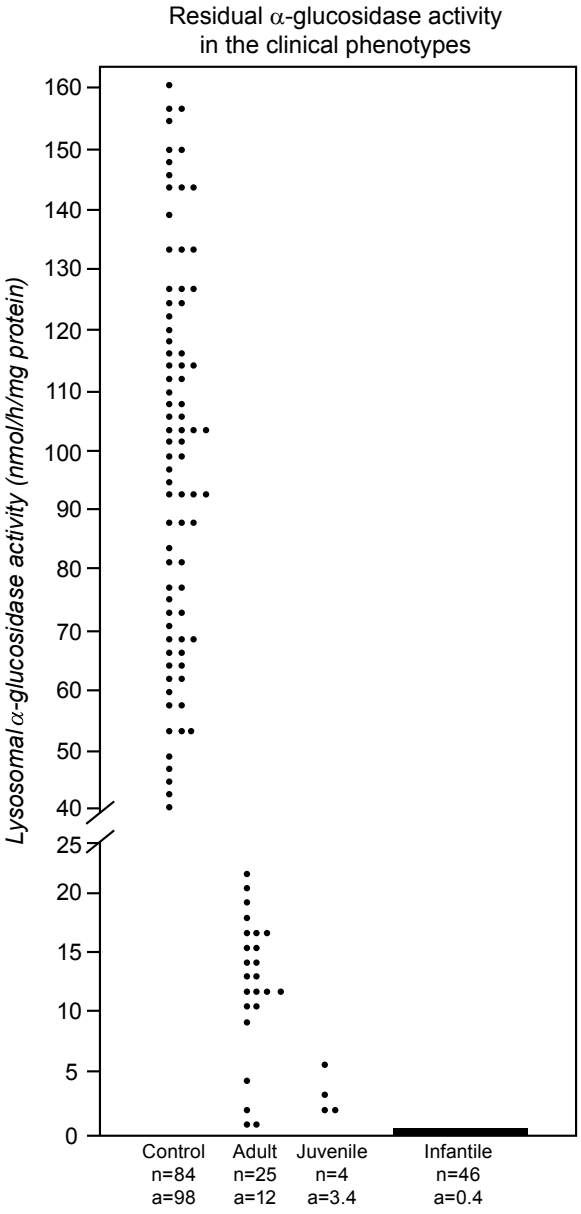

Figure 3 Correlation between clinical phenotype and residual α-glucosidase activity, measured in cultured fibroblasts with the artificial substrate 4-methylumbelliferyl-α-D-glucopyranoside. This figure was taken from Reuser et al., Muscle & Nerve 1995; Suppl 3: S61-S69, with kind permission of John Wiley & Sons, Inc.

Epidemiology

The estimated frequency of Pompe disease is 1 in 40,000 births. This figure is calculated from the carrier frequency that was observed in an unselected sample of newborns screened for the three most common mutations in the Netherlands.[36] These three mutations (IVS1-13T>G, 525delT and del exon 18) together accounted for 63% of the disease-related alleles in the Dutch patient population.[19] Another study determined the carrier status in randomly selected normal individuals from New York by testing for 7 mutations, representing 29% of GAA mutations. This led to the same expected frequency of 1 in 40,000 births.[37] The predicted frequency based on mutation screening was consistent with the birth prevalence of the combined infantile and adult phenotypes calculated from the number of enzymatic diagnoses over a period of 25 years (1:35,000).[38] In a study comparing the birth prevalence of all lysosomal storage diseases (LSDs) in the Netherlands, Pompe disease was the most frequent LSD with a birth prevalence of 2 per 100,000 and accounting for 17% of all enzymatic diagnoses.[39]

Diagnosis

The diagnosis of Pompe disease can be established by demonstrating deficiency of acid α-glucosidase activity or by mutation analysis of the acid α-glucosidase gene. Alpha-glucosidase activity can be determined in fibroblasts, muscle tissue or leukocytes, using the natural substrate glycogen or the artificial substrate 4-methylumbelliferyl-α-D-glucopyranoside (4-MU). The assay in leukocytes is error prone.[40-42] When artificial substrate is used, the presence of maltase-glucoamylase and more neutral maltase activities cause overlap of patient and normal ranges and may lead to false negative results.[43,44] When glycogen is used as substrate, the discrimination of patient and control ranges is far better, and full separation is obtained when acarbose is included in the assay to inhibit maltase-glucoamylase.[45] A complicating factor in this assay is the occurrence of the GAA2 allele coding for an isozyme of acid α-glucosidase with reduced affinity for glycogen.[46-48] GAA2/GAA2 homozygosity has a frequency of about 1 in 1000[46] and does not seem to lead to lysosomal glycogen storage.[46,47] Observations on individuals with the combination of GAA2 and a fully deleterious mutation in the other allele are not available.

The material of choice for diagnosis of Pompe disease is fibroblasts obtained from a skin biopsy and grown under standardized conditions. The assay in fibroblasts using the artificial substrate 4-MU is very sensitive, so that residual activity in the order of 2% can be measured accurately.[4,15] A muscle biopsy is also a good source of material for measuring the α-glucosidase activity, but the method is not very sensitive in that a residual activity of less than approximately 5% tends to disappear in the background. In addition, taking a muscle biopsy is invasive and has, in most cases, no additional value when the diagnosis of Pompe disease is already suspected.[49]

Prenatal diagnosis of classic infantile Pompe disease can be obtained by measuring the enzyme activity in chorionic villi or amniotic cells.[50-52] The method using chorionic villi is most sensitive, it can be performed in an early stage of pregnancy and the time between sampling and diagnosis is very short.[15,53] Maternal contamination can be a problem, but in practice the risk is low when samples are processed in experienced hands.[4,53] DNA analysis takes more time than the enzyme assay as the mutations in both parents must be identified before prenatal diagnosis is possible.[53] However, when the two mutated GAA alleles are known in the index patient and confirmed in both parents, DNA analysis is preferred. In situations where it is difficult to distinguish affected individuals from carriers, mutation analysis is necessary, for example when the affected fetus has residual acid α-glucosidase activity or when a low enzyme activity is found in one of the parents.

Also for heterozygote detection among siblings of patients and their spouses DNA analysis is indicated. Measurement of acid α-glucosidase activity is not recommended for carrier detection, because the activity range of carriers shows overlap with (late-onset) patient and control ranges.[4]

Recently, new methods for the detection of acid α-glucosidase deficiency in dried blood spots have been developed with the underlying idea of application in newborn screening programs. One of these methods uses immune-capturing of the enzyme with an antibody specific for acid α-glucosidase.[54] A second method calculates the ratio between the activity of neutral maltases and the combined activities of acid α-glucosidase and residual maltase-glucoamylase in the presence of maltose. Maltose is used as an inhibitor with a higher affinity to maltase-glucoamylase than to acid α-glucosidase.[55] Finally, Li et al.[56] describe a multiplex assay to simultaneously measure the enzymatic activities in five lysosomal storage disorders (Fabry, Gaucher, Krabbe, Niemann-Pick A/B and Pompe disease) using tandem-mass spectrometry. In this method, acarbose is used as an inhibitor to exclude the interfering maltase-glucoamylase activity.[56]

Treatment

Pompe disease has long been an untreatable disorder, for which only supportive care was available. Very recently recombinant human α-glucosidase as enzyme replacement therapy for Pompe disease has received marketing authorization, and it will soon become available beyond clinical trial settings. Furthermore, gene therapy for the disease is currently under study, but its development is still in a preclinical stage. Also dietary treatment for Pompe disease has been described in several reports; its effects are subject of discussion. A short overview on these treatment strategies is given below. In the past, bone marrow transplantation has also been tried, but no increase in acid α-glucosidase activity could be demonstrated in the muscles and fibroblasts of a treated patient.[57,58] In an animal experiment the transplant of histocompatible bone marrow cells was mimicked

by studying twin calves, of which one was homozygously affected while the other was not. Immune rejection was prevented by chimerism, but no reduction in glycogen concentration was measured in the muscles of the affected twin animals compared to affected single animals.[59]

Gene therapy

The rationale for gene therapy is to introduce the gene coding for the deficient enzyme into the somatic cells, thus creating a permanent enzyme source. To this end, the coding sequence for human acid α-glucosidase is inserted in a viral vector. For Pompe disease, gene therapy using adenoviral (Ad), adeno-associated (AAV) and hybrid Ad-AAV vectors has been investigated in rat, mice and quail.[60-68] Intravenous injection with adenoviral vectors resulted in high α-glucosidase activity in the liver of the treated animals, and high plasma levels of precursor enzyme secreted by the hepatocytes.[61,63-65] Thus, transduced hepatocytes can serve as depot of enzyme available to the heart and skeletal muscles.[63] Intramuscular injections with Ad and AAV vectors led to a sharp increase in acid α-glucosidase activity and correction of glycogen storage in the muscles, but only at the site of injection.[60,62,66,67] An intramuscular injection of a hybrid Ad-AAV vector in the gastrocnemius muscle of neonatal mice, however, did show therapeutic levels of acid α-glucosidase in the adjacent muscles and low levels of acid α-glucosidase activity in the heart.[68] The latest studies have used adeno-associated viruses with improved tissue-targeting features, aiming at expression of acid α-glucosidase in the liver and cross-correction of heart and muscle.[69,70] Taken together, the results of gene therapy tests in animal models are promising, but sustained expression of the gene, prevention of antibody formation against the viral vector and/or α-glucosidase, and safety of the vector are still important issues to be addressed.

Dietary treatment

Another approach in the treatment of Pompe disease is adherence to a high-protein diet or a diet supplemented with branched-chain amino acids. The rationale for this diet is that protein breakdown is increased in patients with Pompe disease.[5,71-73] It has been suggested that this is due to a disturbed carbohydrate metabolism causing the muscle to use protein as an alternative source of energy,[71] but a more likely explanation is increased tissue breakdown caused by severe derangement of the cellular architecture and release of proteolytic enzymes after rupture of swollen lysosomes.[5] A high-protein diet increases the pool of amino acids available for protein synthesis and thus counteracts the net muscle protein breakdown. Supplementing the normal diet with l-alanine would have a comparable effect, as l-alanine decreases the breakdown of branched-chain amino acids for the production of energy, thus helping to preserve muscle protein and muscle function.[32,74] However, the results of these dietary treatments in non-classic Pompe disease are inconclusive, with some studies reporting improvement in respiratory or skeletal muscle function,[5,71,75-80] while others do not.[72,81,82] In classic infantile Pompe disease dietary

therapy does not seem to be effective.[83,84] A review of the effects of dietary therapy in non-classic Pompe disease concluded that only 25% of the cases showed improvement in muscle or respiratory function after a high protein diet.[73] The studies on dietary therapy involved mostly case reports or a small number of patients. Larger, controlled trials are needed to fully evaluate its effects.

Enzyme replacement therapy

At present, the most promising therapeutic option is enzyme replacement therapy. The rationale for this therapy is to treat the disease by intravenous administration of the deficient enzyme. The earliest attempts used α-glucosidase purified from fungi[85,86] or human placenta.[87] Apart from purification problems, the role of cell surface receptors in the uptake of α-glucosidase was unknown at that time.[15] With that knowledge, the development of enzyme replacement therapy was later continued and the uptake of enzyme containing mannose-6-phosphate groups was studied in cultured fibroblasts, muscle cells, and animal experiments. These studies showed that the enzyme was taken up efficiently and that this uptake resulted in the degradation of lysosomal glycogen.[88-93]

After the characterization of the human α-glucosidase gene,[94] efforts were directed towards production of recombinant human acid α-glucosidase containing the mannose-6-phosphate recognition marker. Two systems were successfully developed: production of acid α-glucosidase in transgenic animals[95-97] and in Chinese hamster ovary cells (CHO-cells).[98,99] With both methods a precursor form of human acid α-glucosidase is obtained, that can be harvested from the medium (figure 4). The effects of enzyme replacement therapy were preclinically tested in animal models for Pompe disease. Significant uptake of the recombinant enzyme produced in transgenic mice and rabbits led to normalization of acid α-glucosidase activity and conversion of the 110 kDa precursor to the 76 kDa mature form in heart and muscle tissue of Pompe knock-out mice. Glycogen was degraded in cardiac, skeletal and smooth muscle, but the enzyme was not able to cross the blood-brain barrier.[96,97] Comparable results were obtained with the recombinant enzyme derived from CHO cells that was tested in acid α-glucosidase deficient quail.[100]

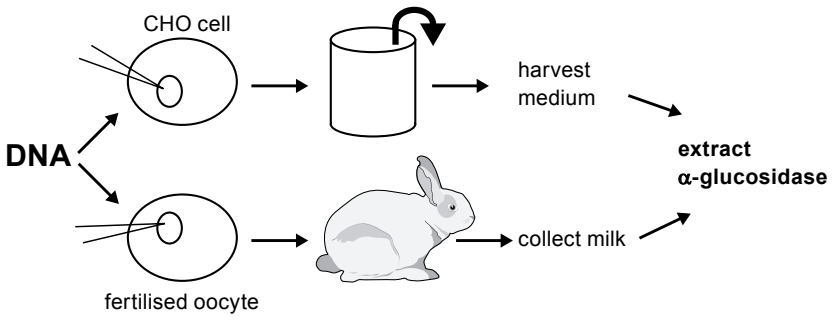

Figure 4
Production of acid α-glucosidase in Chinese hamster ovary (CHO) cells and in the milk of transgenic rabbits.

The clinical safety and efficacy of recombinant human α-glucosidase derived from the milk of transgenic rabbits has been described for six patients with classic infantile Pompe disease[101-105] and for two adolescents and one adult.[106] On a weekly dose of 40 mg/kg, all six patients with classic infantile Pompe disease survived well beyond 2 years of age, cardiac hypertrophy improved significantly, and they gained muscle strength and function. Alpha-glucosidase activity in muscle tissue reached normal limits for all but one patient.[101,102,104,105] Muscle morphology improved in some patients, but not in all, depending on the degree of muscle pathology at start of treatment.[103,104,107] Although significant effects of the treatment with recombinant human α-glucosidase were found, it should be realized that the therapeutic window in classic infantile patients is small and that patients may develop residual disease including contractures and respiratory insufficiency if the treatment is started too late in the disease process.[103]

The three patients with late-onset disease initially received a weekly dose of 10 mg/kg, which was soon increased to 20 mg/kg/wk. Muscle strength and function of the patient who was least affected at start of treatment improved dramatically to normal levels. In the two severely affected patients muscle strength and function improved slightly, but they remained wheelchair-bound. Their pulmonary function stabilized, but they could not be weaned from the ventilator. However, they reported less fatigue and increased quality of life.[106] From the results so far, it can be concluded that the condition of the patient at the start of treatment largely determines the final outcome and that treatment should be started before muscle damage has become irreversible.

The safety and efficacy of acid α-glucosidase derived from CHO-cells seems to be more or less comparable to that of enzyme produced in the milk of transgenic rabbits, but the literature is very scarce. The first published report on CHO-cell derived enzyme replacement therapy dates from 2001 and describes a trial in which three infants were treated initially with 5 mg/kg recombinant human α-glucosidase twice weekly.[108] The two patients who did not respond so well were switched to a higher dose of 10 mg/kg 2-5 times per week,[109] but this led to a transient nephrotic syndrome in one patient.[110] The primary endpoint was heart failure-free survival at one year of age, which was reached by all three infants. Trials continued with recombinant human acid α-glucosidase produced by genetically engineered CHO cells, and over 250 patients worldwide are currently receiving enzyme therapy as participants in a clinical trial or on a 'compassionate use' basis. The dose applied ranges from 20 mg/kg every two weeks to 40 mg/kg/week. Longer follow-up is required to evaluate the full effects and to develop the optimal dosing regimen.

In January 2006 the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMEA) has adopted a positive opinion on the marketing authorization application of Myozyme®, the name given to human recombinant acid α-glucosidase

derived from CHO-cells for enzyme replacement therapy in Pompe disease. Marketing authorization for Myozyme® in the European Union was received March 29, 2006.[111]

1.2 RESEARCH ON RARE DISORDERS

In Europe, a disease is called 'rare' if it affects no more than 5 in 10,000 inhabitants of the member states of the European Union.[112] In the United States this figure is 7 to 8 in 10,000.[113] Thus Pompe disease, with its estimated frequency of 1 in 40,000[36,37] is clearly a rare disorder. The low frequency of these disorders leads to difficulties in diagnosis, research, care and treatment. Physicians may not be familiar with a disease[114-116] and for some disorders accessible diagnostic tests are not yet available. Thus, the diagnosis can be considerably delayed. Once the correct diagnosis is made genetic counseling is often possible, but for many rare disorders treatment is not yet developed. Precise knowledge of the disease mechanism often is lacking and more research is needed to identify possible targets for treatment. Furthermore, the small numbers of patients, the often variable expression and sometimes incompletely known late effects make it difficult to obtain adequate evidence of the efficacy of a therapeutic intervention.[117,118] Relevant studies are only possible by cooperation between a large number of research centers from different countries. Simultaneously, because the market for drugs for rare disorders is limited, it would be very unattractive for pharmaceutical companies to invest in the development of new therapies for these indications.[119,120]

Legislation on orphan medicinal products

To overcome this situation, specific legislation in both the United States (Orphan Drug Act, 1984) and the European Union (EC Directive 141/2000) was made to stimulate the development of so-called 'orphan medicinal products' or 'orphan drugs'. Orphan drugs are defined as medicinal products that are developed for the diagnosis, prevention or treatment of life threatening or chronically debilitating rare disorders. Also products of which the marketing, without extra incentives, would not generate a sufficient return of investments can receive an orphan designation. There must be no other authorized satisfactory product for the condition in question, or if there is, the new product must be of significant benefit to the affected patients.[112,121]

The incentives for the development of orphan medicinal products in the European Union include 10-year market exclusivity, advice on the design of research protocols and requests for registration (protocol assistance), the possibility to use a centralized European Union procedure instead of filing for subsequent national marketing authorizations, and reduction of registration costs.[112] Furthermore, each member state in the European Union must

initiate national measures to focus attention on rare diseases and orphan drugs. In the Netherlands this included the establishment of the Dutch Steering Committee Orphan Drugs (Stuurgroep Weesgeneesmiddelen) by the Minister of Health, Welfare and Sport in 2001.[122] Under the Orphan Drug Act in the United States, companies can also get a tax reduction on costs for research and development. The period of market exclusivity for an orphan medicinal product in the United States is 7 years.[113,120,121]

Between April 2000 and April 2005, more than 260 products have received a designation as 'orphan medicinal product' in the European Union and 22 of those have received market approval. The orphan designations cover a wide range of rare diseases, the majority in the area of cancer (36%), immunology (11%) and metabolism (11%).[112] Recombinant human acid α-glucosidase as enzyme replacement therapy for Pompe disease is one of these recognized orphan products in both the United States and the European Union.[123,124]

The majority (65%) of the marketing authorizations for orphan products issued by the European Medicines Agency were given under 'exceptional circumstances', meaning that the company could not reasonably be expected to provide fully comprehensive evidence on the safety and efficacy of the orphan medicinal product. However, the preclinical and clinical research data showed sufficient potential benefits for patients. The authorization is therefore given under the condition that additional information will be submitted at a later date. This information may consist of additional preclinical or clinical studies or additional data gathered by post-marketing surveillance.[112]

Clinical databases for rare diseases

Clinical databases or disease registries are ongoing listings of observational data, collected on patients who meet specific criteria.[125] The power of such databases lies in the number of patients included and the more or less comprehensive coverage of the patient population.[126] For rare diseases, disease registries make it possible to collect information on a large number of patients from different geographic regions. This large-scale observational data collection is extremely important, because individual centers or physicians will only treat a few patients with a certain rare disorder. Collaboration is necessary to obtain a comprehensive overview of the natural history of a disease, to identify subsets of patients for research studies and clinical trials, to identify prognostic factors related to outcome, and to evaluate treatment possibilities.[125,126]

Examples of such large clinical databases are the registries for rare disorders that are sponsored by pharmaceutical companies as a means to gather information on the disease and, in a later phase, to collect the necessary surveillance data. 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[127-129], Fabry disease[130-132] and Mucopolysaccharidosis type I[133]. Also for Pompe disease a registry has started.[134]

The advantages of centralized data collection for rare disorders are obvious, although selection bias is a major concern.[125,135] The patient population entered into a registry may be biased towards the more severe end of the spectrum, particularly when the disease is difficult to diagnose and milder cases may escape recognition. Care should also be taken in the interpretation of data when the database has been put into use only recently and the number of patients still has to grow. Selection bias not only applies to the selection of patients included in the registry, but in a later phase also to the allocation of treatment. In contrast to a clinical trial, where patients are randomly assigned to a certain treatment group, the prognosis of the patient and the preference of the physician may play a role in when treatment is started and which treatment is given. Furthermore, in most cases there is no specific hypothesis before the data collection starts, which may lead to a lack of information on potentially confounding variables.[125] Finally, when data are collected in the routine care for patients, the type and timing of assessments may vary during follow-up of a patient and across the different centers contributing to the database.

1.3 AIMS AND OUTLINE OF THE THESIS

In 2002 the need to enhance the understanding of the variability, progression and natural history of Pompe disease, and in particular of the non-classic or late-onset form, was recognized by Erasmus MC and the International Pompe Association (IPA), a federation of patient groups worldwide.[136] It was realized that especially in rare disorders like Pompe disease data on the natural course are essential to evaluate any form of future treatment. This led to the development of the IPA/ Erasmus MC Pompe survey, an ongoing international study on the clinical condition of children and adults with Pompe disease in which information is collected by means of self-report questionnaires. Specific for this survey, compared to a registry as described above, is that patients (or their parents) submit their own data. This allows very detailed information, which is potentially more subjective than the data collected in a registry. Second, the same set of assessment tools was used across all countries and at a fixed time interval of 1 year between measurements, leading to a highly structured database. A third important difference is the participation of the patients through patient organizations instead of physicians.

In this thesis the results from the first three years of the IPA/ Erasmus MC Pompe

survey are presented. The aims are to map out the health status of patients with non-classic or late-onset Pompe disease, to provide more insight in the natural course and rate of progression on a group level, and to evaluate specific self-report measurement instruments for use among patients with Pompe disease.

An overview of the study design and assessment scales is given in **chapter 2**. Our findings with respect to the natural course of late-onset Pompe disease start with a review of published case reports in **chapter 3**, followed in **chapter 4** by a detailed description of the natural history and clinical condition of the Dutch participants in the survey. In **chapter 5**, the relation between disease severity and other patient characteristics in the international study population is described. **Chapter 6** provides prospective information on the progression of the disease by presenting the results of the first two years of follow-up. **Chapters 7-9** focus on the results of specific assessment scales: health-related quality of life, fatigue, and the impact of Pompe disease on the daily life of the patients. **Chapter 10** provides a general discussion of the findings described in this thesis, the pros and cons of our approach, and suggestions for future research.

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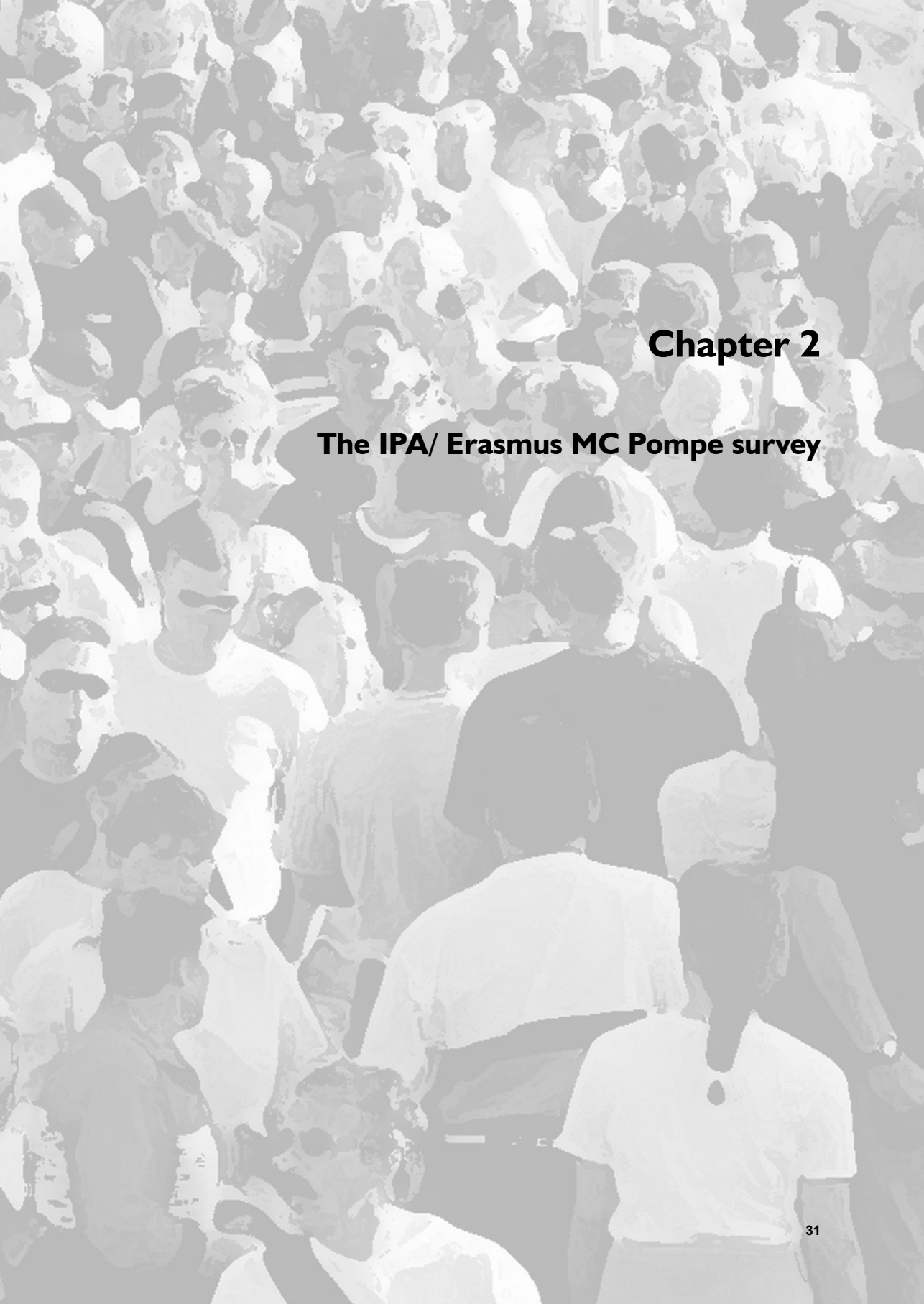

Chapter 2

The IPA/ Erasmus MC Pompe survey

2.1 STUDY DESIGN

The IPA/ Erasmus MC Pompe survey is an ongoing international study in which information is collected on disease history and current status of children and adults with Pompe disease by means of self-report questionnaires. The recruitment of patients, collection of informed consent forms, and the distribution and collection of the questionnaires takes place in close cooperation between Erasmus MC and the national patient organizations affiliated with the International Pompe Association (IPA). In a subgroup of patients longitudinal data were obtained in a yearly follow-up. Based on the results from this subgroup, we have expanded the longitudinal data collection to all participants, starting in the third year after the baseline survey was completed. This thesis describes the results of the baseline survey and the first two years of follow-up in the Dutch subgroup.

Participants

Patients were invited to participate through the IPA-affiliated patient organizations in each country. Inclusion criteria were a diagnosis of Pompe disease, an age above two years, and informed consent from the patient or the parents or guardian. An age above two years was chosen as a criterion because we specifically wanted to include patients with the non-classic or late-onset form of the disease. Classic infantile patients were not included, because (1) our main objective was to map out the heterogeneous non-classic or late-onset phenotypes and (2) in classic infantile patients the disease progresses so rapidly, that there would be no sense in recording the natural course by means of a retrospective questionnaire and a follow-up study with intervals of 1 year. Because we wanted to get an as complete as possible overview of the disease spectrum, we did not a priori make a further subdivision in childhood, juvenile and adult forms of the disease in the analyses of the survey data.

Although the current standard is to determine the level of residual acid α-glucosidase activity in cultured fibroblasts or to perform DNA analysis, diagnostic protocols for the confirmation of Pompe disease vary between countries and laboratories and in time. Therefore, no specific requirements were adopted for the way in which the patients in the IPA/ Erasmus MC Pompe survey were diagnosed. In the Netherlands the variation in diagnostic methods is limited, since there has always been a strong research interest in Pompe disease and exchange of information between diagnostic laboratories. Therefore, the Dutch subgroup in our survey was considered as a reference group in which the enzymatic or molecular diagnosis was verified and compared to the information provided by the patients. In the total, international group, all patients provided information on the year of diagnosis, the diagnostic tests or the tissue specimens used for testing, and the name and affiliation of the physician who made the diagnosis. Seven patients were

excluded from the analyses because they indicated that their diagnosis was not (yet) officially confirmed or because diagnostic information was lacking. In the coming years the project will be expanded so that eventually a complete linkage of mutational, enzymatic and clinical data of all survey participants is reached (see also chapter 10).

Table 1 presents a schematic overview of the number of patients included in the survey analyses described in this thesis (by June 2005; chapter 9). Because it is an ongoing study, new data were still being collected when the data from the first group of patients were already analyzed on a specific topic. This explains the different number of patients described in the different chapters. Figure 1 shows the inclusion in the 2-year follow-up study performed in the Dutch subgroup.

Table 1 Patients included in the IPA/ Erasmus MC Pompe survey analyses by June 2005.

Country/ patient organization	First questionnaires sent out in:	Number of patients by June 2005		
		<18	≥18	Total
The Netherlands[1]	May 2002	4	54	58
United Kingdom	October 2002	3	19	22
Australia[2]	November 2002	-	14	14
Germany[3]	November 2002	11	55	66
United States[4]	January 2003	6	84	90
Canada	March 2003	-	9	9
France[5]	April 2004	1	25	26
Other (via Erasmus MC)[6]	2002-2005	1	5	6
Total		**26**	**265**	**291**

[1]Including 2 patients from Belgium; [2]including 1 patient from New Zealand; [3]including 1 patient from Denmark, 2 patients from Switzerland and 3 from Austria; [4]including 1 patient from Taiwan; [5]patients recruited both via patient organization and Institut de Myologie (Paris); [6]2 patients from Greece, 1 from Luxembourg, 1 from Switzerland, 1 from Italy and 1 from Spain.

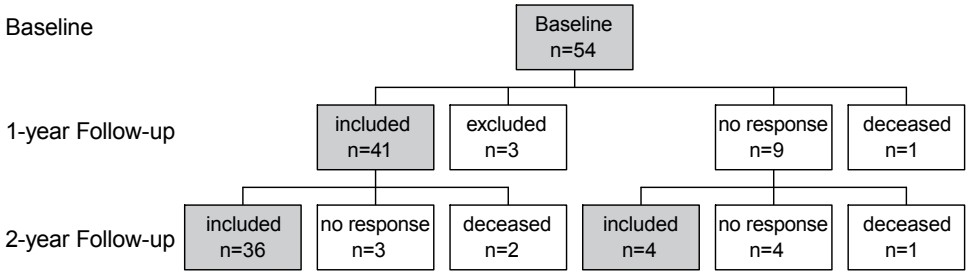

Figure 1 Follow-up of the Dutch patients in the IPA/ Erasmus MC Pompe survey.
One patient was excluded at the 1-year measurement because of start with experimental ERT. Two others were excluded from the follow-up analyses because the diagnostic information was not fully conclusive in retrospect.

Test-retest reliability was carried out at the one-year follow-up measurement; 38 patients participated. They repeated the different questionnaires approximately one month after the one-year measurement. This time frame was chosen because it was expected to be long enough to prevent the patients from remembering their first ratings and short enough to prevent changes in their clinical situation.

Questionnaires

The IPA/ Erasmus MC Pompe survey comprised a baseline questionnaire on medical history and current condition developed specifically for patients with Pompe disease. This 'Pompe Questionnaire' was completed for both children and adults and the results were used to study the natural course of the disease and the disease severity in the patient population. The issues addressed in the Pompe Questionnaire were identified by a literature study of more than 100 publications on patients who did not fulfill the criteria for classic infantile Pompe disease as described by Van den Hout et al.[1] Fourteen topics were covered: diagnosis, family history, childhood, mobility, specific movements, breathing, sleeping, eating, other complaints, daily activities, job or study, modifications to the home and use of care, and hospital stays and treatments. The follow-up questionnaire was a shorter version containing items on current mobility, ability to perform specific movements, breathing, sleeping, eating, and specific complaints. Additionally, a number of assessment scales were included: an adapted version of the Pediatric Evaluation of Disability Inventory, the Fatigue Severity Scale, the Rotterdam Handicap Scale and the Medical Outcomes Survey Short Form-36 health survey. The latter three were only completed by the patients of 18 years and older (table 2). These scales will be discussed in more detail in section 2.2.

The Pompe Questionnaire and the scales included in the IPA/ Erasmus MC Pompe survey were reviewed by a panel of 6 senior staff members from Erasmus MC from the departments of neurology, pediatric neurology, pediatrics, internal medicine and clinical

genetics. A second review was made by six medical specialists from other academic hospitals in the Netherlands (3 neurologists, 2 pediatricians, and 1 clinical geneticist) and by five patients with late-onset Pompe disease. The final Pompe Questionnaire was then translated into English, German and French by certified translators. For the assessment scales previously validated translations were used whenever possible, but French and German versions of the Fatigue Severity Scale and Rotterdam Handicap Scale were not yet available. These were therefore made by the same certified translators. The translations were reviewed and discussed with the researchers and the IPA patient representatives from the different countries and where necessary, unclear items were adapted. The development of the Pompe questionnaire is described in more detail in the 'Patients and methods' section of chapter 4. In the following section, the choice of assessment scales for the follow-up of patients with Pompe disease is discussed.

Table 2 Questionnaires included in the IPA/ Erasmus MC Pompe survey.

	Baseline		1- and 2-year follow-up		3-year follow-up	
	International study population		Dutch subgroup		International study population	
	<18 years	≥18 years	<18 years	≥18 years	<18 years	≥18 years
Pompe Questionnaire	x	x				
Follow-up Pompe Questionnaire			x	x	x	x
Adapted PEDI	x	x	x	x		
FSS		x		x		x
RHS		x		x		x
SF-36		x		x		x

PEDI=Pediatric Evaluation of Disability Inventory; FSS=Fatigue Severity Scale; RHS=Rotterdam Handicap Scale; SF-36=Medical Outcomes Survey Short Form-36 health survey.

2.2 CHOICE OF ASSESSMENT SCALES

Different levels of measurement

The consequences of disease can be measured on different levels. Until 2001, disease consequences were classified by the World Health Organization (WHO) according to the international classification of impairments, disabilities, and handicaps (ICIDH) defined in 1980.[2] Following this classification, the consequences of disease could be measured on the level of impairment, disability and handicap. In this model, impairment was defined as any loss or abnormality of psychological, physiological, or anatomical structure or function; a disturbance at the organ level. Disability was defined as a restriction in the ability to perform an activity in the manner considered normal for a human being; a disturbance at the person level, resulting from impairment. 'Handicap' represents the disadvantage for an individual, resulting from impairment or disability, which limits or prevents the fulfillment of a 'normal' social role.[2,3]

In 2001 a revision of the ICIDH framework resulted in the international classification of functioning, disability and health (ICF),[4] in which a person's functioning or disability is conceived as a dynamic interaction between health conditions and environmental and personal factors. These interactions are schematically depicted in figure 2. In this new framework, disability is the umbrella term for impairments of body structure or function, limitations in activities, or restrictions in participation. 'Activity' is the execution of a task or action by an individual and 'participation' is a person's involvement in life situations and indicates the social impact of a certain health condition.[4] These are thus the more positively termed equivalents of the 'disability' and 'handicap' concepts in the previous WHO framework.

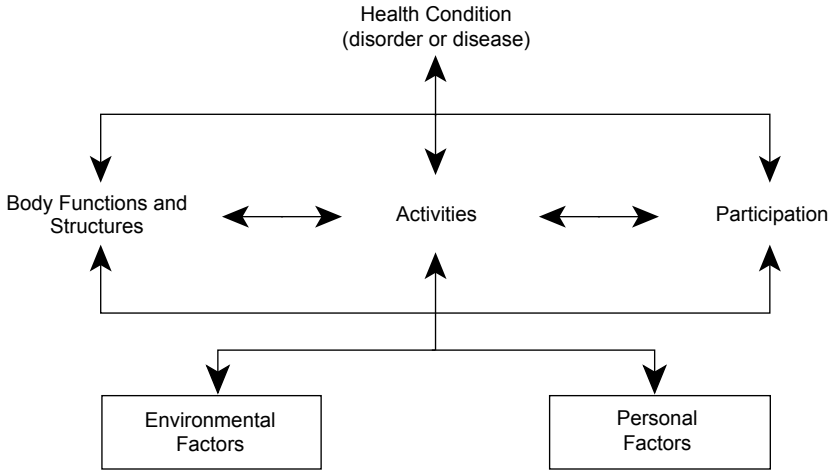

Figure 2 Interactions between the components of the international classification of functioning, disability and health (World Health Organization, 2001).[4]

In addition to the measurement of outcome on the separate levels described above, health-related quality of life scales include the patient's perspective in the evaluation of health status and changes in health.[5-7] Although there is no universal consensus on the definition of health-related quality of life, the concept is similar to the WHO definition of health as 'a state of complete physical, mental and social well being, and not merely the absence of disease or infirmity'.[5,8] In general, health-related quality of life encompasses three major dimensions: physical health, mental health and social health. Physical health includes signs and symptoms of disease, daily functioning, pain, and general health. Examples of mental health are emotional state, intellectual functioning, and perceived well being. Social health comprises the performance of social roles and the relationship with family and friends.[5-7]

Scale requirements

When choosing an outcome measure, the first question should be on which level one would like to evaluate. A second important consideration is the purpose of the measurement: distinction between patients, assessment of the prognosis, or the evaluation of treatment. In this respect it is important to realize that the validation of an outcome measure for one of these purposes does not mean that it is also the most appropriate for the other two.[9-11] Third, the application of the measure should be taken into account, for example whether one wants to follow an individual or a group.[12,13] Practicality of the scale is also important.[6] Ideally, questionnaires and scales used to measure outcome should be simple, brief, user friendly, require little or no special training, and provide results that are easy to interpret.[12,14,15]

Psychometric properties: validity, reliability and responsiveness

Irrespective of its purpose, any scale must be valid and reliable. A scale is called 'valid' when it measures what it is intended to measure. The validity of a scale is first assessed by the judgment of experts whether the scale looks reasonable (face validity) and whether all relevant aspects of the area under study are represented (content validity). Validity can be further assessed by comparing the scale with a 'gold standard', a widely accepted and commonly used measure (criterion-related validity). In most cases however, such a gold standard will not exist. The validity of the scale then needs to be assessed by a series of correlations with other measures that are assumed to be related in a certain way to the scale under evaluation, together called 'construct validity'. For example, a measure of muscle strength is expected to correlate positively with a measure that assesses mobility (convergent construct validity). Alternatively, muscle strength is expected to correlate better with a physical functioning scale than with a social functioning scale (discriminant construct validity).[10,14,16,17]

'Reliability' concerns the precision with which a scale measures a certain variable, i.e. it

should measure outcome in a way that is consistent, stable over time, and reproducible. When there is no change in the variable there should also be no change in its score on the measurement scale. Reliability can be subdivided into different types: internal consistency, test-retest reliability, inter-rater reliability, and parallel forms reliability. Internal consistency is the extent to which the items of a scale measure the same concept, also called homogeneity of the scale. Test-retest reliability refers to the agreement in score when the same person completes the same scale twice. Inter-rater reliability is the agreement in score when different investigators evaluate the same patient. Finally, parallel forms reliability is the extent of agreement between two versions of the same measure, for example two versions of a memory test to prevent a learning effect after completion of the first test.[12,14] For the scales used in the IPA/ Erasmus MC Pompe survey, the first two types of reliability are the most interesting, because it are self-report scales of which only one version exists.

Besides validity and reliability, responsiveness or 'sensitivity to change' is an important characteristic of a scale. A scale is called 'responsive' when it is able to detect clinically meaningful changes over time.[10,14,18,19] This is especially relevant when the purpose of the scale is to document the natural course of a disease or to evaluate the effect of treatment. Note that the responsiveness is likely to be low when the within-person variability in stable subjects is large (i.e. low test-retest reliability).[9,19,20]

Scales used in the IPA/ Erasmus MC Pompe survey

By nature of the study, all scales used in the IPA/ Erasmus MC Pompe survey are self-report questionnaires. The scales were chosen in such a way that the survey would include at least one scale that addresses activity limitations, one that addresses restrictions in participation and one assessing health-related quality of life. In the following paragraphs a short overview of these scales is given.

Adapted Pediatric Evaluation of Disability Inventory

In the baseline survey, an adapted version of the Pediatric Evaluation of Disability Inventory (PEDI) was included as a measure of disability or activity limitations. The original PEDI assesses functional ability of children on three scales: Self Care, Mobility and Social Function. It consists of 196 items that can be scored either 'not able to' or 'capable'. The scores of patients can be compared to age-matched controls up to 7.5 years of age (normative scores). According to the authors, the PEDI can also be used for children older than 7.5 years with severe limitations in their functional abilities. In these cases a 'scaled score' between 0 and 100 is calculated, based on a Rasch model of increasing item difficulty.[21] Table 3 shows some examples of PEDI topics, in which every next item represents a more difficult activity. Although its name suggests otherwise, the PEDI is in fact not purely a disability scale because it also includes items on the participation level, especially in its Social Function scale.

Table 3 Examples of items of the (original) Pediatric Evaluation of Disability Inventory.

Mobility domain	Unable	Capable
J. Outdoor locomotion: distance/ speed		
40. Moves 10-50 feet (1-5 car lengths)		
41. Moves 50-100 feet (5-10 car lengths)		
42. Moves 100-150 feet (35-50 yards)		
43. Moves 150 feet and longer, but with difficulty (stumbles; slow for age)		
44. Moves 150 feet and longer with no difficulty		
K. Outdoor locomotion: surfaces		
45. Level surfaces (smooth sidewalks, driveways)		
46. Slightly uneven surfaces (cracked pavements)		
47. Rough, uneven surfaces (lawns, gravel driveways)		
48. Up and down incline or ramps		
49. Up and down curbs		

Although the PEDI was originally developed for use in children, it also seemed useful for the measurement of slight changes in severely affected patients with late-onset Pompe disease, who received experimental enzyme replacement therapy in our hospital. This experience led us to develop a pilot version for use as a self-completion questionnaire in both children and adults. For this adapted version the Self Care and Mobility scales of the validated Dutch version[22,23] were taken as a starting point. The Self Care scale included items such as combing hair, washing oneself, and putting on clothes. The mobility scale included items such as moving inside the house, climbing stairs, and transfers from one place to another. All items were rephrased for an adolescent and adult patient population. All items were rewritten to make them suitable for self-completion, and some items were complemented with explanations from the manual. A few topics were left out because they were only appropriate for small children, leading to a final number of 55 items for the adapted Self Care and 60 for the adapted Mobility scale.

We were, however, not fully satisfied with its performance. It turned out to be too long and too difficult to complete in a standardized way for use as a self-report questionnaire. We therefore decided to discontinue the process of further improving and validating the adapted version, and it is currently not included in the international follow-up study. The already collected results were used to gain more knowledge on the level of disability across the patient population and to identify important limitations in movements and

activities that might be useful for follow-up of untreated patients or for the evaluation of the effect of treatment.

Fatigue Severity Scale
We specifically wanted to include a quantitative measure of fatigue in our survey, because it was a frequently reported symptom in patients visiting our center but had not received much attention in the literature. The survey was a good opportunity to study fatigue in more detail among patients with late-onset Pompe disease. Measurement of fatigue is difficult, because it may be a rather subjective experience with both physical and mental aspects. In their review on the assessment of fatigue, Dittner et al. define fatigue as extreme and persistent tiredness, weakness or exhaustion that can be mental, physical or both. They also acknowledge that 'different scales may be measuring fundamentally different aspects of the fatigue experience or even potentially different constructs'.[24]

For the IPA/ Erasmus MC Pompe survey the Fatigue Severity Scale (FSS) was used. This is a brief and simple self-report questionnaire with 9 statements on fatigue.[25] 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 FSS was chosen because it is short and easy to complete and has demonstrated good psychometric properties, including responsiveness to change, in different patient groups.[25-27] Its frequent use in various studies[24] facilitates comparison with other study populations.

Fatigue as measured by the Fatigue Severity Scale is difficult to classify according to the WHO framework. Fatigue itself would best be classified as an impairment in body function, but the items used in the FSS address in fact the impact of fatigue on daily functioning and social roles instead of the severity of fatigue-related symptoms.[28]

Rotterdam Handicap Scale
The Rotterdam Handicap Scale (RHS; also called Rotterdam 9-items scale) was included as a measurement instrument on the level of participation. Because it was developed when the first WHO classification[2] was still in use, it has 'handicap' instead of 'participation' in its name, but it measures the same concept. Measuring the impact of a disease on the level of participation provides insight into the burden of illness for the affected patients and gives an indication of what can be won when muscle damage is prevented or when further progression of the disease is stopped.

The Rotterdam Handicap Scale was developed and validated in a Dutch population of patients with immune-mediated polyneuropathies.[29] Items were recruited using the ICIDH taxonomy[2] as a foundation. The scale consists of 9 questions on the topics mobility indoors, mobility outdoors, kitchen tasks, domestic tasks indoors, domestic

tasks outdoors, leisure activities indoors, leisure activities outdoors, traveling and work or study. The scores per item range from 1 ('unable to fulfill the task or activity') to 4 ('complete fulfillment 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 items). The RHS score thus ranges from 9 ('unable to fulfill any task/ activity') to 36 ('able to fulfill all applicable tasks or activities'). The scale's validity, reliability and responsiveness were demonstrated among patients with immune-mediated polyneuropathies.[29]

The RHS was chosen for use in our survey because it was specifically designed to purely assess handicap or participation, without mixing with disability measures, and because it was well evaluated. Moreover, its items were deemed very relevant for late-onset Pompe disease. In the WHO framework, 'handicap' comprises six dimensions: physical independence, mobility, occupation, social integration, economic self-sufficiency, and orientation.[2,3] Because the RHS was developed for use in immune-mediated polyneuropathies, the WHO handicap dimension of 'orientation' was not included as this dimension is not affected in peripheral nervous system disorders.[29] As the ability to orient oneself in relation to the surroundings is not affected in late-onset Pompe disease either, this did not prevent use of the RHS in the IPA/ Erasmus MC Pompe survey.

SF-36 health survey

The 'Medical Outcomes Survey Short Form-36 health survey' (SF-36) is a generic health status questionnaire that attempts to measure all important aspects of health-related quality of life. It was developed for use in the Medical Outcomes Study (MOS), a large research project in which advancing the methods used for routine monitoring of patient outcomes was a major goal.[30] Included were those health domains that were most often measured in health surveys at that time, as well as additional concepts emerging from empirical studies.[31] The SF-36 consists of 36 items and comprises eight subscales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. Change in health is scored separately. The number of items per domain varies from 2 (social functioning and bodily pain) to 10 (physical functioning) and the number of response choices per item from 2 to 6. The items are summed per subscale and transformed into scores between 0 and 100. A higher score represents better function or less pain.[31,32]

The SF-36 was designed for use in a wide range of populations, irrespective of the underlying condition. This makes comparison across different health conditions possible. Furthermore, it has been translated and cross-culturally validated for use in more than 40 languages.[33-35] This was one of the reasons why the SF-36 was chosen as a measure of health-related quality of life in our international patient survey. Other reasons were its

brevity, for example compared to the Sickness Impact Profile,[36] the availability of different norm groups and its extensively evaluated psychometric properties.[31,32,37-39]

In the following chapters the results from the literature review, the Pompe Questionnaire and the follow-up study are presented first (**chapter 3-6**). The results from the selected assessment scales are presented in **chapter 7-9** in the order in which the data were analyzed. The English versions of the Pompe Questionnaire, the SF-36 health survey, the Fatigue Severity Scale and the Rotterdam Handicap Scale are included in **appendix A-D**.

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Chapter 3

The natural course of non-classic Pompe disease; a review of 225 published cases

L.P.F. Winkel[1,4], M.L.C. Hagemans[1], P.A. van Doorn[2], M.C.B. Loonen[2], W.J.C. Hop[3], A.J.J. Reuser[4], A.T. van der Ploeg[1]

[1]Department of Pediatrics, Division of Metabolic Diseases and Genetics, [2]Department of (Pediatric) Neurology, [3]Department of Epidemiology and Biostatistics, [4]Department of Clinical Genetics, Erasmus MC Rotterdam, the Netherlands

J Neurol 2005;252(8):875-884

Abstract

Pompe disease is a neuromuscular disorder caused by deficiency of lysosomal acid α-glucosidase. Recombinant human α-glucosidase is under evaluation as therapeutic drug. In light of this development we studied the natural course of cases not fitting the definition of classic infantile Pompe disease. Our review of 109 reports including 225 cases shows a continuous spectrum of phenotypes. The onset of symptoms ranged from 0 to 71 years. Based on the available literature, no criteria to delineate clinical subtypes could be established.

A common denominator of these cases is that first symptoms were related to or caused by muscle weakness. In general, patients with a later onset of symptoms seemed to have a better prognosis. Respiratory failure was the most frequent cause of death. CK, LDH, ASAT, ALAT and muscle glycogen levels were frequently but not always elevated. In most cases a muscle biopsy revealed lysosomal pathology, but normal muscle morphology does not exclude Pompe disease. In 10% of the cases in which the enzyme assay on leukocytes was used, a normal α-glucosidase activity was reported.

Data on skeletal muscle strength and function, pulmonary function, disability, handicap and quality of life were insufficiently reported in the literature. Studies of non-classic Pompe disease should focus on these aspects, before enzyme replacement therapy becomes generally available.

Keywords

α-glucosidase, glycogenosis, lysosomal storage disorder, muscular dystrophy

Introduction

Pompe disease is a metabolic myopathy caused by the deficiency of acid α-glucosidase needed for the degradation of lysosomal glycogen.[1-3] With studies on enzyme therapy well underway it becomes increasingly important to recognize signs and symptoms of the disease properly and to establish the diagnosis without delay.[4-6] Accurate knowledge on the natural course of the disease is further required to set endpoints for pivotal clinical trials and to decide in each individual case at what moment enzyme therapy should be started once it is generally available.

In 1932 J.C. Pompe presented the first case report. It concerned a patient with a hypertrophic cardiomyopathy and progressive generalized muscle weakness.[7] The child died at eight months of age. This severe form of the disease is quite well delineated.[8-11] Symptoms start at a median age of 1.6 months, patients die at a median age of 6 to 8 months, a hypertrophic cardiomyopathy is characteristically present, and developmental milestones like rolling over, sitting and standing are not achieved. This is the classic infantile form of Pompe disease.

Milder forms were described later. These were called muscular variant, nontypical infantile, childhood, juvenile, adolescent, adult and late-onset forms of Pompe disease. Guidelines for sub-classification are not clearly set.[1,12-22] This review depicts the features of 225 cases of Pompe disease that do not fit the description and course of the classic infantile form, as extracted from 109 publications.

Methods

We included all case reports identified via Pubmed by a search for 'late(-)onset Pompe disease', 'acid maltase deficiency', 'glycogenosis type II', 'glycogenosis type 2' and 'childhood-', 'juvenile-', 'adult-' and 'non(-)typical infantile Pompe disease'. Case reports cited in the collected articles and case reports not identified via Pubmed were added to the list. Articles written in English, French, German or Dutch were included. Excluded were publications lacking clinical information, cases with normal acid α-glucosidase activity in muscle tissue or fibroblasts and cases described as Danon's disease.[23-29] We further excluded all cases that fulfilled the criteria of classic infantile Pompe disease, which were earlier included in a review on the natural course of infantile Pompe disease.[10] This led to a collection of 225 cases in 109 articles.[12-22,30-127]

In order to identify subtypes of Pompe disease we grouped the patients by age at onset of symptoms, more or less following the terminology 'nontypical infantile', 'childhood', 'juvenile' and 'adult'. This led to a division in four groups: <1 year, 1 to 6 years, 6 to 18 years, and ≥18 years. We then compared the patients in these four groups with regard

to general characteristics, clinical manifestations and course of disease, enzymatic, histological and other laboratory findings. If particular symptoms or signs were not reported, they were scored as negative. Laboratory findings were scored as abnormal or normal, and by exact value when reported by the authors.

The data were analyzed using SPSS version 10.1. We used descriptive statistics and frequencies for all calculations in this report. Data are presented as medians, unless otherwise indicated.

Results

General overview of the study population

We collected 225 case reports of patients with Pompe disease who did not have the classic infantile phenotype. The case reports originated from 19 countries, mostly from the United States (30%), France (16%) and the Netherlands (15%), but also for example from Japan (6%) and South Africa (2%). The distribution of age at time of description is presented in figure 1. Forty-three percent of the patients were female. Remarkably, when the patients were subdivided into groups based on age at onset, there was a predominance of affected males in the younger age groups. Although the medians for doctor's delay, age at description, age at start of ventilation and age at death differed between the four groups, the ranges overlapped considerably (table 1). For example, one patient with symptoms in the first year of life was diagnosed at the age of 17 and was still alive at the age of 28. Another patient who experienced first symptoms between 6 and 18 survived beyond 61 years. The oldest patient (71 years) presented with symptoms at the age of 68.

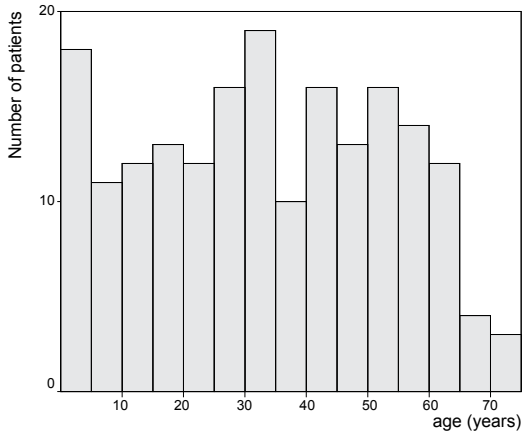

Figure 1 Age distribution at time of description of 189 patients with non-classic Pompe disease. The deceased patients are excluded.

First symptoms were described for 207 of the 225 cases (figure 2). Most often mentioned were symptoms and signs related to muscle weakness (80%). These comprised abnormal walking, difficulty with climbing stairs, delayed motor development and hypotonia. Second most frequent were respiratory problems; these were described in 11% of the cases. Respiratory failure was the presenting symptom in 2% of the cases.

Patients deceased at time of description

The distribution of age at death is presented in figure 3. Thirty-six patients had died at a median age of 24.5 years (range 0.9 to 66 years). The most frequent cause of death was respiratory failure (72%, age 0.9 to 66 years). Nine patients died despite the initiation of artificial ventilation. Pneumonia as cause of respiratory failure was reported six times. Other causes of death were rupture of a cerebral aneurysm (n=4, age 16 to 41 years); cardiac failure (n=1, age 35 years) and intractable fever (n=2, age 4.5 and 5 years).

The deceased patients had experienced their first symptoms significantly earlier (at the age of 7, range 0 to 60 years vs. 24 years, p=0.018, Mann-Whitney test) and were significantly younger at the time of diagnosis (24 years, range 0.7 to 65 years vs. 33 years, p=0.037, Mann-Whitney test) than the patients who were still alive at time of description. The doctor's delay, the percentage of patients using artificial ventilation and the age at start of artificial ventilation did not differ.

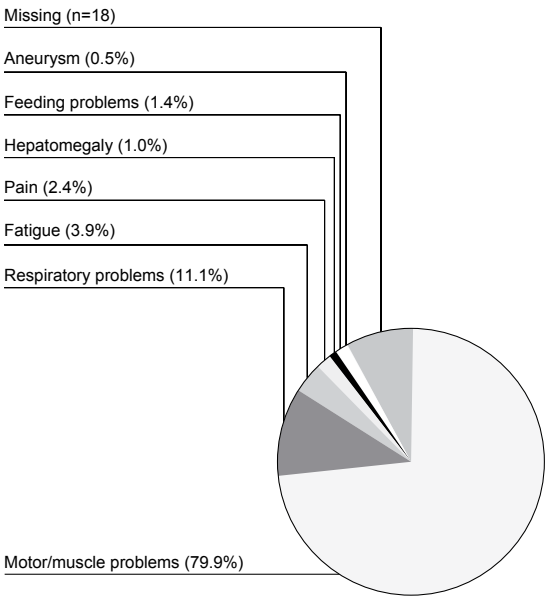

Figure 2 Distribution of first symptoms of 225 patients with non-classic Pompe disease as described in the literature.

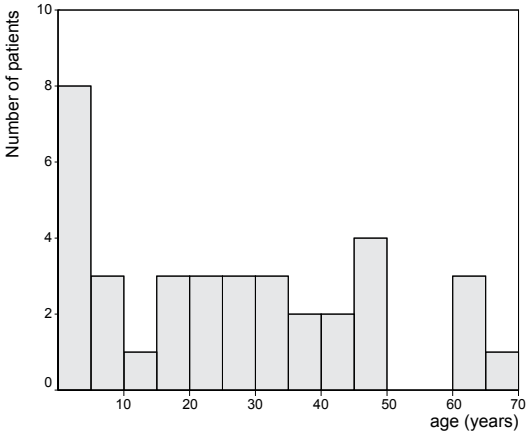

Figure 3 Age distribution at time of death of 36 patients with non-classic Pompe disease described in the literature.

Comparison of symptoms and signs between subgroups

The frequency of symptoms and signs reported for the 225 patients over the disease period described are listed in table 2. Virtually all patients experienced symptoms related to loss of muscle function (95%). Forty-four percent of the patients were reported to have respiratory difficulties. Initiation of artificial ventilation was documented for 28% of all cases. Cerebral aneurysms were found in six cases (3%).

We further investigated whether the age of onset was related to a particular subset of symptoms and to the rate of disease progression. Symptoms related to muscle and respiratory function were reported frequently in all groups. An enlarged tongue, hypotonia, and also scoliosis, were mostly reported for patients with onset of symptoms before the age of 1. However, they were also documented for patients who presented later. Delayed motor milestones, feeding problems and hepatomegaly were only reported for patients with first symptoms under 6 years of age. Cardiac hypertrophy was only found in a subset of patients presenting before the age of 1 year, but echocardiography data were rarely available for the older patients.

Table 1 General characteristics of 225 patients with non-classic Pompe disease reported in the literature. Figures are presented as median (range) unless otherwise indicated.

		Age at onset	
	Whole Group (n=225)	0-1 years (n=32)	1-6 years (n=24)
Sex (% male)	57%	63%	79%
Age at onset, y	24 (0-68) n=172	0.25 (0-1) n=31	2.0 (1.1-4.5) n=19
Age at diagnosis, y	33 (0.1-71) n=206	3.8 (0.1-17) n=20	7 (1.6-32) n=32
Doctors' delay, y	7 (0-47) n=157	3.7 (0.9-17) n=19	6 (0-28) n=19
Age at description, y	33 (0.8-71) n=189	4.1 (0.8-28) n=20	7 (2.5-32) n=20
Age at start of ventilation, y	34 (3-59) n=49	7.5 (3-18) n=6	7 (7-24) n=3
Age at start of wheelchair use, y	16 (3-49) n=6	3.5 (3-4) n=2	7 n=1
Age at death, y	24.5 (0.9-66) n=36	6.1 (0.9-24) n=12	22.6 (6.5-28) n=4

Enzymatic, histological and other laboratory findings
Table 3 shows the diagnostic tools as described for the 225 cases. CK was elevated in 91%, LDH in 96%, ALAT in 94% and ASAT in 95% of the described cases. All patients with normal CK levels (n=12) presented with symptoms after 18 years of age. In four cases with normal CK levels, ALAT and ASAT were also measured and were elevated in two cases.

In 208 of the 225 cases the diagnosis Pompe disease was confirmed by measurement of α-glucosidase deficiency in leukocytes, fibroblasts and/or in muscle tissue. Various substrates were used (i.e. the artificial substrate 4-methylumbelliferyl α-D-glucopyranoside or the natural substrates glycogen and maltose). Measurement in fibroblasts or muscle biopsy specimens always showed deficiency of α-glucosidase. Nine out of 89 patients (10%) had deficient α-glucosidase activity in muscle or fibroblasts (n=8) or increased muscle glycogen content (n=1), but a normal α-glucosidase activity in leukocytes.

In 17 cases the diagnosis was not based on the measurement of α-glucosidase activity, but on the finding of an increased glycogen content or abnormal muscle morphology. Fifteen out of 74 patients had normal muscle glycogen content (20%). Thirteen of them presented with symptoms after the age of 18.

	6-18 years (n=30)	18 years and older (n=139)
	63%	51%
	12 (6-17) n=20	35 (18-68) n=102
	17 (6-61) n=32	43 (18-71) n=134
	11 (0-47) n=20	7 (9-34) n=99
	17 (6-61) n=25	44 (19-71) n=124
	18.5 (15-31) n=6	38 (21-59) n=34
	32 (25-39) n=2	49 n=1
	25.1 (15-40.5) n=5	44.9 (25-66) n=15

Table 2 Described symptoms in 225 patients with non-classic Pompe disease related to age at onset. Figures are presented as number (%). Not reported symptoms were scored as not present.

		Age at onset			
	Whole Group n=225	0-1 years n=32	1-6 years n=24	6-18 years n=30	18 years and older n=139
Muscular symptoms					
Muscle weakness	213 (95)	31 (97)	23 (96)	26 (87)	133 (96)
Walking problems	106 (47)	23 (72)	20 (83)	10 (33)	53 (38)
Problems rising	59 (26)	20 (63)	8 (33)	5 (17)	26 (19)
Problems climbing stairs	58 (26)	18 (56)	9 (38)	5 (17)	26 (19)
Problems sporting/running	40 (18)	7 (22)	9 (38)	5 (17)	19 (14)
Delayed motor milestones	31 (14)	26 (81)	5 (21)	0	0
Use of wheelchair	18 (8)	4 (1)	2 (8)	3 (10)	9 (6)
Difficulty lifting objects	5 (2)	0	0	0	5 (4)
Difficulty combing hair	3 (1)	0	0	0	3 (2)
Respiratory symptoms					
Respiratory symptoms	99 (44)	17 (53)	6 (25)	12 (40)	64 (46)
Artificial ventilation	62 (28)	13 (41)	3 (13)	5 (17)	41 (30)
Skeletal symptoms/ deformities					
Lordosis/kyphosis/scoliosis	45 (20)	3 (9)	6 (25)	7 (23)	29 (21)
Scapula alata	5 (2)	1 (3)	3 (13)	1 (3)	0
Foot abnormalities	5 (2)	1 (3)	1 (4)	2 (7)	1 (1)
Cardiac symptoms					
Hypertrophic cardiomyopathy	12 (5)	12 (38)	0	0	0
Cor pulmonale	4 (2)	0	0	1 (3)	3 (2)
Other heart abnormalities	9 (4)	4 (1)	2 (8)	0	3 (2)
Neurological symptoms					
Low/ absent reflexes	37 (16)	6 (19)	5 (21)	3 (10)	23 (17)
Hypotonia	25 (11)	17 (53)	2 (8)	2 (7)	4 (3)
Pain	13 (6)	0	1 (4)	1 (3)	11 (8)
Aneurysmata	6 (3)	1 (3)	1 (4)	2 (7)	2 (1)
Epilepsy	2 (1)	0	0	0	2 (1)
Other symptoms					
Fatigue	23 (10)	2 (6)	2 (8)	3 (10)	16 (12)
Large tongue	20 (9)	13 (41)	1 (4)	1 (3)	5 (4)
Feeding problems	14 (6)	12 (38)	1 (4)	0	1 (1)
Underweight	9 (4)	1 (3)	3 (13)	1 (3)	4 (3)
Abnormal speech	9 (4)	2 (6)	1 (4)	0	6 (4)
Hepato(spleno)megaly	8 (4)	5 (16)	3 (13)	0	0
Abnormal mental development	3 (1)	1 (3)	1 (4)	0	1 (1)
Hyperparathyreoidism	1 (0.5)	0	0	1 (3)	0

Muscle tissue specimens were mostly heterogeneously affected. PAS positive (diastase sensitive) vacuoles were observed on light microscopy, and membrane bound glycogen on electron microscopy. Some case reports mentioned that type I fibers were more affected than type II. In 97% of 74 cases the muscle biopsy revealed lysosomal pathology. Glycogen accumulation was additionally reported in eccrine glands, pericytes, endothelial cells, fibroblasts, smooth muscle cells, and Schwann cells of small nerve fibers of skin and muscle.[87] Notably, glycogen was found in smooth muscle of the basilar artery in a patient who had died of a ruptured cerebral aneurysm.[82]

Electromyography showed profuse myotonic discharges, sometimes combined with fibrillations. Measurement of pulmonary function was only reported in 94 out of 225 cases.

In 40 patients one or both mutant alleles were identified. The most common mutation found in the α-glucosidase gene was the IVS1-13T→G (c.-32-13T>G, n=32). The age range of patients having this mutation was 2 to 53 years; median age 35 years. One patient was found to be homozygous for the IVS1-13T→G mutation.

Table 3 Diagnostic tools and biochemical markers in 225 patients with non-classic Pompe disease reported in the literature.

Diagnostic tools	n	% false negative
AGLU in fibroblasts	24	0
AGLU in muscle	153	0
AGLU in leukocytes	89	10
Muscle glycogen	74	20
Muscle morphology	74	3
CK	138	9
LDH	46	4
ALAT	34	6
ASAT	55	5

AGLU=α-glucosidase activity; ASAT=aspartate aminotransferase; ALAT=alanine aminotransferase; CK=creatine kinase; LDH=lactate dehydrogenase. A normal α-glucosidase activity in fibroblasts or muscle was used as exclusion criterion for this study.

Discussion

Our study shows that Pompe disease presents as a spectrum of disease phenotypes. The disease occurs worldwide and may present at any age from infancy to late adulthood. Subdivision of the patients by age of onset did not identify specific subsets of symptoms or different rates of disease progression that could serve as criteria for subtyping. Symptoms that are also found in classic Pompe disease, such as a hypertrophic cardiomyopathy, hepatomegaly and developmental delays, occurred more often in the groups with an early onset of symptoms. In all age groups there were patients with a more rapid and patients with a slower course of disease, but in general patients with a later onset of symptoms seemed to have a better prognosis.

We found an almost equal male-female distribution for the patients with onset of symptoms above the age of 18 years, but below the age of 18 there were slightly more affected males than females. This was also found in the group of patients with classic Pompe disease,[10] but we do not have an explanation for this given the autosomal recessive inheritance pattern.

Symptoms and signs of non-classic Pompe disease as described in the literature were mostly related to muscle weakness. Forty percent developed respiratory problems related to respiratory muscle weakness, and one-third finally required artificial ventilation. Respiratory failure was rarely the first presentation, but it was the most frequently reported cause of death. Less than 40% of the deceased patients were mentioned as having used artificial ventilation. Although the older literature in particular will not reflect the current situation, it points to the fact that follow-up and support of the respiratory function in patients with non-classic Pompe disease certainly deserves attention.[128] The second most common cause of death was rupture of a cerebral aneurysm (4 out of 36). The reported prevalence of a cerebral aneurysm among the described patients with non-classic Pompe disease was 2.7% (6 out of 225), which seems slightly higher than the prevalence of 1.9% (range 1.5 to 2.4%) found in the general population.[129] It should be noted that the Pompe patients in this review were not systematically screened for the presence of a cerebral aneurysm. A higher frequency of (cerebral) aneurysms could be explained by the glycogen accumulation that has been demonstrated in smooth muscle cells of both humans and mice with Pompe disease.[82,87,130,131] Such pathology deserves special attention, since prolonged intravenous administration of recombinant human α-glucosidase to both humans and mice resulted in clearance of glycogen from smooth muscle cells.[6,131,132]

Biological indicators of non-classic Pompe disease are increased CK, LDH, ASAT and/ or ALAT levels in blood, but normal levels do not exclude the disease. For CK this confirms the findings of Ausems et al. who reported earlier that measurement of CK is a sensitive marker for Pompe disease. In that study CK levels were increased in all patients, including

five patients who were still asymptomatic.[133] Two cases in our literature review had a normal CK value, but increased ALAT and ASAT levels. We found earlier in patients with classic infantile Pompe disease that serum ALAT, ASAT and LDH levels increased with disease progression and were more sensitive follow-up parameters than CK.[10] These findings indicate that CK, ALAT, ASAT and LDH, when used in combination, can be useful markers to include Pompe disease in the differential diagnosis. Membrane bound glycogen observed by electron microscopy, or PAS positive vacuoles visualized by light microscopy may further direct to the diagnosis, and are better diagnostic markers than increased glycogen levels in muscle tissue sections. Importantly, 20% of patients with non-classic Pompe disease had a normal muscle glycogen content. Likewise, not all muscle biopsies disclosed morphologic abnormalities. In the literature this was most often reported in patients presenting with symptoms after the age of 18 years. We conclude that the diagnosis Pompe disease can not be established or excluded on basis of clinical testing or biological markers alone, and should always be confirmed by demonstrating α-glucosidase deficiency or deleterious mutations in both α-glucosidase alleles. The enzymatic assay is most sensitive on fibroblasts, but can also be done on a muscle biopsy specimen.[134] From this literature review it becomes clear, that measurement of α-glucosidase activity in leukocytes may give false negative results. This may be due to the presence of neutral maltases.[134,135]

Not all information appeared well documented in the literature. The time frame in which the disease progresses from first symptoms to various disease specific events, for example difficulties in climbing stairs, rising from a chair, need of walking aids and wheelchair dependency, could inadequately be extracted from the literature. Sequential measurements of pulmonary function were also rarely reported. Ventilator use was documented for 28% of the patients, but most reports lacked information on whether the patient was partially or completely ventilator dependent and whether ventilation was performed only during the night (in supine position) or also during the day, via a nose hood or via a trachea canulla. Wheelchair use was only documented in 18 case reports and use of walking aids was rarely recorded. More detailed information should also be obtained on how progressive loss of muscle function affects daily life activities and quality of life. We emphasize the importance of studying these aspects of the natural course of non-classic Pompe disease in a well-defined cohort of patients, before enzyme replacement therapy becomes generally available.

Acknowledgements

This work was sponsored by the Sophia Foundation for Medical Research (312, L.P.F.W). The authors thank Tom de Vries Lentsch for the layout of the figures.

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Chapter 4

Clinical manifestation and natural course of late-onset Pompe disease in 54 Dutch patients

M.L.C. Hagemans[1,5], L.P.F. Winkel[1], P.A. van Doorn[2], W.J.C. Hop[3], M.C.B. Loonen[4], A.J.J. Reuser[5], A.T. van der Ploeg[1]

[1]Department of Pediatrics, Division of Metabolic Diseases and Genetics, [2]Department of Neurology, [3]Department of Epidemiology and Biostatistics, [4]Department of Child Neurology, [5]Department of Clinical Genetics, Erasmus MC Rotterdam, the Netherlands

Brain 2005;128(Pt 3): 671-677

Abstract

Late-onset Pompe disease (acid maltase deficiency, glycogen storage disease type II) is a slowly progressive myopathy caused by deficiency of acid α-glucosidase. Current developments in enzyme replacement therapy require detailed knowledge of the kind and severity of symptoms and the natural course of the disease in the patient population. A detailed questionnaire covering the patients' medical history and current situation was developed and information was gathered from 54 Dutch patients. The mean age of the participants was 48.6 ± 15.6 years. The first complaints started at a mean age of 28.1 ± 14.3 years and were mostly related to mobility problems and limb-girdle weakness. Fifty-eight percent of the adult patients indicated the presence of mild muscular symptoms during childhood. Twenty-eight percent of the patients waited more than 5 years for the final diagnosis after the first visit to a physician for disease-related complaints. At the time of questionnaire completion, 48% of the study population used a wheelchair and 37% used artificial ventilation. Movements such as rising from an armchair, taking stairs or getting upright after bending over were difficult or impossible for more than two-thirds of the respondents. The age at onset, the rate of disease progression and the sequence of respiratory and skeletal muscle involvement varied substantially between patients. Seventy-six percent of the participants indicated being troubled by fatigue and 46% by pain. This survey has mapped the age at onset, presenting symptoms, heterogeneity in progression and range of disease severity in a large group of Dutch patients. We conclude that early manifestations in childhood require proper attention to prevent unnecessary delay of the diagnosis. The follow-up of patients with late-onset Pompe disease should focus on respiratory and limb-girdle muscle function, the capacity to perform daily activities, and the presentation of fatigue and pain.

Keywords

Pompe disease, glycogen storage disease type II, α-glucosidase, acid maltase, natural course

Introduction

Pompe disease, also known as acid maltase deficiency or glycogen storage disease type II, is an autosomal recessive disorder in which deficient activity of the enzyme acid α-glucosidase causes intralysosomal accumulation of glycogen in skeletal muscle and other tissues.[1] The number of individuals born with the disease is predicted as 1 in 40,000.[2,3] Infantile and late-onset forms of the disease can be distinguished, reflecting differences in age at onset, severity of symptoms and rate of disease progression.[1,4] Classic infantile Pompe disease presents in the first months of life and most infants die within 1 year from cardiorespiratory insufficiency.[1,5] Late-onset Pompe disease comprises all milder subtypes, including childhood-, juvenile- and adult-onset disease. It presents predominantly as a slowly progressive proximal myopathy. Respiratory problems are a major cause of death.[1,4]

A registered therapy is not yet available, but enzyme replacement therapy (ERT) for Pompe disease is currently under development. The preliminary results are promising. The administration of recombinant human α-glucosidase from rabbit milk expanded the life span of patients with the infantile form of the disease, and corrected cardiac hypertrophy.[6,7] Beneficial effects of ERT were also reported for patients with late-onset Pompe disease.[8] Further clinical trials on the safety and efficacy of ERT are needed to obtain approval of this therapy. Detailed knowledge on the natural course, rate of progression, range of disease severity and distribution of specific symptoms in untreated patients is needed to set clinical end-points and to provide comparison data to judge fully the effects of ERT in future.

The natural course of infantile Pompe disease has been reviewed,[5,9,10] but information on the late-onset form is scarce and limited to small numbers of patients. To obtain more knowledge of this patient population, we sent out a questionnaire to all members of the Dutch Neuromuscular Diseases Association (VSN) registered as having late-onset Pompe disease.

Patients and methods

Questionnaire development

A self-completion questionnaire covering the patients' medical history and current situation was developed. We performed a literature study of more than 100 case reports of patients with childhood, juvenile and adult forms of Pompe disease to identify symptoms and signs possibly related to Pompe disease. Questions were included after review and discussion by a panel of experts on Pompe disease at Erasmus MC. This panel consisted of six senior staff members from our departments of neurology, pediatric neurology, pediatrics, internal medicine and clinical genetics, all involved in research projects on

Pompe disease. Six medical specialists (three neurologists, two pediatricians and one clinical geneticist) with experience in the field of Pompe disease from other academic hospitals in the Netherlands evaluated the draft version of the questionnaire. Changes were implemented according to their suggestions. Finally, the questionnaire was tested in a group of five patients with late-onset Pompe disease. Again changes were made where necessary, mostly to prevent overlap in questions and to improve clarity.

The questionnaire was developed to cover almost all aspects of the disease and consisted of 14 topics (diagnosis, family history, childhood, mobility, specific movements, breathing, sleeping, eating, other complaints, daily activities, job or study, modifications to the home and use of care, hospital stays and treatments) and 78 (subdivided) questions. The present study includes the outcome of questions from the first nine topics ('diagnosis' to 'daily activities'). The questionnaire consisted of both open-ended and response choice items. For every topic, a possibility was given to add extra information. The mobility and specific movements sections, for example, consisted of questions of the following kind: 'are you able to….' with as response choices: 'without any problems', 'with difficulty' or 'no'.

Study population

After approval of the study by the medical ethics committee of Erasmus MC, 80 members of the VSN, registered as having Pompe disease and older than 2 years of age, were asked to participate. Between May 2002 and January 2003, 56 patients, or their parents, gave written informed consent and returned a completed questionnaire. For two patients, the parents filled out the questionnaire. For some of the adult patients, a family member or friend helped with the completion of the questionnaire because writing was difficult for the patient.

Patients provided information about the year of diagnosis, the name of the physician who made the diagnosis and the hospital to which that physician was affiliated. The clinical and laboratory diagnoses of the respondents were verified. One patient, who had indicated beforehand that there was no full certainty about his diagnosis, indeed did not have Pompe disease and was excluded from the study. For the other patients, the diagnosis could be confirmed. One patient had the classic infantile form of Pompe disease, but was still alive at 2.5 years of age receiving experimental treatment with ERT. This patient was also excluded from the current analyses, leading to a final study population of 54 patients.

In order to obtain some information from the group of non-responders, we asked them to complete six short questions on age, sex, age at first complaints, use of wheelchair, use of artificial ventilation and own rating of disease severity (hardly affected, mild, moderate, severe or very severe). Ten of the 24 initial non-responders replied to this second call.

Data handling and analysis

To ensure patient privacy, each patient received a unique study number, which was used in all analyses. The returned forms were scanned and the answers were entered automatically into a pre-designed database by means of the Teleform program (Teleform version 8.2, Cardiff Software Inc., CA). One investigator (M.H.) corrected the answers not recognized by the computer and checked all original forms for the occurrence of questions, remarks or any other added writing. Missing data, out-of-range values, inconsistencies, errors and omissions detected while analyzing the data were checked on the original forms and corrected in the database when necessary.

When patients were asked about the start of certain symptoms or use of aids, they could either provide the year or indicate how long ago it was in categories of 5 years. When the patient gave an indication of the number of years ago, the age at these time points was estimated as follows: for 0 to 5 years ago, 2.5 years were subtracted from the date of questionnaire completion; for 5 to 10 years ago, 7.5 years were subtracted; and so on. When this information was not available either, the variable was left out for that patient.

All variables were summarized using descriptive statistics, including mean, SD, median, ranges, percentages and/or frequencies. Valid percentages (not including missing values in the calculation) are presented. Missing data did not exceed 2% (n=1) unless otherwise indicated. All analyses were performed using SPSS for Windows (version 10.1, SPSS Inc., Chicago, IL).

Results

General characteristics

A total of 54 patients (39% male, 61% female) from 45 families were included in this analysis. The response rate was 70%. Fifty-two patients had Dutch and two patients Belgian nationality. The mean age at the time of data collection was 48.6 ± 15.6 years (range 3.9 to 81.2 years; figure 1A). The 10 initial non-responders (three male, seven female) tended to be older (mean age 57.0 ± 13.7 years, range 36 to 72 years) than the study population. Most non-responders (six out of nine, one did not answer this question) rated the severity of their disease as 'moderate'. Four non-responders used a wheelchair and one used artificial ventilation. Data from the initial non-responders were not included in the analyses.

Presenting symptoms

The mean age at which the patients experienced their first complaints was 28.1 ± 14.3 years (29.1 ± 13.6 years when excluding the two patients younger than 12 years). Patients were asked for the nature of these complaints. Two or more complaints were counted if these occurred within the same year. Most first problems were related to mobility

and limb-girdle weakness. Problems in running and doing sports were indicated by 67%, climbing stairs by 28%, rising from an armchair by 20%, walking by 17%, and rising from a lying position by 11% of the participants. Fatigue (24%) and muscle cramps (17%) also were frequent first complaints. Less common, but noteworthy as a first symptom, were low back pain, problems in raising the head and problems in getting up after bending over. Respiratory complaints were mentioned only once as a first symptom.

Based on the distribution of the age at first complaints, 18% of the patients already had symptoms of Pompe disease before the age of 12 years. However, when specifically asked, 58% of the adult patients indicated problems during childhood, which in retrospect could have been related to Pompe disease. Examples are running more slowly than other children, being unable to keep up with other children during physical exercise or when playing games, often falling or a 'funny' gait. Twenty-nine percent did not have problems during childhood and 13% could not remember.

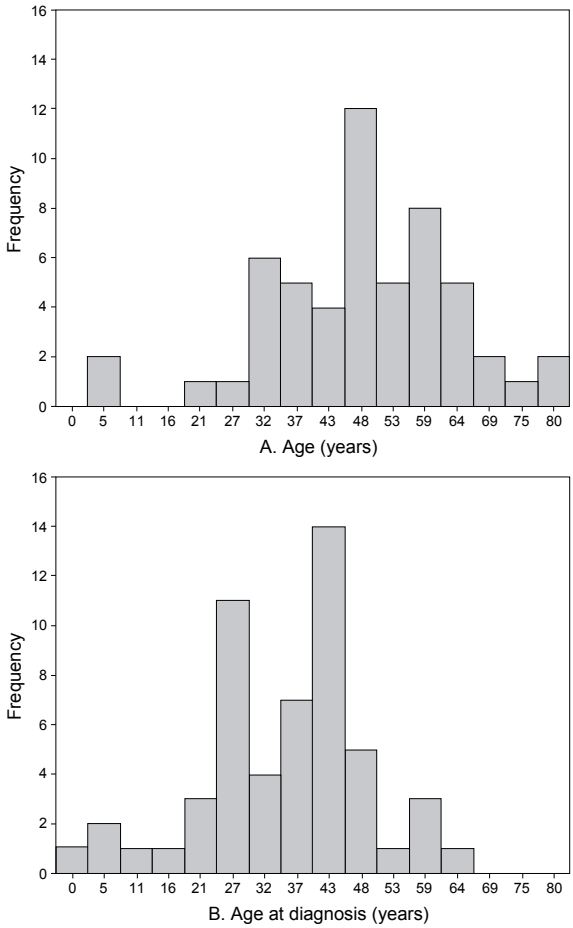

Figure 1 Age distribution of 54 Dutch patients with late-onset Pompe disease at the time of questionnaire completion (A) and at diagnosis (B).

Diagnosis

The mean age at diagnosis was 35.4 ± 13.9 years, ranging from shortly after birth to 63 years (figure 1B). When the patients younger than 12 years of age were excluded, the mean age at diagnosis was 36.7 ± 12.5 years. Forty patients provided information on the time between the first visit to a physician for complaints related to Pompe disease and the diagnosis. Fifty-three percent of them were diagnosed within 1 year. However, for 20% the diagnosis took between 1 and 5 years and for 28% as long as 5 to 30 years. Four patients were initially diagnosed as having spinal muscular atrophy (n=1), Duchenne (n=1) or Becker muscular dystrophy (n=2). Eight patients were diagnosed pre-symptomatically. The reason for diagnostic testing in these cases was a diagnosis of Pompe disease in a brother or sister or the finding of abnormal blood values, for example during a routine medical check-up. Only one of these patients (aged 45 years) was still asymptomatic, 19 years after diagnosis.

Mobility and specific movements

At the time of completion of the questionnaire, 87% of the respondents experienced problems with walking, varying from imbalance or a waddling gait to a complete inability to walk. The use of aids among the respondents is presented in table 1. Fifteen percent used walking aids, but did not need a wheelchair. Forty-eight percent used a wheelchair. Half of them always needed their wheelchair for mobility. The other half alternated the use of a wheelchair with the use of walking aids such as a walking frame or a cane, depending on the distance to be covered. The mean age at which patients started to use a wheelchair was 46.1 ± 12.4 years, ranging from 22 to 71 years.

Table 1 Use of aids in 54 patients with late-onset Pompe disease.

Mobility; use of walking aids	n	Artificial ventilation	n
No aids	20	No	18
		Yes	2
Walking aid (e.g. cane)	8	No	5
		Yes	3
Wheelchair alternated with walking aid	14	No	8
		Yes	6
Fully wheelchair dependent	12	No	3
		Yes	9

To gain insight into the extent of disability, the patients were asked whether they could perform a number of specific movements (table 2). The table includes 51 patients older than 18 years; one adult patient did not answer these questions. The two youngest patients both had difficulty with taking stairs. The 4-year-old also had difficulty with rising from a lying position on the ground and the 6-year-old with jumping.

Twenty-one patients (39%) indicated restricted movement in one or more joints (contractures), especially in the shoulders (n=14), hips (n=10), neck (n=8), and knees (n=7). Fifty-one percent of all respondents had a lordosis. Five out of 48 patients reported a scoliosis; one of them had been operated on for this. The patients reporting scoliosis all experienced their first complaints before 21 years of age. Twenty-eight percent of the respondents had problems with raising their head or keeping their head upright.

Table 2 Ability to perform specific movements of 51 adult patients with late-onset Pompe disease.

Movements	Without any problems (%)	With difficulty (%)	Not possible (%)
Raise arms above head	55	29	16
Getting upright after bending over	14	45	41
Rise from an armchair	12	53	35
Rise from a lying position on the ground	8	37	55
Jump	6	29	65
Go up and down a staircase (n=49)	2	57	41
Raise legs from surface when lying on back	2	43	55
Rise from a squatting position (n=50)	2	22	76

Respiratory problems

In our study population, 20 patients (37%, figure 2) used artificial ventilation: non-invasive by nose hood or facemask (n=16) or invasive by trachea canulla (n=4). The median duration of artificial ventilation was 11.5 hours per day (range 8 to 24 hours). All 20 patients needed ventilation during the night. Twelve patients used it during the daytime as well, three of them only after exercise. The mean age of the ventilator-dependent patients was 56.7 ± 13.2 years (range 32 to 81 years) and the mean age at the start of using artificial ventilation was 48.6 ± 16.3 years (range 15 to 78 years). Six patients started using artificial ventilation in the same year that they were diagnosed. The time between first complaints and diagnosis for these patients was 24.8 ± 15.5 years, ranging from 1 to 39 years.

Thirty-five percent of the patients who did not use artificial ventilation were not able to lie flat on their back while sleeping. A history of respiratory problems such as pneumonia (11 out of 49), bronchitis (eight out of 47) and colds (nine out of 46) was relatively frequent in the study sample.

Course of the disease

Figure 2 shows the age distribution of the respondents at several events in the course of Pompe disease. It is obvious from the wide distribution of each variable that there is substantial variation between patients. To shed more light on individual differences in the course of the disease, we compared the age at wheelchair use and age at start of using artificial ventilation (figure 3). Three participants started the use of artificial ventilation in the same year that they needed a wheelchair. Six patients first needed a wheelchair and six patients first needed artificial ventilation.

Pain and fatigue

Pain and fatigue are rather subjective and non-specific complaints, but have a strong impact on a patient's well being. Of the patients in our study population, 76% indicated being troubled by fatigue. The questions relating to pain in our survey revealed that 46% of the participants experienced pain 'often' or 'always' in one or more areas of the body. Pain in the legs was the most frequent and was mentioned by 33% of the participants. Muscle pains and muscle cramps were experienced mostly in the upper arms and upper legs.

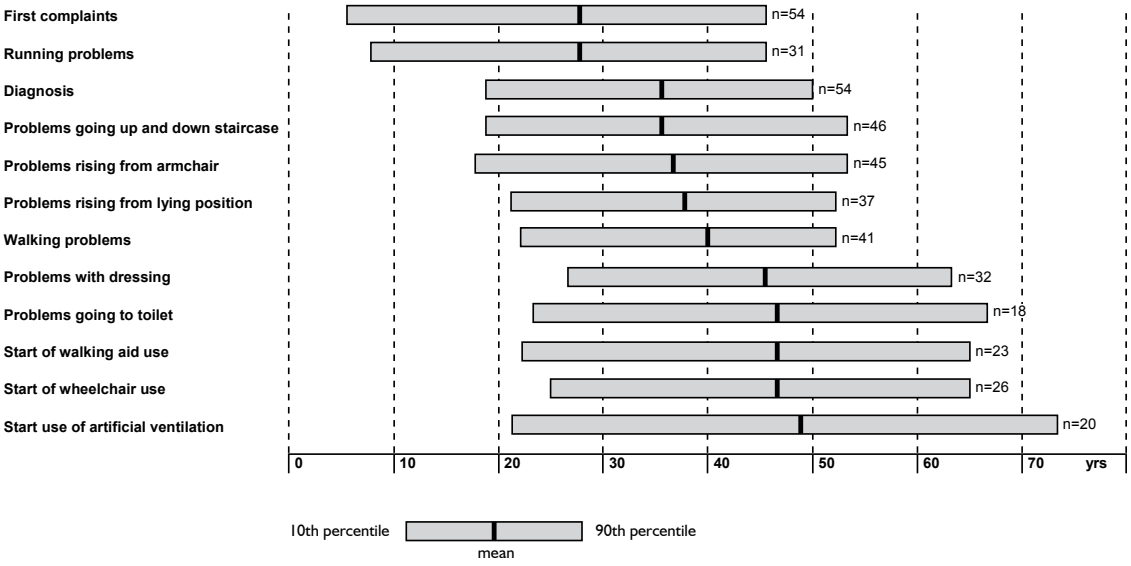

Figure 2 Age distribution for specific events in the course of the disease for 54 late-onset Pompe patients. The number behind each bar indicates how many patients provided information on the time of these events.

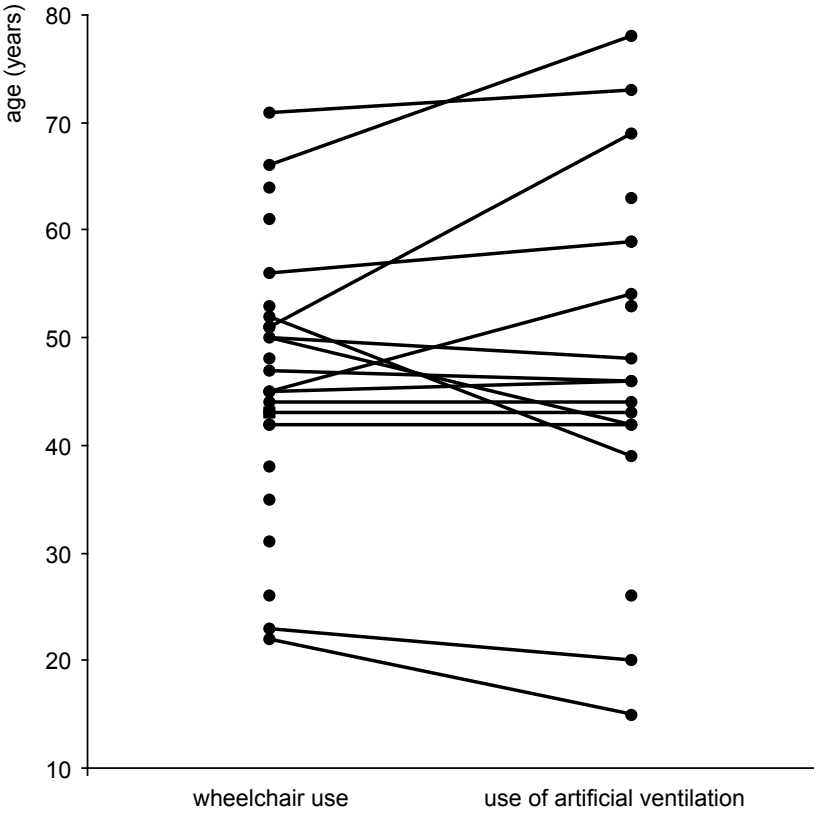

Figure 3 Age at wheelchair use and use of artificial ventilation in 31 patients with late-onset Pompe disease. The age at start of using a wheelchair and the age at start of using artificial ventilation are connected with lines for patients using both aids (n=15).

Discussion

The direct occasion for this study was the development of ERT for Pompe disease, necessitating accurate knowledge on the natural course of the disease in order to determine endpoints for clinical studies and to judge fully the therapeutic effects. The present study provides a detailed overview of the range of disease severity and the distribution of specific symptoms in 54 Dutch patients with late-onset Pompe disease. The study confirms the picture of a progressive proximal myopathy: limb-girdle weakness (as measured by the ability to perform movements such as rising from an armchair, taking stairs or getting upright after bending over) and resulting problems in mobility were present in a large proportion of our study population. Respiratory problems were also frequent, and the need for artificial ventilation was high. The results obtained from our study illustrate the extent of disability in this population.

Six patients needed artificial ventilation in the same year that they were diagnosed. This is a lower proportion than the 30% of patients presenting with respiratory insufficiency reported in the literature.[4,11] For these six patients, the time between first complaints and diagnosis was long (25 years on average). Only one patient in our study mentioned respiratory problems as a first complaint. This suggests that those who presented with respiratory insufficiency already had other, unrecognized symptoms at an earlier age. Our data further show that respiratory insufficiency in late-onset Pompe disease may present at any age and even when patients have only mild muscular symptoms. We therefore stress that respiratory function measurements should be included in the regular follow-up of all patients with late-onset Pompe disease in order to make timely interventions possible.

The first complaints of our participants were mostly related to an impaired motor function, for example problems in doing sports or climbing stairs. These first complaints occurred at an average age of 28 years. In earlier reports, a mean age at onset of 36 years was found.[12,13] The difference may be explained by variation in patient selection and the inclusion of smaller numbers of patients in the latter studies.

When we specifically asked for any problems during childhood, more than half of the adult patients answered in the affirmative. This is in line with the findings in a French study on the genotype-phenotype correlation in late-onset Pompe disease, reporting mild muscular symptoms during childhood in 16 out of 21 patients.[12] Although the complaints during childhood were mostly subtle, it is important to realize that early manifestations can occur. General awareness of this fact will help to prevent the large diagnostic delays as found in the present study.

The course of the disease varied substantially between patients with respect to both age at onset and rate of disease progression. Furthermore, no clear pattern could be

discerned in the sequence of involvement of respiratory and skeletal muscles. This lack of correlation between respiratory and motor function was noted before[12,13] and makes it difficult to classify patients into groups of disease severity for the definition of inclusion and exclusion criteria for clinical studies. Most existing scales for the assessment of disability status are based on differences in motor function, such as the Walton scale[12] and the Overall Disability Sumscale.[14] To evaluate disease severity in late-onset Pompe disease, it may be more appropriate to measure a patient's ability to perform activities of daily living and to assess the level of handicap using standardized functional outcome measures.[15] Pelvic and paraspinal muscle strength, muscle function and respiratory function will also be suitable as follow-up measures to document the natural course of the disease in untreated patients and as clinical outcome parameters to evaluate the effect of therapy.

Pain and fatigue were common among the patients in this study. Fatigue also was an important first symptom in our patient group, which confirms earlier results.[16] Although pain and fatigue are considered subjective and are associated with a variety of disorders, they deserve further attention in relation to Pompe disease. The measurement of pain and fatigue could prove useful in the evaluation of treatment effects, and instruments such as the Fatigue Severity Scale[17,18] or the Brief Pain Inventory[19,20] should be tested in this specific population.

A few remarks should be made on the composition of our study sample and on the reliability of our results. First, we are aware that the recruitment of patients through a patient organization is a potential source of selection bias, as this group may be particularly motivated and perhaps more severely affected. Apart from that, the least affected patients may not be recognized and thus not diagnosed as having Pompe disease. However, the range in symptoms and severity of the presently described sample varies from almost asymptomatic to wheelchair and ventilator dependent, and the age of the participants ranged from 4 to 81 years. We therefore believe that we have covered the whole spectrum of disease severity, although we cannot be sure about the real proportion of severe versus mildly affected patients. A second, related, issue is the lack of patients in the age range of 7 to 20 years. A possible explanation would be that many younger patients have only mild symptoms and are not diagnosed until adulthood.

Thirdly, it is unlikely that differences between the study population and the non-responders have introduced bias. First, because the response rate was very high for a postal questionnaire study, and secondly because there were no clues that they were more (or less) severely affected than the study sample. The non-responders tended to be older, but the age range in this rather small group was wide (36 to 72 years).

A last point that should be discussed is the reliability of patient and parent reports as used in the present study. For most variables, we are fairly confident that our estimation

of their frequency among our study participants is reliable. Patients are very capable of indicating if they are able to perform certain activities. They also remember well when they started to use a wheelchair or a ventilator, because the use of these aids marks an important change in daily life. It is more difficult to recall, for example, 'first difficulties in rising from a lying position'. These data should therefore be interpreted with caution and can only be used for an estimation of the group average.

This questionnaire survey has mapped the age at onset, the presenting symptoms, the heterogeneity in progression and the range of disease severity in a sample of 54 Dutch patients with late-onset Pompe disease. We conclude that mild muscular symptoms during childhood should receive more attention to prevent large diagnostic delays. Irrespective of the extent of skeletal muscle involvement and age, periodic measurement of the respiratory function of patients with late-onset Pompe disease is needed to make timely interventions possible. Attention should also be paid to pain and fatigue, as these symptoms are more frequent than previously thought. Follow-up studies in untreated patients are needed to document prospectively the natural course and to identify patient characteristics or biological markers that predict the progression of the disease.

Acknowledgements

We wish to thank W.F. Arts, H.A. Büller, G. de Jong, H. de Klerk, J. Wokke, M. Ausems, J. Smeitink, P. Smit, J. Kuks, M. de Visser and B. Poorthuis for advise and support, the Dutch Neuromuscular Diseases Association (VSN) for their help in the organizational part of the study, K. Sieradzan for the development of the database and his help in data management, T. de Vries Lentsch for layout of the figures, and all participants.

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Chapter 5

Disease severity in children and adults with Pompe disease related to age and disease duration

M.L.C. Hagemans[1,3], L.P.F. Winkel[1], W.J.C. Hop[2], A.J.J. Reuser[3], P.A. van Doorn[4], A.T. van der Ploeg[1]

[1]Department of Pediatrics, Division of Metabolic Diseases and Genetics, [2]Department of Epidemiology and Biostatistics, [3]Department of Clinical Genetics, [4]Department of Neurology, Erasmus MC Rotterdam, the Netherlands

Neurology 2005; 64(12): 2139-2141

Abstract

Information about 255 children and adults with Pompe disease was gathered through a questionnaire. Disease severity was associated with disease duration and not with age; an early manifestation of the disease implied earlier wheelchair or ventilator dependency. The patient group under age 15 included a subgroup with a more severe and rapid course of the disease. They require more intensive follow-up and early intervention, before irreversible damage has occurred.

Introduction

Pompe disease (glycogen storage disease type II) is a progressive metabolic myopathy caused by deficiency of acid α-glucosidase, an enzyme needed for the degradation of lysosomal glycogen. This deficiency results in glycogen storage in virtually all tissues but most notably in skeletal muscle.[1] The predicted frequency of the disease is 1 in 40,000.[2,3] Different clinical subtypes are recognized: a severe infantile form of the disease and a more slowly progressive 'late-onset' form occurring in children and adults.[1]

Currently, enzyme replacement therapy with recombinant human α-glucosidase is under investigation. The results of the first trials are promising,[4-7] but the treatment is invasive[5,6] and will be expensive. Indication and timing of the treatment are important issues. Therefore, knowledge on the natural course of the disease and the composition of the patient population is essential. Such information is insufficiently available for the heterogeneous late-onset form of the disease. In this article, we present cross-sectional data from 255 children and adults with Pompe disease obtained by a postal questionnaire. We describe their current situation and relate information on disease severity to age and disease duration.

Methods

In an ongoing research project on the natural course of patients with late-onset Pompe disease,[8,9] 255 patients of different nationalities were recruited through the International Pompe Association (IPA). They were registered as having Pompe disease and older than 2 years. After informed consent was obtained, the participants completed a questionnaire covering their medical history and current situation.[9] The Dutch version of the questionnaire was translated into English and German by certified translators. For the current analyses, information on age, sex, diagnosis, use of respiratory support, use of walking aids or wheelchair, use of nutritional support, and first symptoms was used.

Variables are presented using median and interquartile range (IQR). For categorical variables, percentages or frequencies are given. Patients were divided by disease duration into four groups (<5, 5 to 10, 10 to 15, and ≥15 years) and by age into five groups (<15, 15 to 30, 30 to 45, 45 to 60, and ≥60 years). Differences in use of supportive measures between age groups and groups based on disease duration were evaluated by the χ^2 test for trend. The relation between age or disease duration with the number of hours of respiratory support was calculated by the Spearman correlation coefficient. To simultaneously study the contribution of age and disease duration to disease severity, logistic regression analysis was performed with wheelchair use and use of respiratory support as dependent variables.

Results

The distribution of age, age at first complaints, and age at diagnosis in the study population are presented in figure 1. Fifty-one percent of the participants were women and 49% were men. Forty-four percent of the study population used a wheelchair. Twenty-four percent alternated the use of a wheelchair with walking aids, and 21% used the wheelchair for practically all mobility. Respiratory support was used by 45% of the participants: Eleven percent received invasive ventilation via a tracheotomy, 29% noninvasive ventilation via a face mask, and for 5%, the method of ventilation was not recorded. The median number of hours of ventilation per day was 10.5 (IQR 8 to 17 hours). Nutritional support was used by 8% of the participants (percutaneous endoscopic gastrostomy tube, n=18; nasogastric tube, n=2).

Figure 2A shows wheelchair use and use of respiratory support related to age. The proportion of patients using a wheelchair did not differ significantly between age groups. The use of respiratory support increased slightly with age (p for trend 0.03). The percentage of patients using respiratory support was lowest in the group under age 15 (26%), but the number of hours of ventilation per day was highest (median 24 hours compared with median 9 to 12 hours in the older age groups). Figure 2B shows wheelchair use and use of respiratory support related to disease duration. The percentage of patients using a wheelchair, the percentage using respiratory support, and the number of hours of respiratory support per day all increased with disease duration ($p<0.001$). In a simultaneous evaluation of the effect of age and disease duration on the prevalence of wheelchair use and respiratory support, only disease duration remained an important factor. With every additional year since diagnosis, the odds for wheelchair use increased by 13% and the odds for respiratory support by 8% (both $p<0.001$).

The presence of a small subgroup among the patients under age 15 requiring the most intensive respiratory support led us to investigate this age group in more detail. In the table, a comparison between the patients with and without respiratory support is made. The patients younger than age 15 who used respiratory support were all wheelchair dependent and required nutritional support. Compared with the patients without respiratory support in the same age group, they had earlier first complaints, an earlier diagnosis, and earlier wheelchair use. All experienced their first complaints before age 2, and four already had problems within the first year: They were ‘floppy’, had difficulty drinking, and did not meet milestones such as standing or walking or only with a large delay.

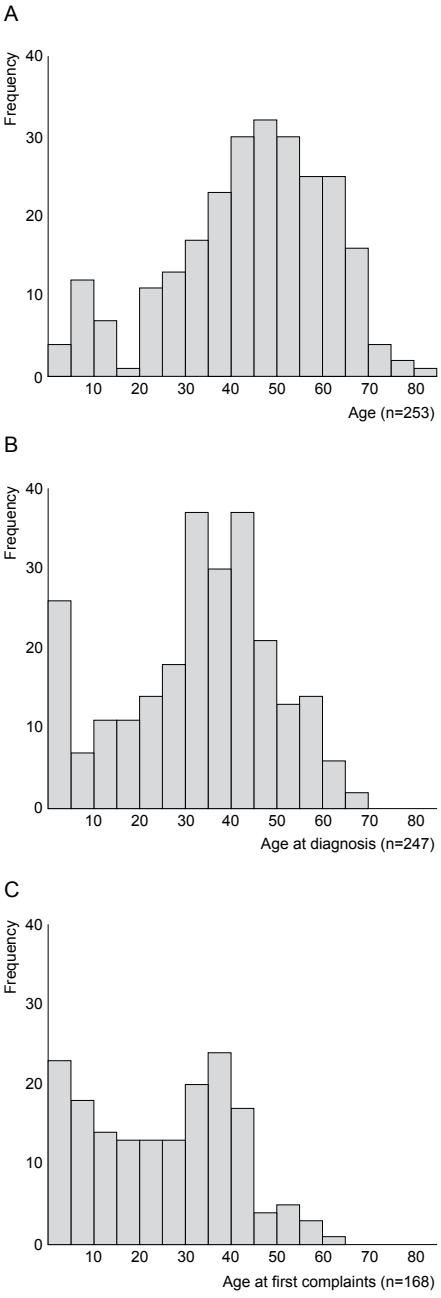

Figure 1 Distribution of age (A), age at diagnosis (B), and age at first complaints (C) in the study population. Range for age: 2.6 to 81 years; range for age at diagnosis: 0 to 66 years; range for age at first complaints: 0 to 62 years.

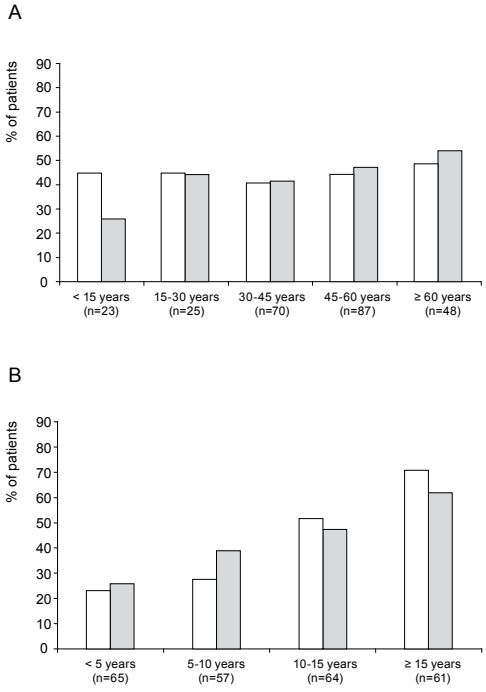

Figure 2 (A) Wheelchair use and use of respiratory support related to age in 253 children and adults with Pompe disease. (B) Wheelchair use and use of respiratory support related to disease duration in 247 children and adults with Pompe disease. White represents wheelchair use; gray shading represents use of respiratory support.

Table Comparison between patients younger than 15 years with and without respiratory support.

	Respiratory support	
	Yes, n=6	No, n=17
Sex, no. girls	3	2
Wheelchair use, n (%)	6 (100)	3 (21)
Full-time use, n	6	1
Use of PEG or nasogastric tube, n (%)	6 (100)	0
Present age, y	7.4 (5.5-10.2)	6.9 (5.3-10.8)
Age at diagnosis, y	0.5 (0-1.7)	2.1 (1.4-3.2)
Age at first complaints, y	0.2 (0-1.5)	1.3 (0.5-4.4)
Age at start of wheelchair use, y	2.9 (1.6-4.4)	5.0
Age at start of nutritional support, y	2.6 (1.7-4.9)	-
Age at start of respiratory support, y	3.1 (2.0-4.9)	-
Respiratory support (range), h/24 h	24 (12-24)	-

Figures on age are presented as medians (interquartile range). For those patients using no respiratory support, wheelchair use and age at first complaints were missing for n=3. PEG=percutaneous endoscopic gastrostomy.

Discussion

We studied the relationship between disease severity, age, and disease duration in a group of 255 children and adults with Pompe disease. Disease severity (wheelchair use, use of respiratory support, and number of hours of respiratory support per day) increased with disease duration but was not related to the actual age of the participants. Only the use of respiratory support differed between age groups, and this was due mainly to the low percentage of patients using respiratory support in the youngest age group. Logistic regression analyses confirmed that the effect of disease duration was independent of age. In general, this means that it does not matter how old or young a patient is; the longer the time since diagnosis the higher the probability of wheelchair or ventilator dependency. This also underscores that Pompe disease is a genuine spectrum and may start at any age.

The group of patients younger than age 15 deserves special attention. Although this group had a relatively low proportion of patients who needed respiratory support, the patients who did use ventilation needed it almost continuously. When studying the latter group in more detail, we noticed that all patients requiring respiratory support also needed a wheelchair and nutritional support. Although their age did not differ much from the young patients without respiratory support, they had earlier first complaints, an earlier diagnosis, and an earlier start of wheelchair use. Taken together, there seems to be a subgroup of young patients with a more rapid and severe course of the disease. Patients with first complaints in the first year of life may be the patients previously described as 'nontypical infantile'.[10] In this respect, the age distribution of the study population is also of interest. A relatively high number of patients were under age 15, followed by a low number between ages 15 and 20. We speculate that the course of disease is rapidly progressive in part of these children, who therefore might not reach age 20.

Taking into account that enzyme therapy elicits a better effect when the patient is still in a reasonable condition,[6] these children should be followed closely to install therapy before irreversible damage has occurred.

Acknowledgements

The authors thank all participants and IPA representatives for their contribution to the study.

This study was a joint initiative of the International Pompe Association (IPA) and Erasmus MC and was financed in part by IPA. As of August 2004, Drs. Van der Ploeg and Reuser have provided consulting services for Genzyme under an agreement between Genzyme and Erasmus MC.

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Chapter 6

Course of disability and respiratory function in untreated late-onset Pompe disease

M.L.C. Hagemans[1,4], W.J.C. Hop[2], P.A. van Doorn[3], A.J.J. Reuser[4], A.T. van der Ploeg[1]

[1]Department of Pediatrics, Division of Metabolic Diseases and Genetics,
[2]Department of Epidemiology and Biostatistics, [3]Department of Neurology,
[4]Department of Clinical Genetics, Erasmus MC Rotterdam, the Netherlands

Neurology 2006; 66(4): 581-583

Abstract

Fifty-two untreated patients with late-onset Pompe disease completed questionnaires about their clinical condition and level of handicap at baseline and at 1-year (n=41) and 2-year follow-ups (n=40). During this period, declines in functional activities, respiratory function, handicap and survival were recorded on a group level. This study illustrates the progressiveness of late-onset Pompe disease and indicates the need for close clinical follow-up of both children and adults with this disorder.

Introduction

Pompe disease (glycogen storage disease type II or acid maltase deficiency) is a lysosomal disorder in which deficiency of acid α-glucosidase causes intralysosomal accumulation of glycogen in all tissues but most notably in skeletal muscle.[1] Currently enzyme replacement therapy is under development for this so far untreatable disorder.[2-4]

Pompe disease has an estimated frequency of 1 in 40,000 births.[5] This makes it difficult to obtain an accurate view of the natural course of the disease and to design clinical trials. Besides the classic infantile form of Pompe disease, which is fatal in the first year of life,[6] a spectrum of less severe phenotypes exists, with age at onset varying from early childhood to late adulthood.[1] The rate of progression of this 'late-onset' form of Pompe disease is not sufficiently known.

Methods

The study is part of an ongoing research project on the natural course of late-onset Pompe disease.[7,8] After obtaining informed consent, 52 Dutch baseline participants were asked to complete a follow-up questionnaire after 1 year (t=1; n=41) and again after 2 years (t=2; n=40).

The baseline questionnaire has been described previously.[7] The follow-up questionnaires were shorter versions and included questions about use of respiratory support, number of hours of ventilation per day, use of wheelchair or walking aids, and the ability to perform certain functional activities. For patients aged 18 years and older, the level of handicap was assessed by the Rotterdam Handicap Scale (RHS). The scale consists of nine questions on the topics of mobility indoors and outdoors, kitchen tasks, domestic tasks indoors and outdoors, leisure activities indoors and outdoors, traveling, and work/study. The total score ranges from 9 to 36, with higher values representing a lower level of handicap.[9]

Differences between patient groups were tested with independent-samples t-tests (age, age at diagnosis, and disease duration) and χ^2 tests (sex, wheelchair use, and use of respiratory support). The change in ability to perform certain functional activities and the change in number of hours of respiratory support per day between t=0 and t=2 were evaluated using the paired Wilcoxon test. Longitudinal analysis of the RHS scores, allowing for missing data, was performed using repeated-measures analysis of variance in the total group and in subgroups divided by age (with the median as the cutoff point) and disease duration (in four groups: <5, 5 to 10, 10 to 15, and ≥15 years) using the SAS PROC MIXED statistical program (SAS Institute Inc., Cary, NC).

Results

The mean age of the baseline participants was 48 ± 16 years (range 4 to 81 years). The mean age at diagnosis was 35 ± 14 years, and the mean disease duration was 13 ± 9 years. Sixty percent of the participants were women. Twenty-four patients used a wheelchair, and 19 used respiratory support at baseline. No significant differences in baseline characteristics were found between those who returned the questionnaires at t=1 or t=2 and those who did not respond.

Four patients died during the 2 years of follow-up. The reported causes of death were cardiorespiratory insufficiency during an episode of influenza, cor pulmonale, cerebral vascular disorder, and cancer. Age at death varied from 44 to 68 years. Three patients used respiratory support. No significant differences in age at baseline, age at diagnosis, or disease duration were found between the deceased and the other patients.

Two patients started to use a wheelchair, and two patients progressed from partial to full wheelchair use. The table shows the changes in ability to perform certain functional activities between t=0 and t=2. A decrease was found in the ability to ride a bicycle (p=0.025) and the ability to jump (p=0.034). The abilities to get upright after bending over and to raise the arms above the head decreased as well, but these were not significant at the 0.05 level. No change was found in the percentage of patients able to rise from an armchair, run, walk stairs, rise from a lying position, raise the legs from the surface when lying on the back, or rise from a squatting position (last three activities not shown in the table).

Between baseline and the 2-year follow-up measurement, three patients started to use respiratory support (8 to 9 hours/day). The age at baseline of these patients varied from 34 to 66 years, and the disease duration varied from 19 to 21 years. Five patients increased the number of hours of ventilation per day. The mean number of hours of respiratory support per day increased between baseline and t=2 (p=0.01).

The mean RHS score decreased from 25.5 at t=0 to 24.3 at t=2 (p=0.035; 95% CI for mean decrease in 2 years: 0.3 to 2.1). Figure A shows the RHS scores of the adult patients at t=2 plotted against the score at t=0. For the majority of patients, the RHS score decreased, indicating a higher level of handicap. The RHS score showed a gradual decrease of 1.9 points with every 5 years of disease duration at baseline (p for trend=0.006), but the change in RHS scores over the 2-year follow-up period was similar for patients with different disease duration (figure B). Age did not influence the course over time, but the youngest age group had higher RHS scores at all time points.

Table Changes in ability to perform functional activities in 2-year follow-up of adult patients with Pompe disease.

Movement or activity	n		t=0 (%)	t=2 (%)	p value*
Ride a bicycle	35	Without any problems	11.4	5.7	0.025
		With difficulty	31.4	28.6	
		Not able to do	57.1	65.7	
Jump	37	Without any problems	8.1	5.4	0.034
		With difficulty	32.4	21.6	
		Not able to do	59.5	73.0	
Get upright after bending over	37	Without any problems	13.5	10.8	0.096
		With difficulty	48.6	40.5	
		Not able to do	37.8	48.6	
Raise the arms above the head	37	Without any problems	59.5	51.4	0.132
		With difficulty	32.4	35.1	
		Not able to do	8.1	13.5	
Rise from an armchair	36	Without any problems	16.7	11.1	0.480
		With difficulty	52.8	58.3	
		Not able to do	30.6	30.6	
Run	37	Without any problems	2.7	2.7	0.564
		With difficulty	10.8	8.1	
		Not able to do	86.5	89.2	
Walk stairs	31	Without any problems	3.2	6.5	1.000
		With difficulty	71.0	64.5	
		Not able to do	25.8	29.0	

*Comparisons were made between the baseline and 2-year measurement for the patients over 18 years for whom data from both measurements were available using the Wilcoxon test.

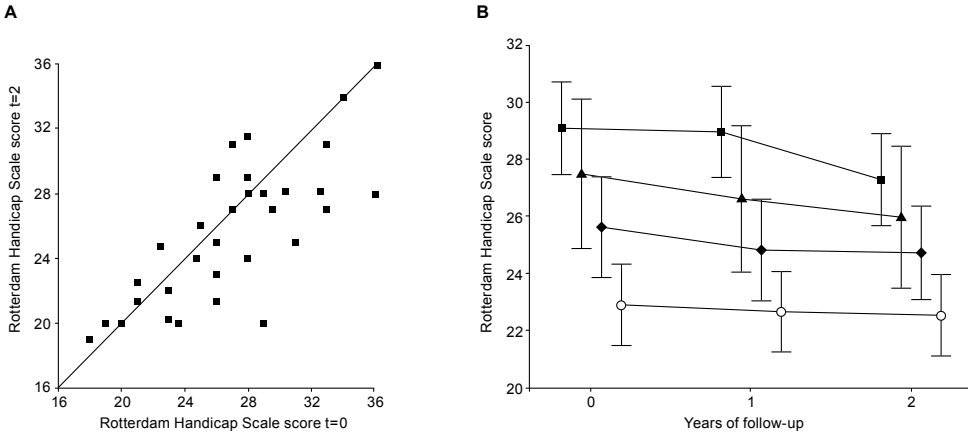

Figure Rotterdam Handicap Scale scores of adult patients with Pompe disease. (A) Paired scores at baseline and after 2 years. The diagonal line represents the line of identity. (B) Change in scores over 2 years, grouped by disease duration. Squares represent patients with less than 5 years of disease duration (n=13), triangles represent 5 to 10 years (n=5), diamonds represent 10 to 15 years (n=11), and circles represent 15 years or more (n=17). Values are expressed as mean ± SEM.

Discussion

In this study, we describe the changes in 2 years in a group of untreated patients with late-onset Pompe disease. The wide ranges in age, age at diagnosis, disease duration, wheelchair use, and use of respiratory support at baseline show that our study population covers a broad spectrum of disease severity and not a particular subgroup of patients. There was also no specific loss to follow-up.

Four patients died during these 2 years. Three of them used respiratory support, but they did not have further common characteristics that could have predicted their early death. In two patients, the cause of death (cardiorespiratory insufficiency and cor pulmonale) was most likely related to Pompe disease. The cerebral vascular pathology is probably also related. In literature, two patients with Pompe disease were described who died of a cerebral aneurysm and had glycogen accumulation in the smooth muscle of the basilar artery.[10]

In 2 years, we found a significant increase in the number of hours of respiratory support per day and a significant decrease in specific functional activity items such as the abilities to jump and to ride a bicycle. Smaller decreases were found in the abilities to get upright after bending over and to raise the arms above the head. In other movements or activities, no change was recorded; this may partly be because the ability to perform these activities was already limited at baseline, for example for running and walking stairs.

The RHS score showed a significant gradual decrease of 2 points with every 5 years of disease duration, which is in line with the observed mean decrease of approximately 1 point during the 2-year follow-up period. This information is important because it shows that late-onset Pompe disease should be viewed as a progressive disorder for which timely intervention is required to prevent further loss of function.

Acknowledgements

The authors thank the patients and the International Pompe Association for their contribution to the study.

This study was a joint initiative of the International Pompe Association (IPA) and Erasmus MC and was financed in part by IPA and Genzyme Corp., Boston, MA. As of August 2004, Drs. Van der Ploeg and Reuser provide consulting services for Genzyme under an agreement between Genzyme and Erasmus MC.

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Chapter 7

Late-onset Pompe disease primarily affects quality of life in physical health domains

M.L.C. Hagemans[1,5], A.C.J.W. Janssens[2], L.P.F. Winkel[1], K.A. Sieradzan[3], A.J.J. Reuser[4], P.A. van Doorn[3], A.T. van der Ploeg[1]

[1]Department of Pediatrics, Division of Metabolic Diseases and Genetics, [2]Department of Public Health, [3]Department of Neurology, [4]Department of Clinical Genetics, Erasmus MC Rotterdam, the Netherlands

Neurology 2004;63(9):1688-1692

Abstract

Objective: To investigate quality of life in an international population of patients with late-onset Pompe disease.

Methods: Data on quality of life (SF-36), age, sex, disease duration, wheelchair use, and use of artificial ventilation were collected for 210 adults with Pompe disease from Australia, Germany, the Netherlands, the United Kingdom, and the United States. SF-36 scores were compared between countries and related to patient characteristics. In addition, for the Dutch subgroup (n=51), comparisons with the general population and 1-year follow-up assessments were performed.

Results: No significant differences between countries were found for the four physical health scales. Mean scores on the vitality, role functioning-emotional, and mental health scale differed between countries, but these differences were not consistent. Wheelchair use was associated with lower physical and social functioning scores (B=-23.6 and -15.1, $p<0.001$), and the use of artificial ventilation with lower physical functioning scores (B=-8.4, $p=0.004$). Patients reported significantly poorer quality of life than the general population on the physical functioning, role functioning-physical, general health, vitality, and social functioning scales. No significant differences in SF-36 scores were found between the baseline and 1-year follow-up measurement.

Conclusions: Patients with late-onset Pompe disease are, on average, markedly affected on the physical health domains of quality of life, but score only slightly lower than the general population on the mental health domains.

Introduction

Pompe disease is a hereditary lysosomal storage disorder with an incidence of 1:40,000 births.[1] Deficiency of the enzyme acid α-glucosidase leads to accumulation of glycogen and finally to destruction of muscle tissue. The clinical spectrum ranges from a rapidly progressive infantile form leading to death within the first year of life to a slowly progressive late-onset form of the disease that affects mobility and respiratory function.[2-4] Currently enzyme replacement therapy is under development for this so far untreatable disorder. Preliminary results for both infantile[5] and late-onset[6] patients are promising, and further clinical trials are underway.

Enzyme replacement therapy will be costly and it is expected that patients will need regular intravenous administrations for the rest of their lives. Careful evaluation of the therapeutic value is therefore important. Besides standardized clinical and laboratory measures, this evaluation should comprise the measurement of quality of life as an indicator of the effect of treatment on the well being of patients. For this purpose, data obtained in a well-defined patient population before the onset of treatment are necessary. Such studies have not been carried out.

In this study we investigated the quality of life of patients with late-onset Pompe disease using the SF-36. Because the disease is rare, and new clinical trials on enzyme replacement therapy will very likely include patients from various countries, the study was conducted in an international population.

The aim of the present article is fivefold. First, we describe and compare quality of life of patients with late-onset Pompe disease from five different countries. Second, we present the psychometric properties of the SF-36 in this patient population, and third, we investigate the relationship between patient characteristics and quality of life. In the Dutch subgroup we then compare the quality of life of patients with late-onset Pompe disease with general population values and evaluate the changes in SF-36 scores over 1 year.

Methods

Patients and procedures

The study was part of an ongoing research project on the natural course of patients with late-onset Pompe disease. The medical ethics committee of Erasmus MC approved the project and all patients provided written informed consent. Patients were recruited through patient organizations affiliated with the International Pompe Association (IPA) in Australia, Germany, the Netherlands, the United Kingdom and the United States. Inclusion criteria were a diagnosis of Pompe disease and an age above 2 years. For the

SF-36 substudy patients younger than 18 years were excluded. All questionnaires were provided by our study center and distributed in a single mailing through the patient organizations in each country. The completed questionnaires were either sent directly to Erasmus MC or first collected by the local IPA representative. One year after the baseline measurement, the Dutch patients completed a follow-up questionnaire. To examine the test-retest reliability of the SF-36 in this population, a third assessment was performed within 1 month.

Data collection

SF-36

Quality of life was assessed using the SF-36 health survey. The SF-36 comprises four physical health scales (physical functioning, role limitations due to physical problems, bodily pain, and general health perceptions) and four mental health scales (vitality, social functioning, role limitations due to emotional problems, and mental health). Items are summed per scale and transformed into scores between 0 and 100, with higher values representing better function.[7] The SF-36 has been used in many different conditions, including the lysosomal storage disorders Fabry and Gaucher disease[8-11] The SF-36 was translated into more than 40 languages, which made it particularly appropriate for our international study population. In the present study, the following validated and cross-culturally adapted translations were used: Dutch, English (Australian), English (UK), English (US) and German.[12,13]

Other variables

In the baseline questionnaires, date of birth, year of diagnosis, sex, wheelchair use, and use of artificial ventilation were recorded. Duration of disease was obtained by subtracting year of diagnosis from date of questionnaire completion. Participants in the follow-up study among Dutch patients were further asked to indicate on a five-point scale whether their physical situation had improved a lot, improved a little, remained the same, deteriorated a little, or deteriorated a lot since the baseline measurement and to add a short explanation.

Statistical analysis

The returned questionnaire forms were scanned and the answers were automatically entered into a pre-designed database by means of the Teleform program (Teleform version 8.2, Cardiff software Inc., CA). One investigator (M.H.) corrected the answers not recognized by the computer. For the SF-36 scores, missing data handling and checks on data quality were performed as recommended.[14] No inconsistencies occurred.

To examine the psychometric performance of the SF-36, we evaluated the internal consistency, test-retest reliability, and the percentage of floor and ceiling effects for each scale. Internal consistency was assessed by Cronbach's α and test-retest reliability by the

intraclass correlation coefficient (ICC). Floor and ceiling effects were considered present when more than 20% of the participants had the lowest (0) or highest possible score (100) on a scale. Differences between countries in general characteristics were assessed by one-way analysis of variance (ANOVA) and Kruskal-Wallis tests. Differences in SF-36 scores between countries were tested by ANOVA. To compare quality of life in the Dutch subgroup with general population values, univariate analyses of variance with age and sex as covariates were performed. Values for the Dutch general population were obtained from a population-based study providing Dutch normative data for the SF-36.[15] The original data on quality of life, age, and sex were available for analysis (n=1742). To investigate the influence of patient characteristics on SF-36 scores, multiple regression analyses with disease duration, wheelchair use, use of artificial ventilation, age, and sex as independent variables were performed. To compare quality of life between patients with different degrees of disability, the total population was divided into four groups: patients who used neither a wheelchair nor artificial ventilation, patients who used only a wheelchair, patients who used only artificial ventilation, and patients who used both. The data were adjusted for age and sex. To compare the baseline and follow-up SF-36 scores in the Dutch subgroup paired samples t-tests were used. A p-value <0.05 was considered significant in all instances. All analyses were performed using SPSS for Windows (version 10.1, SPSS Inc. Chicago, IL).

Results

Study population

Of the 422 patients invited between May 2002 and May 2003, 237 participated in the study. The response rate was 100% in Australia, 77% in Germany, 70% in the Netherlands, 58% in the United Kingdom, and 44% in the United States. The SF-36 was completed by patients of 18 years and older (n=214). Two patients were excluded because too many SF-36 data were missing and two patients were excluded because they did not complete the SF-36 in their native language. The study population thus included 210 adult Pompe patients. The general characteristics of the respondents for each country are shown in table 1. Age, sex, duration of disease, wheelchair use, and use of artificial ventilation did not differ significantly among the five countries.

Psychometric properties of the SF-36

The percentage of missing values for each SF-36 scale in the total group of 210 participants was lowest for the mental health scale (0%) and highest for the role functioning-emotional scale (4.5%). Internal consistency of the eight SF-36 scales was good with coefficient α ranging from 0.78 to 0.92. Test-retest reliability was good for all scales (ICC 0.74 to 0.91) except for the role functioning-emotional scale (ICC=0.37). Floor effects were present for the physical functioning (22%) and role functioning-physical (30%) scales. Ceiling effects were found for the role functioning-physical (30%), bodily pain (21%), role functioning-emotional (63%), and social functioning (20%) scales.

Differences between countries

Table 2 presents the mean SF-36 scores of late-onset Pompe patients from the five countries. No significant differences between countries were found for the four physical health scales. The mean scores on three of the four mental health scales differed between countries (p=0.01 for vitality, p=0.03 for role functioning-emotional, and p=0.04 for mental health). Dutch patients tended to score higher on the mental health and vitality scales, while German patients had higher scores on the role functioning-emotional scale. There was, however, no consistent pattern of differences in SF-36 score among the five countries.

Table 1 General characteristics of patients with late-onset Pompe disease from five countries.

	Australia	Germany	The Netherlands
n	14	48	51
Mean age , y (SD)	46.8 (14.9)	46.2 (12.4)	50.6 (13.3)
% women	64	51	63
Median disease duration, y (interquartile range)	12 (5-18)	9 (4-15)	12 (4-19)
% wheelchair use	36	41	49
% use of artificial ventilation	64	40	37

* p-value for between-country differences (analysis of variance and Kruskal-Wallis tests)

Table 2 Mean SF-36 scores of patients with late-onset Pompe disease from five countries.

Scales	Australia (n=14)	Germany (n=48)	The Netherlands (n=51)
Physical health			
Physical functioning	25.0	23.8	26.0
Role functioning-physical	46.2	52.3	49.5
Bodily pain	61.1	67.4	70.9
General health	46.5	48.6	50.8
Mental health			
Vitality	43.6	48.1	51.5
Social functioning	58.9	69.9	67.8
Role functioning-emotional	56.4	86.8	79.3
Mental health	67.1	64.7	75.5

* p-value for between-country differences (analysis of variance)

Comparison with general population

For the Dutch patients (n=51), the adjusted mean SF-36 scores were compared to the general population (figure 1). Overall, patients with late-onset Pompe disease reported significantly poorer quality of life on the physical functioning, role functioning-physical, general health, vitality, and social functioning scales ($p<0.001$ on all scales). The difference was most profound for the physical functioning scale: the adjusted mean score of patients was 29.3 compared to 83.1 of the general population. No significant differences were found for the bodily pain, role functioning-emotional, and mental health scales.

Relationship between SF-36 scores and clinical characteristics

Figure 2 presents the adjusted mean SF-36 scores in four groups of patients with different degrees of disability, as defined by wheelchair use and use of artificial ventilation. The groups differed only on the physical functioning, social functioning, and role functioning-emotional scales.

United Kingdom	United States	Total	p*
20	77	210	
49.6 (13.2)	47.4 (14.3)	48.1 (13.5)	0.52
42	52	54	0.48
12 (4-16)	11 (6-16)	11 (5-17)	0.43
58	45	46	0.67
60	46	45	0.23

United Kingdom (n=20)	United States (n=77)	Total (n=210)	p*
17.5	25.3	24.3	0.75
32.0	44.0	46.2	0.44
62.9	60.9	65.0	0.21
51.3	45.8	48.2	0.73
37.2	40.6	44.8	0.01
63.2	63.3	65.6	0.52
68.4	67.3	73.9	0.03
66.8	71.5	70.2	0.04

Multivariate regression analyses showed that patients who needed a wheelchair scored on average 23.6 points lower on the physical functioning scale and 15.1 points lower on the social functioning scale than patients who did not need a wheelchair (B=-23.6 and -15.1, p<0.001). The use of artificial ventilation was associated with lower physical functioning scores (B=-8.4, p=0.004). Independent from wheelchair use and use of artificial ventilation, a longer disease duration was associated with lower physical functioning scores (B=-0.5, p=0.01), but with higher role functioning-physical scores (B=1.0, p=0.04) and higher mental health scores (B=0.5, p=0.02).

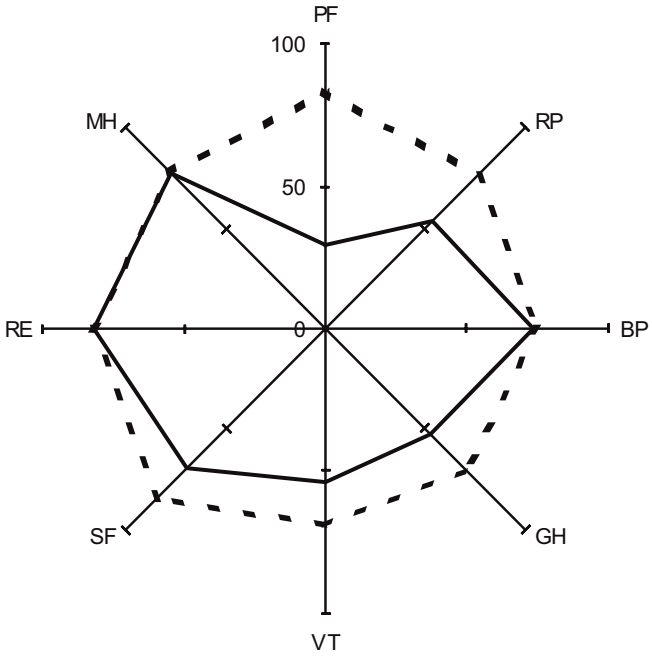

Figure 1 Quality of life in 51 Dutch late-onset Pompe patients compared to the Dutch general population. Solid line=Pompe (n=51), dashed line=general population (n=1742). Values are mean scores for SF-36 scales, adjusted for age and sex. The center of the graph represents the lowest possible score on each scale. PF=physical functioning, RP=role functioning-physical, BP=bodily pain, GH=general health, VT=vitality, SF=social functioning, RE=role functioning-emotional, MH=mental health.

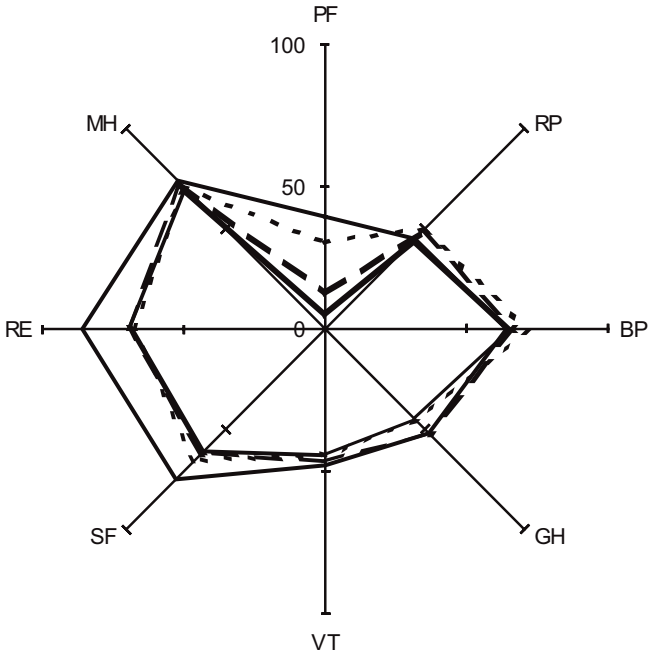

Figure 2 Quality of life in late-onset Pompe patients related to disability.
Solid line=no wheelchair, no artificial ventilation (n=74), dashed line=only wheelchair (n=32), dotted line=only artificial ventilation (n=35), thick black line=wheelchair and artificial ventilation (n=56). Values are mean scores for SF-36 scales, adjusted for age and sex. The center of the graph represents the lowest possible score on each scale. Data on wheelchair and ventilator use were missing for 13 of the 210 participants. PF=physical functioning, RP=role functioning-physical, BP=bodily pain, GH=general health, VT=vitality, SF=social functioning, RE=role functioning-emotional, MH=mental health.

Follow-up

Of the 51 Dutch patients who started the study, 38 completed the 1-year follow-up questionnaire. One of the patients had died between the baseline and follow-up measurement; for the other non-responders at follow-up the reason was not recorded. Age, sex, duration of disease, wheelchair use, and dependency on artificial ventilation did not differ significantly between patients who participated at the 1-year follow-up (n=38) and those who did not (n=13).

Twenty-seven of the 38 participants indicated deterioration in their physical situation over the last year, as measured on the five-point scale. None of the participants reported improvement. Most patients (n=15) reported increased muscle weakness or a diminished walking ability. Of this group, seven patients also mentioned deterioration in pulmonary function. Three patients experienced deterioration in pulmonary function but not in skeletal muscle function. No significant differences in scores were found for any of the SF-36 scales between baseline and 1-year follow-up, whether including all patients or only the 27 who indicated deterioration in their clinical condition.

Discussion

Although Pompe disease is rare, we obtained data from 210 patients from five countries. We found that late-onset Pompe patients scored low on the physical health scales of the SF-36, while their scores on the mental health scales remained relatively high.

The SF-36 was chosen as a measure of quality of life because it is widely used in a variety of health conditions, and validated translations were available in several languages. Because the instrument had not been used before in late-onset Pompe disease, an evaluation of its psychometric properties in this population was indicated. We found good internal consistency on all scales and good test-retest reliability on all but one scale. In combination with a low percentage of missing values these findings suggest that the SF-36 is a useful instrument for the assessment of quality of life in patients with late-onset Pompe disease. Floor effects were found for the physical functioning and role functioning-physical scales and ceiling effects for the role functioning-physical, bodily pain, role functioning-emotional, and social functioning scales. Comparable percentages of floor and ceiling effects on these scales were also reported for other patient populations.[16,17] These effects make the scales less responsive to changes at the ends of the scale, which should be kept in mind when studying very healthy or very ill patients.

Before further interpreting the results, the composition of the study population should be discussed. The recruitment of patients through patient organizations is a potential source of selection bias, as this group may be particularly motivated and perhaps more severely affected. However, it should be noted that our study population covers the entire range of disease severity, from mildly affected to fully wheelchair and ventilator dependent. Furthermore, despite differences in response rate, general patient characteristics were comparable across countries.

No significant between-country differences were found for the physical health scales. Although the scores on some of the mental health scales differed between countries, these differences were not consistent in direction and magnitude. We therefore conclude that this international sample of 210 patients can be considered as one reference group for future studies.

Patients with late-onset Pompe disease in the Dutch subgroup reported significantly poorer quality of life compared to the general population on all physical health scales except bodily pain and on the scales vitality and social functioning. The mental health and role functioning-emotional scores of the patients were equivalent to the scores of the general population. This can be explained by the fact that in late-onset Pompe disease, limitations in daily activities develop over a long period. During this period patients may have adapted to the situation and adjusted their expectations ('response shift').[18,19] Given the comparability between the patient populations from different countries, we conclude that the results in the Dutch subgroup can be generalized to the international population of patients with late-onset Pompe disease.

The SF-36 physical functioning scale clearly discerned the four patient groups with different disability status. In contrast, the role functioning-physical, bodily pain, general health, vitality, and mental health scales did not differ between groups. On the role functioning-emotional and social functioning scales, patients who did not use a wheelchair or artificial ventilation scored relatively high and could be discerned from the three groups of patients using one or both of these aids. Among these last three groups no difference in score was found, suggesting that the extent of disability does not influence the SF-36 scores on these domains. Together with the independent positive effect of disease duration on the role functioning-physical and mental health domains, this may be another indication of adaptive coping behavior in this patient population.

No significant differences in SF-36 scores were found between the baseline and the 1-year measurement in the group who indicated a change in their overall physical situation. This could mean that the changes in physical situation were not accompanied by a change in quality of life. Another possibility is that the changes in physical situation were accompanied by a change in quality of life, but that the SF-36 was not able to capture these changes. The fact that the SF-36 did not show a difference from the baseline measurement on physical functioning, although on this domain a relevant change was reported, supports the second explanation. The SF-36 is a generic measure of quality of life and apparently does not cover all aspects relevant for late-onset Pompe disease. We therefore recommend adding symptom-specific quality of life scales. Domain-specific scales such as fatigue, depression and handicap scales may also be relevant when the aim is to measure the impact of the disease on a patient's well being.

On balance, patients with late-onset Pompe disease score markedly low on the physical health scales of the SF-36. At the same time they function relatively well on the mental health domains of quality of life, probably as a result of adaptive coping with the disease. The international patient population in the present study is a suitable reference group for future studies in late-onset Pompe disease. In these future studies, symptom-specific instruments should supplement the SF-36 in the measurement of quality of life.

Acknowledgements

The authors thank Ria Broekgaarden (Vereniging Spierziekten Nederland), Randall and Marylyn House (Acid Maltase Deficiency Association, US), Thomas Schaller (Selbsthilfegruppe Glycogenose Deutschland), Allan Muir (Association for Glycogen Storage Diseases, UK) and Bob Morrison (IPA representative, Australia), for help in the organizational part of the study.

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Chapter 8

Fatigue: an important feature of late-onset Pompe disease

M.L.C. Hagemans[1,4], S.P.M. van Schie[1], A.C.J.W. Janssens[2], P.A. van Doorn[3], A.J.J. Reuser[4], A.T. van der Ploeg[1].

[1]Department of Pediatrics, Division of Metabolic Diseases and Genetics, [2] Department of Public Health, [3] Department of Neurology, [4]Department of Clinical Genetics, Erasmus MC Rotterdam, the Netherlands

Submitted

Abstract

Objective: To investigate the prevalence and severity of fatigue in adult patients with Pompe disease.

Methods: The Fatigue Severity Scale (FSS) was assessed in an international population of 225 adults with Pompe disease, a metabolic disorder presenting as a slowly progressive proximal myopathy. The FSS scores were compared to those of healthy controls and the relationship between the level of fatigue and other patient characteristics was investigated.

Results: The mean age of the participants was 47 (SD 13) years and the mean disease duration 11 (SD 8) years. Forty-three percent used a wheelchair and 46% had respiratory support, 29% needed both. Sixty-seven percent of the participants had a FSS score $\geq$5, indicating severe fatigue. The mean FSS score was 5.2 (SD 1.5), which was significantly higher than that of healthy controls ($p<0.001$). Fatigue was not related to age, sex or disease duration. Patients who used a wheelchair or respiratory support were on average more fatigued than those who did not ($p=0.01$). However, of the patients who did not use these aids, 59% also had a FSS score $\geq$5. FSS scores were highest among patients who reported a high frequency of sleep disorders, but patients who never experienced sleep difficulties were also fatigued (mean FSS score=4.8).

Conclusion: Fatigue is highly prevalent among both mildly and severely affected adult patients with Pompe disease. The FSS appears a useful tool in assessing fatigue in Pompe disease.

Keywords

Pompe disease, α-glucosidase, lysosomal storage disorder, myopathy, Fatigue Severity Scale

Introduction

Pompe disease (glycogen storage disease type II, acid maltase deficiency) is an autosomal recessive disorder caused by deficiency of the enzyme acid α-glucosidase. As a result of this deficiency, lysosomal glycogen cannot be degraded and accumulates in the lysosomes of virtually all body tissues.[1,2] This leads to a broad clinical spectrum ranging from a severe, classic infantile phenotype with generalized muscle weakness, a hypertrophic cardiomyopathy and death usually before the first year of life[3] to a slowly progressive proximal myopathy without involvement of the heart. Patients on this end of the spectrum are described as having 'late-onset'[4,5] or 'non-classic'[6] Pompe disease and may present at any age, sometimes as late as the sixth decade of life. Eventually they may become wheelchair-bound and dependent on artificial ventilation.[1,2]

Besides symptoms related to weakness of the skeletal and respiratory muscles, non-motor problems such as fatigue can also have a profound and disabling impact on the patients' lives. Fatigue is difficult to define, as it is often a non-specific and subjective complaint. Two suggested definitions are 'extreme and persistent tiredness, weakness or exhaustion-mental, physical or both'[7] and 'difficulty in initiation of or sustaining voluntary activities'.[8] Although fatigue is a frequent symptom in many chronic disorders, it has received little attention in Pompe disease and was only sporadically reported.[9-13] In a recent study on the clinical condition of late-onset Pompe patients we found that 76% of the study population reported symptoms of fatigue and that fatigue was among the first complaints for 24%.[4] In the present study, we investigated the prevalence and severity of fatigue in more detail in a large, international group of adult patients with Pompe disease and studied the associations between fatigue and several other patient characteristics.

Methods

Patients and procedures

Data were obtained between May 2002 and January 2004 as part of an ongoing international study on the natural course of Pompe disease in children and adults.[4,14,15] The medical ethical committee of Erasmus MC approved the project and the participants provided informed consent. Patients were recruited through patient organizations affiliated with the International Pompe Association (IPA). Participants were asked to complete a booklet of questionnaires, including one on fatigue for the patients of 18 years and older. The levels of fatigue in our study population were compared to those of healthy controls that were described previously in a study on immune-mediated polyneuropathies. This comparison group consisted of 113 healthy persons, 48% female, with a mean age of 54 (SD 15) years.[16]

Fatigue assessment

The severity and impact of fatigue was assessed using the Fatigue Severity Scale (FSS).[17] The total FSS score is the average of the 9 item scores and ranges from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'). Scores of 4 and higher indicate that patients are suffering from fatigue and scores of 5 and higher that patients are suffering from severe fatigue.[16,18,19] We used the validated English and Dutch translations of the FSS,[16,17] and a German version that was translated by a certified translator. The FSS has demonstrated good internal consistency, reliability and validity in studies among patients with multiple sclerosis, immune-mediated polyneuropathies and chronic hepatitis C[16,17,20] and is easy to complete. In the present study, individual item scores were missing for only 4% of the study population; the maximum number of missing items per patient was 3. When individual item scores were missing, the FSS score was calculated with the remaining items.

Other information

Additional information was gathered on date of birth, year of diagnosis, sex, use of wheelchair or walking aids, use of respiratory support, number of hours respiratory support per day, and presence of sleep disorders as indicated by the patient ('never', 'occasionally', or 'often'). Disease duration was calculated as the time between diagnosis and questionnaire completion.

Statistical analyses

Differences between countries in age, age at diagnosis, disease duration and FSS score (UK, USA, the Netherlands and Germany) were tested using one-way analysis of variance (ANOVA) and in sex, wheelchair use and use of respiratory support by χ^2 tests. Mean scores of our study population were compared to the scores of healthy controls by calculating the t ratio using the published mean and standard deviation.[16,21] Internal consistency was evaluated with Cronbach's α coefficient and test-retest reliability with the intraclass correlation coefficient.[22] The test-retest reliability was determined in a subgroup of 34 Dutch patients who completed the FSS twice, with approximately one month between both measurements. The relation between FSS score and age, disease duration and number of hours ventilation per day was evaluated with Spearman's rank correlation coefficient. Differences in mean FSS score between groups based on wheelchair and ventilator use and on the self-reported frequency of sleep disorders were tested with ANOVA. All analyses were performed using SPSS for Windows (version 11.5). A p-value ≤ 0.05 was considered statistically significant.

Results

Patient characteristics

Two hundred twenty-five patients of 18 years and older completed the FSS. The mean age

of the study population was 47 (SD 13) years and 54% were women. The mean disease duration was 11 (SD 8) years. Forty-three percent used a wheelchair and 46% used respiratory support, 29% needed both. The study population included patients from the United States (n=75), the Netherlands (n=50), Germany (n=50), the United Kingdom (n=17), Australia (n=13), Canada (n=8), Austria (n=3), Switzerland (n=2), Belgium, Denmark, Italy, Luxembourg, Spain, New Zealand and Taiwan (all n=1). No statistically significant differences in patient characteristics between the countries were found.

FSS scores

The mean FSS score of the study population was 5.2 (SD 1.5). Seventy-eight percent of the patients had a FSS score of 4 or higher ('fatigued') and 67% a FSS score of 5 or higher ('severely fatigued'). The distributions of item scores are presented in the table. Items on which 75% or more of the patients scored 5 or higher were mainly related to physical functioning: 'my fatigue prevents sustained physical functioning', 'fatigue interferes with my physical functioning' and 'exercise brings on my fatigue'. Sixty-five percent of the patients classified fatigue among their three most disabling symptoms.

The mean FSS score of our study population was significantly higher than the score of healthy controls (mean FSS score 2.9, $p<0.001$). Although the mean FSS score of the German Pompe patients was lower than the scores of patients from the United kingdom, the United States and the Netherlands (figure 1), it was still significantly higher than that of the Dutch healthy controls ($p<0.001$). The FSS showed excellent internal consistency in our international study population (Cronbach's $\alpha=0.92$ 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).

Table Means and distribution of Fatigue Severity Scale item scores of 225 adult patients with Pompe disease.

Item	Mean	Score distribution (%)		
		1-3	4	5-7
My motivation is lower when I am fatigued	5.7	9	3	88
Exercise brings on my fatigue	5.7	10	6	84
Fatigue interferes with my physical functioning	5.5	14	5	81
My fatigue prevents sustained physical functioning	5.4	18	6	76
I am easily fatigued	5.3	16	9	75
Fatigue interferes with carrying out certain duties and responsibilities	5.0	23	7	70
Fatigue interferes with my work, family, or social life	4.9	24	9	67
Fatigue is among my three most disabling symptoms	4.8	29	6	65
Fatigue causes frequent problems for me	4.8	26	11	63

Item scores range from 1 (strongly disagree) to 7 (strongly agree). The items are ranked by descending mean item score.

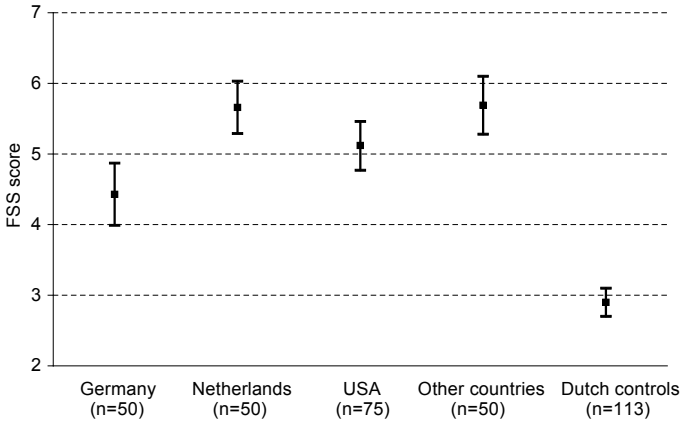

Figure 1 Mean scores (95% CI) on the Fatigue Severity Scale of adult patients with Pompe disease from different countries.

FSS scores differed significantly between countries when tested with ANOVA ($p<0.001$). Scores of healthy controls were obtained from the literature.[16]

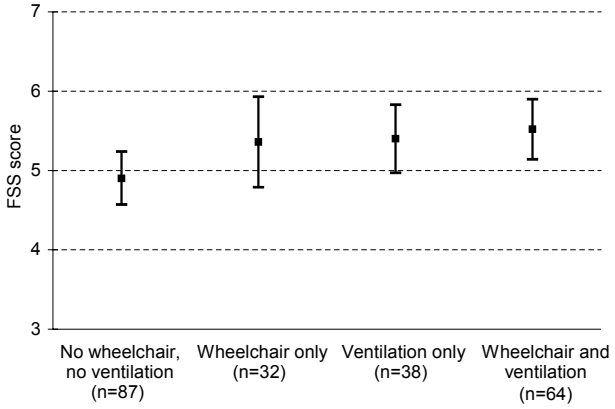

Figure 2 Mean scores (95% CI) on the Fatigue Severity Scale of adult patients with Pompe disease related to wheelchair use and use of respiratory support.

Relationship between fatigue and patient characteristics

FSS scores were not related to sex ($p=0.26$), age or disease duration ($r=-0.05$ and -0.03, $p>0.47$). Figure 2 shows the FSS score in groups based on wheelchair and ventilator use. When tested in four groups, no significant differences in FSS score were found, but patients who did not use a wheelchair or respiratory support were less fatigued than those who used one or both of these aids (FSS score=4.9 vs. 5.4, $p=0.01$). However, even in the group of patients who did not use a wheelchair or respiratory support, 71% had a FSS score ≥4 and 59% had a FSS score ≥5. Within the group of patients who used respiratory support, FSS scores were not correlated to the number of hours of ventilation per day ($r=0.06$, $p=0.57$). Although the FSS scores differed significantly between patients reporting 'never', 'occasionally' and 'often' sleep disorders, the scores were high in all three groups (mean FSS score 4.8, 5.3 and 5.6, respectively; $p=0.01$).

Discussion

This study shows that fatigue is prevalent in the entire spectrum of mildly and severely affected adult patients with Pompe disease. The FSS scores in this international group of Pompe patients were significantly higher than the scores of healthy controls. Although we found a significant difference in FSS score between patients with and those without wheelchair or respiratory support, even in the least affected group more than half of the patients had FSS scores ≥5, indicating severe fatigue. FSS scores were not correlated with the duration of disease. The high level of fatigue in our study population, as measured with the FSS, is comparable to that of other chronic disorders such as postpoliomyelitis syndrome (mean score 5.7, mean age 52, SD 8, n=65)[23] and multiple sclerosis (mean score 5.3, mean age 45, SD 10, n=25).[17]

Although all mean FSS scores were high, significant differences existed between patients from different countries. The lowest scores were obtained in the German population. This could not be explained by differences in general characteristics. It is conceivable that the impact of fatigue differs somewhat across countries, since social attitudes, expectations and roles may differ as well.[24] It should also be noted that the German translation of the FSS had not been used before and needs further (cross-cultural) validation. Yet, excellent internal consistency in all languages, as well as good reliability, suggests that the FSS can be a useful tool for assessing fatigue in Pompe disease.

For an optimal treatment of fatigue it is important to know why it is so prominently present in Pompe disease. In a recent review the contribution of 'central' and 'peripheral' components to fatigue in neurological disorders has been discussed.[8] In Pompe disease, a peripheral cause of fatigue, resulting from muscle weakness, is perhaps the most likely explanation. Especially relevant with respect to fatigue in Pompe disease is weakness of the respiratory muscles. Respiratory insufficiency may lead to fragmented sleep, which in turn may lead to daytime sleepiness and fatigue.[5] In the present study, patients who reported 'often' or 'occasionally' sleep disorders were on average more fatigued, but patients who reported to have 'never' sleep difficulties also had high FSS scores. It is possible that fragmented sleep due to respiratory insufficiency has remained unnoted in some of the patients in the latter group, and we and others previously advised that respiratory function should be monitored in all patients with Pompe disease, irrespective of their motor function.[4,25,26]

Another possible explanation is the relationship between fatigue and depression.[27-29] We did not investigate the presence of depression specifically, but found earlier that patients with Pompe disease score equal to the general population on the mental health scale of the SF-36, a health-related quality of life questionnaire.[14] Nevertheless it is recommended to study the possible influence of depression in more detail in future studies, for example by means of the Hospital Anxiety and Depression Scale.[30]

Thus, although a peripheral cause of fatigue is probably the most important factor, the underlying mechanisms of fatigue in Pompe disease are in fact not known yet and a possible central contribution should not a priori be excluded in future studies. Noteworthy, in a pilot study with enzyme replacement therapy (ERT) in three patients with moderate to severe late-onset Pompe disease, less fatigue and increased energy was one of the first improvements reported by the patients.[31] This was independent of disease severity and motor response to treatment. It would therefore be interesting to include a standardized measure of fatigue in future clinical trials on the effect of ERT. In multiple sclerosis, Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy adherence to an aerobic training program resulted in a significant decrease in fatigue and an improvement in physical fitness and quality of life.[32,33] Part of the training effect is probably due to increased fitness of the participants and social aspects of the intervention,[32] and in this respect it is worthwhile to study the effects of a medically supervised low-intensity training program on fatigue and general well being of patients with Pompe disease.

In conclusion, our findings indicate that fatigue is highly prevalent among adult patients with Pompe disease. It is present in both mildly and severely affected patients and is independent of disease duration. The FSS appears a useful tool for the assessment of fatigue in adult patients with Pompe disease. Further research is needed to unravel the pathophysiological mechanism and to identify targets for fatigue management.

Acknowledgements

The authors thank the patients and the International Pompe Association for their contribution to the study and Tom de Vries Lentsch for preparing the figures.

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Chapter 9

Impact of late-onset Pompe disease on daily life and participation

M.L.C. Hagemans[1,4], P. Laforêt[5], W.J.C. Hop[2], I.S.J. Merkies[6], P.A. van Doorn[3], A.J.J. Reuser[4], A.T. van der Ploeg[1].

[1]Department of Pediatrics, Division of Metabolic Diseases and Genetics,
[2] Department of Epidemiology and Biostatistics, [3] Department of Neurology,
[4]Department of Clinical Genetics, Erasmus MC Rotterdam, the Netherlands
[5] Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière,
Assistance Publique-Hôpitaux de Paris, France
[6]Department of Neurology, Spaarne Hospital, Hoofddorp, the Netherlands

Submitted

Abstract

Background: Pompe disease is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase and affecting muscle strength and respiratory function. With the prospect of enzyme replacement therapy, insight into the social consequences of the disease becomes even more relevant. The Rotterdam Handicap Scale could be a good instrument to assess these consequences among adult patients with Pompe disease.

Objective: To measure the impact of the disease on the level of participation (defined as a person's involvement in life situations; previously called 'handicap') and to evaluate the applicability of the Rotterdam Handicap Scale (RHS) for its use in Pompe disease.

Methods: 257 adults with Pompe disease from different countries completed the RHS, the SF-36 health survey, and a questionnaire on medical history and current disease status. RHS scores were compared between patient groups from different countries and related to patient characteristics and SF-36 scores. The psychometric properties of the RHS were evaluated.

Results: The mean RHS score in the total, international population was 25.9 ± SD 6.5 on a scale of 9 to 36 (higher scores indicating better participation). No significant differences in RHS score were found between countries or between the different language versions of the RHS. Individual item scores were lowest for the items 'domestic tasks indoors', 'domestic tasks outdoors', and 'work/study'. The RHS showed good internal consistency, excellent test-retest reliability, and did not have floor or ceiling effects. The mean RHS score differed significantly between patients with and without respiratory support (22.9 vs. 28.5, $p<0.001$) and patients with and without a wheelchair (20.9 vs. 29.5, $p<0.001$). Although the use of respiratory support strongly correlated with wheelchair use, both factors were independently related to the RHS score. The effect of wheelchair use, however, was much larger than the effect of respiratory support. The RHS correlated significantly with all SF-36 subscales except mental health.

Conclusions: The Rotterdam Handicap Scale showed good psychometric properties in a large group of adults with Pompe disease and seems suitable for the assessment of participation in this patient population. Pompe disease has a large impact on the daily life of patients, and in particular on the ability to fulfill their work or study.

Introduction

Pompe disease (glycogen storage disease type II or acid maltase deficiency) is an autosomal recessive disorder characterized by progressive loss of muscle- and respiratory function. The symptoms are caused by deficiency of the lysosomal enzyme acid α-glucosidase, resulting in storage of membrane bound glycogen.[1] The disease is rare with an estimated frequency of 1 in 40,000 births[2,3] and could until recently only be treated with supportive measures such as the use of overnight ventilation. A causal treatment, enzyme replacement therapy, is now in the final stages of development for both the severe classic infantile and the more slowly progressive late-onset or non-classic forms of the disease.[4-7]

Several measures have been used to assess disease severity in Pompe disease and to evaluate treatment effects. Following WHO's international classification of functioning, disability and health (ICF), the consequences of disease can be measured on three dimensions: impairments of body functions and structure (body level), activity limitations (individual level), and restrictions in participation, previously known as 'handicap' (societal level).[8] The effects of enzyme therapy in late-onset Pompe disease have been evaluated on the level of body function, for example by the measurement of skeletal muscle strength and pulmonary function.[5] These are the direct physiological consequences of the underlying enzyme deficiency and the accumulation of glycogen. Other measures evaluated outcome on the individual level, assessing activity limitations such as difficulties in walking or climbing stairs. For example, for patients on enzyme replacement therapy an improvement of muscle function was found using the Gross Motor Function Measure.[5,9] In children and adolescents with Pompe disease, disability has been assessed using an adapted version of the Pediatric Evaluation of Disability Inventory.[10,11]

The third level of measurement, which assesses participation restrictions, has not received much attention in Pompe disease so far. 'Participation' is defined as the nature and extent of a person's involvement in life situations. In the previous WHO framework (international classification of impairments, disabilities, and handicaps; ICIDH)[12] this concept was referred to as 'Handicap'. It comprises six dimensions: physical independence, mobility, occupation, social integration, economic self-sufficiency, and orientation[8] and indicates the social impact of a certain health condition. With new therapeutic options underway, this becomes more and more relevant for patients with Pompe disease. Measuring the impact of the disease on the level of participation provides insight into the burden of illness for the affected patients, but also gives an indication of what can be won when muscle damage is prevented or when further progression of the disease is stopped. The Rotterdam Handicap Scale could be a suitable instrument to assess participation in Pompe disease, because it is a brief and simple scale that showed good psychometric properties in other patient groups[13] and its items seem relevant for patients with late-onset Pompe disease.

The aim of this study, therefore, was to measure the impact of Pompe disease on daily life and participation and to evaluate the applicability of the Rotterdam Handicap Scale in an international population of adult patients.

Methods

Patients and procedures

Data were obtained as part of an ongoing study on the natural course of late-onset Pompe disease.[14-16] Patients were recruited through patient organizations affiliated with the International Pompe Association (IPA) in Australia, Canada, Germany, France, the Netherlands, the United Kingdom and the United States. A few patients who did not belong to a patient organization participated directly through our research centre at Erasmus MC. In France, patients were recruited both through the French patient organization and through the Institut de Myologie. The medical ethics committees of Erasmus MC and the Institut de Myologie approved the study and informed consent was obtained from the participants. Inclusion criteria for the present study were a diagnosis of Pompe disease and an age of 18 years or older.

Measurements

All patients received a self-report questionnaire, gathering information on medical history, current disease status and use of care. In the present study, information on date of birth, year of diagnosis, sex, nationality, use of wheelchair or walking aids, and use of artificial ventilation was used.

To assess participation, the Rotterdam Handicap Scale (RHS) was used. This scale was developed and validated in a Dutch population of patients with immune-mediated polyneuropathies aged 14 to 84 years (median 56).[13] For the present study we used the existing Dutch and English versions of the RHS, and a French and a German version that were translated by certified translators. Before adding the RHS to the questionnaire study, it was reviewed for its applicability in this patient population by a panel of researchers and physicians with experience in the field of Pompe disease and by a test group of five patients. The RHS consists of 9 questions on the topics mobility indoors, mobility outdoors, kitchen tasks, domestic tasks indoors, domestic tasks outdoors, leisure activities indoors, leisure activities outdoors, traveling and work or study. The scores per item range from 1 ('unable to fulfill the task or activity') to 4 ('complete fulfillment of the task or activity'). The total score ranges from 9 ('unable to fulfill any task or activity') to 36 ('able to fulfill all applicable tasks or activities'). In the present study, an RHS score was not calculated when 3 or more individual item scores were missing or non-applicable. This was the case for 2% of the completed RHS questionnaires. In case there were 1 or 2 missing or non-applicable items, a pro rata adjustment was made based on the remaining items.[13]

Health-related quality of life was assessed using the SF-36 health survey. The SF-36 is a multidimensional instrument including 8 subscales: physical functioning (10 items), role limitations due to physical problems (4 items), bodily pain (2 items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items), and mental health (5 items). One separate item assesses changes in health. Items are summed per scale and transformed into scores between 0 and 100. Higher values represent better function.[17,18] The SF-36 has been used in many different conditions and has been translated into more than 40 languages. In the present study, the following validated and cross-culturally adapted versions were used: English (USA), English (UK), English (Australian), Dutch, German, and French.[19,20]

Statistical analyses

Differences between countries were tested using one-way analysis of variance (ANOVA) for age, age at diagnosis, disease duration and RHS score and χ^2 tests for sex, % wheelchair use and % use of artificial ventilation. Differences in RHS scores between patients who completed the English, Dutch, German and French versions of the RHS were also tested with ANOVA.

To examine the psychometric properties of the RHS in this patient population, we evaluated the internal consistency (Cronbach's α), test-retest reliability (intraclass correlation coefficient) and the presence of floor and ceiling effects (percentage of participants with the lowest or highest possible score). The test-retest reliability was determined in a subgroup of 29 Dutch patients, who completed the RHS twice with a period of approximately one month between both measurements.

The relation between RHS score and age, disease duration, number of hours of ventilation/day, and SF-36 subscores was evaluated with Spearman correlation coefficients. The relationship between the RHS score and age and disease duration was also studied simultaneously using linear regression analysis. Differences in RHS score between men and women, wheelchair- and non-wheelchair users, and patients with and without artificial ventilation were evaluated by independent samples t-tests. Differences in RHS score between groups based on use of wheelchair and artificial ventilation and on use of wheelchair and walking aids were tested with ANOVA. All analyses were performed using SPSS for Windows (version 11.5). A p-value ≤ 0.05 was considered statistically significant. Results are presented as mean $\pm$ SD unless otherwise indicated.

Results

Study population

Of the 265 adult patients included in the study by June 2005, two did not complete the RHS and six had too many missing or non-applicable items to calculate the RHS

score. Thus, data from 257 patients were included in the analyses. The study population comprised patients from the United States (n=83), the Netherlands (n=51), Germany (n=50), France, (n=21), the United Kingdom (n=19), Australia (n=12), Canada (n=8), Austria (n=3), Switzerland (n=2), Belgium, Denmark, Greece, Italy, Luxembourg, New Zealand, Spain, and Taiwan (all n=1). Table 1 summarizes the general characteristics of the total group. Between-country comparisons were made for the United States, the United Kingdom, France, Germany, and the Netherlands; the other countries had a too limited number of patients. Age, age at diagnosis and disease duration did not differ significantly between countries, but it was noted that the French patients had the highest mean age (53 ± 13) and the shortest disease duration (7 ± 7, median 4). Wheelchair use ranged from 25% in the French group to 58% in the United Kingdom group, and use of respiratory support from 31% in the Dutch group to 63% in the United Kingdom group. These differences were, however, not statistically significant, possibly due to some rather small groups.

Table 1 General characteristics of the study population (n=257).

	Mean ± SD	Median (range)
Current age, y	48 ± 13	48 (19-79)
Age at diagnosis, y	37 ± 14	38 (0-68)
Disease duration, y	11 ± 8	10 (0-32)
	%	
Women/ men	53/ 47	
Wheelchair use	42	
Use of respiratory support	46	
Both wheelchair and respiratory support	28	

RHS scores

For the 257 adult patients who completed the RHS, the mean score was 25.9 ± 6.5 (median 27). The mean RHS scores ranged from 25.5 in Germany to 27.7 in France, but the differences between countries were not statistically significant. There were also no significant differences in mean scores between the patients who completed the English, Dutch, French and German versions of the RHS. No significant differences in mean RHS score were found between men and women. Table 2 shows the scores per individual item. The highest scores (meaning the least restrictions) were found for the items 'mobility indoors' and 'leisure activities indoors', the lowest for 'domestic tasks indoors', 'domestic

tasks outdoors', and 'work/study'. Noteworthy, 40% of the patients indicated that they were not able to fulfill their prior job or study.

Psychometric properties and correlations

The internal consistency of the RHS was good with a Cronbach's α of 0.87 in the total group, ranging from 0.75 for the French version to 0.90 for the English version. Test-retest reliability as measured in the Dutch subgroup was excellent with an intraclass correlation coefficient of 0.94. No substantial floor and ceiling effects were found: only 1% of the participants had the lowest possible score of 9 and only 8% the highest possible score of 36.

The RHS score was significantly correlated with age ($r=-0.18$, $p=0.004$) and disease duration ($r=-0.48$, $p<0.001$). In a simultaneous evaluation of both variables, only disease duration remained an important factor ($p<0.001$). The mean RHS score differed significantly between patients with and without respiratory support (22.9 vs. 28.5, $p<0.001$) and between patients with and without a wheelchair (20.9 vs. 29.5, $p<0.001$). Although the use of respiratory support strongly correlated with wheelchair use, ANOVA showed that both factors were independently related to the RHS score. The effect of wheelchair use, however, was much larger than the effect of respiratory support (figure 1). Figure 2 shows the difference in RHS scores between groups with increasing use of mobility aids ($p<0.001$). Among the patients who used respiratory support, the correlation between the number of hours of ventilation and the RHS score was -0.59 ($p<0.001$, figure 3). Table 3 shows the relations between the RHS and the various domains of the SF-36 health survey. The RHS correlated significantly with all subscales except for the mental health domain. The largest correlation ($r=0.83$, $p<0.001$) was found with the physical functioning scale of the SF-36.

Table 2 Means and distribution of Rotterdam Handicap Scale item scores of 257 adults with Pompe disease.

			Item score (% of patients)*				
Item	Mean score	Median score	0 (NA)	1	2	3	4
1. Mobility indoors	3.7	4	0	2	5	14	79
2. Mobility outdoors	3.1	3	2	5	18	34	41
3. Kitchen tasks	3.0	3	0	12	16	33	39
4. Domestic tasks indoors	2.4	2	3	21	28	25	23
5. Domestic tasks outdoors	2.1	2	2	31	35	18	15
6. Leisure activities indoors	3.8	4	0	0	4	10	85
7. Leisure activities outdoors	2.6	3	0	13	35	32	19
8. Drive a car, go by bus or ride a bicycle	2.6	3	2	17	26	29	27
9. Work/ study	1.9	1	14	40	9	12	25

Score 0=not applicable; Score 1=unable to fulfill these activities; Score 2=able to fulfill (a minimum of) these activities, mostly with the help of another person, or able to fulfill (partly) adapted work/study; Score 3=able to fulfill these activities mostly independently, sometimes needing help of another person, or able to fulfill partially the prior job/study; Score 4=able to fulfill these tasks independently, or able to fulfill completely the prior job/study.

Table 3 Correlations between the RHS and the SF-36 subscales for 257 adults with Pompe disease.

	Spearman's rank correlation coefficient	p-value
Physical functioning	0.83	<0.001
Role functioning-physical	0.22	0.001
Bodily pain	0.14	0.024
General health	0.17	0.007
Vitality	0.15	0.016
Social functioning	0.28	<0.001
Role functioning-emotional	0.14	0.032
Mental health	0.11	0.072

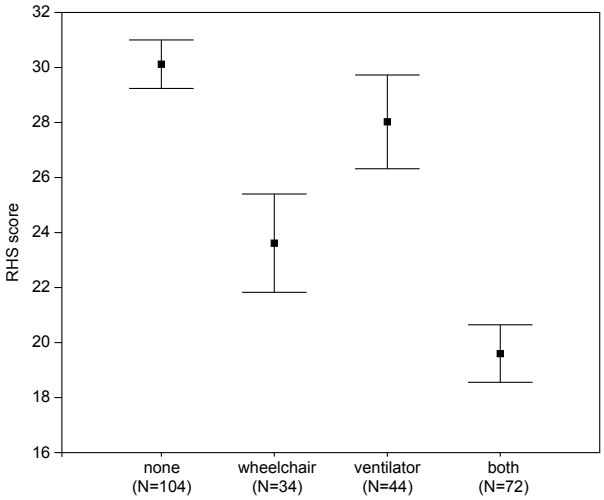

Figure 1 Mean scores (95% CI) on the Rotterdam Handicap Scale of adult patients with Pompe disease related to wheelchair use and use of respiratory support.

'None'=no wheelchair use, no use of artificial ventilation; 'wheelchair'=only wheelchair use; 'ventilator'=only use of ventilation; 'both'=use of both wheelchair and ventilation. All pairwise differences were significant ($p<0.02$). Information on use of wheelchair and/or respiratory support was missing for 3 patients.

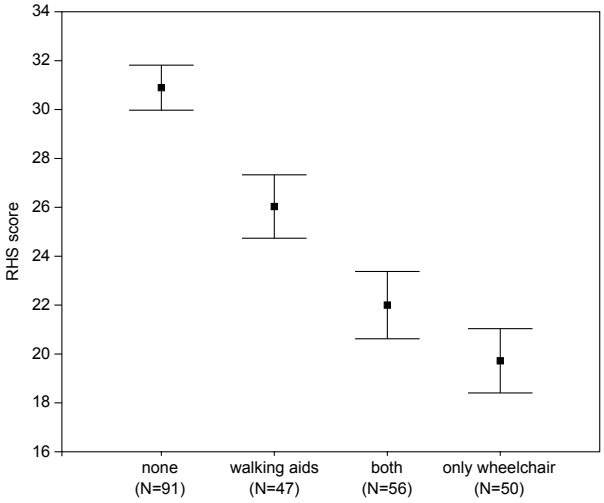

Figure 2 Mean scores (95% CI) on the Rotterdam Handicap Scale of adult patients with Pompe disease related to the use of mobility aids.

'None'=no use of mobility aids; 'walking aids'=only use of walking aids; 'both'=wheelchair alternated with walking aids; 'only wheelchair'=full wheelchair use. All pairwise differences were significant ($p<0.02$). Information on use of wheelchair and/or walking aids was missing for 13 patients.

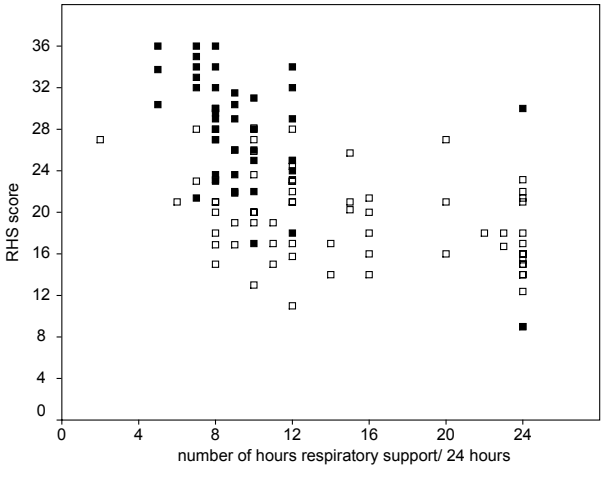

Figure 3 Correlation between RHS score and the number of hours ventilation/ 24 hours for 116 patients using respiratory support.

The open squares represent patients who also use a wheelchair; the closed squares represent patients who do not use a wheelchair.

Discussion

The prospect for patients with Pompe disease has changed considerably over the past years, in which enzyme replacement therapy moved from laboratory and animal studies[21-28] towards a real treatment option.[4-7] In this changing scene, knowledge of the social consequences of the disease becomes important with respect to the goals of treatment, estimation of costs, and reimbursement issues. This study is the first to systematically investigate the level of participation (formerly called handicap) in adults with Pompe disease. We found that the median RHS score was 27, whereas the maximum, which would be scored by an average healthy person, is 36. For comparison, the median score among patients with immune-mediated polyneuropathies was 31.5.[13] The clearly reduced average RHS score in Pompe disease indicates that in general, the disorder has a large impact on the daily life of patients. The individual item scores show that 40% of the participants were not able to return to their former job or study, while another 9% could do so only partially. Domestic tasks, both in- and outdoors, can be performed only minimally or not at all for more than half of the participants. On the other end, indoor mobility, including moving around in a wheelchair, and indoor leisure activities can be performed independently by 79% and 85%, respectively.

It could be argued that the low average RHS score that was found in the present study was due to the recruitment of patients through a patient organization, which could have led to a more severely affected study population. However, based on the wide range in age and disease severity and the general comparability across countries we believe that our international study population is representative for the entire population of adults with Pompe disease. For the separate countries, some form of selection bias might have played a role, especially in the relatively small patient groups.

The Rotterdam Handicap Scale was specifically developed to assess handicap as defined by the WHO, with particular focus on the dimensions physical independence, mobility, occupation, and social integration.[12,13] Although it was developed for use in immune-mediated polyneuropathies,[13,29-31] the scale assesses handicap in general and its items were considered very suitable for Pompe disease both by the patients and an expert panel. Because the RHS had not been used before in this disorder, and different translations were used, we also performed an evaluation of its psychometric properties. Good internal consistency[32] was found for all language versions. Test-retest reliability was excellent and the scale did not show a floor or ceiling effect. The mean scores did not differ significantly between patients from different countries and between patients who completed different language versions. The RHS score further showed significant differences between groups with different levels of severity, as assessed by the use of walking aids, wheelchair and artificial ventilation. This indicates the scale's discriminative ability.

Merkies et al. have assessed responsiveness to change of the Rotterdam Handicap Scale

in their study population of patients with immune-mediated polyneuropathies, and found good standardized-response mean scores.[13] We did not specifically evaluate the responsiveness to change in our study population, but when evaluating the changes that occurred in the course of two years in the Dutch subgroup of patients we found that the mean RHS score decreased significantly from 25.5 to 24.3 in these two years.[33]

When examining the relationship between the RHS score and other patient characteristics, we found that the mean RHS score decreased with increasing age and disease duration. Just like we found before for the percentage of patients using a wheelchair or artificial ventilation,[16] disease duration was the most important factor.

Being wheelchair-bound obviously hampers daily activities such as domestic tasks, outdoor leisure activities and traveling. We found that the level of participation decreased gradually with increasing use of mobility aids. The use of respiratory support had less impact on the level of participation than the use of a wheelchair. This is not surprising, since the RHS items are strongly directed towards body functionality. Patients who need ventilation only during the night may not experience many limitations during the day, when they do not use the ventilator. Indeed, we found a significant negative correlation between the number of hours respiratory support/ 24 hours and the RHS score. However, from figure 3 it also becomes clear that the decrease in RHS score with increasing use of ventilation is probably more related to the fact that the patients with more than 12 hours of ventilation/ 24 hours almost all needed a wheelchair as well.

The RHS score was significantly correlated to all SF-36 subscales except mental health. The scales 'social functioning', 'role functioning-physical', and 'role functioning-emotional' in fact also measure aspects of participation and societal roles,[18] so the correlation with the RHS score is in line with expectations and confirms the validity of the RHS for the measurement of participation in adults with Pompe disease.

In conclusion, the Rotterdam Handicap Scale showed good psychometric properties in this new patient population and seems suitable for the assessment of participation in late-onset Pompe disease. This study shows that Pompe disease has a large impact on the level of participation, and in particular on the ability of the patients to fulfill their work or study. In the light of upcoming new treatment possibilities for Pompe disease, further research into the impact of the disease on employment and the use of medical, paramedical and informal care seems indicated.

Acknowledgements

The authors thank the patients and the International Pompe Association (IPA) for their contribution to the study, and Tom de Vries Lentsch for layout of the figures.

The study was a joint initiative of the International Pompe Association and Erasmus MC and was sponsored in part by IPA.

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Chapter 10

General discussion

Over the past years, the continued efforts in research and development of enzyme replacement therapy gave new perspectives for patients with Pompe disease. Pioneering clinical trials have shown that this new therapy is capable of stabilizing or even improving the disease course. However, the number of patients that were included in the trials so far is small and it is to be expected that the full effect of the treatment can only be judged after many years of experience. Contrasting the course of disease in treated patients against data on the natural history and standardized follow-up of both treated and untreated patients will be essential.

In 2002 the International Pompe Association (IPA) and Erasmus MC recognized the need to enhance the understanding of the natural history of Pompe disease in children and adults, and the IPA/ Erasmus MC Pompe survey was started as a joint initiative. The goal of this project was to gather as much information as possible on the natural course and on the severity of disease in the patient population by means of self-report questionnaires. A second objective of this survey was to test the value of specific measurement scales for the assessment of disease severity and of changes over time. At this moment more than 300 Pompe patients have participated in this survey through Erasmus MC, the Institut de Myologie in Paris, and the IPA-affiliated patient organizations in Australia, Canada, France, Germany, the Netherlands, the United Kingdom and the United States. This thesis covers the baseline survey in the international patient population and the first two years of follow-up in the subgroup of Dutch patients. In this chapter the main findings are reviewed and some methodological issues are addressed. Finally, perspectives for future research and follow-up of patients are discussed.

10.1 MAIN FINDINGS

Natural course and clinical spectrum

The broadness of the clinical spectrum of Pompe disease has often been addressed in the literature[1,2] and is again striking in the large group of patients described in this thesis. From the data presented in chapter 3 to 5 a picture emerges of an extremely heterogeneous disease manifestation, with a wide range in age at onset, age at diagnosis, and progression of weakness in skeletal and respiratory muscles leading to artificial ventilation or wheelchair use. For most patients skeletal muscle weakness precedes diaphragm weakness, but this sequence does not hold for all patients. In accordance with our findings presented in chapter 4, a recent study on respiratory function and limb muscle weakness in 29 adults with Pompe disease found a significant, but weak correlation between respiratory and locomotor function, and the need for routine serial evaluations of both functions in patients with Pompe disease was stressed.[3]

The results presented in chapter 3 indicate that there is considerable overlap in symptoms and signs when patients are classified based on age at onset, and that no criteria could be defined to delineate distinct clinical subtypes. In chapter 4 it was noted that 60% of the adult patients already experienced mild muscular symptoms in childhood, again indicating that age at onset *alone* does not predict the severity and course of the disease. Chapter 5 further shows that the percentage of mildly and severely affected patients does not differ much between age categories, but that disease severity increases with the time since the start of disease symptoms. This implies that in general, the rate of disease progression is comparable between those patients whose symptoms start at a very young age and those who experience their first complaints much later. The fact that the 'starting point' differs but not the further course implies that the patients with an early start of symptoms on average will reach 'endpoints' like wheelchair and ventilator dependency at a younger age. In our study population we also found a subgroup (~25%) of patients under 15 years of age who needed intensive respiratory support, nutritional support in the form of tube feeding, and who were fully wheelchair dependent. The natural course in this subgroup of patients was more rapid and most of them already experienced problems within the first year of life (chapter 5). This subgroup of patients may compare to what has been called 'nontypical infantile Pompe disease' by Slonim et al.,[4] further highlighting the genuine spectrum of disease. In chapter 3 (table 2) it is shown that the patients in this subgroup with age at onset before the first year may have symptoms in common with classic infantile Pompe patients, such as hypertrophic cardiomyopathy, enlarged tongue, feeding problems and hepato(spleno)megaly. However, the results presented in this chapter also indicate that it is impossible to clearly delineate this subtype clinically or to predict the disease course. Genotype analysis together with detailed cellular and biochemical analyses might have prognostic value for these patients.

In chapter 6, prospective data on the natural course of the disease are presented for the Dutch participants. Already in this relatively small group of patients, changes were observed in mobility, respiratory support, functional activities and level of handicap over two years time. Late-onset Pompe disease is known as a slowly progressive disorder, but 'slow' clearly is a relative notion. Our results show that a few years may make the difference between being wheelchair dependent or not and between needing overnight ventilation or not. From the clinical trials with recombinant human α-glucosidase that have been performed at Erasmus MC,[5-8] we have learned that treatment needs to be started before irreversible muscle damage has occurred, and that the therapeutic window in patients with classic infantile Pompe disease is much smaller than in patients with a less rapidly progressive course. It was further noted that it is possible for mildly affected patients to regain muscle strength and function to near normal levels, while for severely affected patients stabilization of muscle- and pulmonary function seems the highest attainable goal.[8] However, it should be realized that the number of patients included in these trials was limited and that the exact 'point of no return' is still not known.

In this light, it is very difficult to determine the optimal time of intervention. It could be argued that, when broad scale enzyme replacement therapy becomes available, all patients with Pompe disease should start treatment as soon as the diagnosis is made. This is certainly true for patients with the classic infantile form of Pompe disease, where every day counts. For the other patients, however, this might not be the best strategy, as the number of patients who are diagnosed pre-symptomatically will grow over the next years with the development of new diagnostic procedures. The upcoming new techniques for determining acid α-glucosidase activity in neonatal blood spots[9-11] will not only detect classic infantile patients without any residual acid α-glucosidase activity, but also those with low level activity and a delayed onset of symptoms. The results from this thesis have elaborately shown the heterogeneity in age at onset of symptoms and rate of progression. This would mean that pre-symptomatic patients start to receive weekly or biweekly invasive, time-consuming and expensive infusions with enzyme replacement therapy, while possibly they could have remained symptom-free without treatment for perhaps more than 10 years after diagnosis. On the other hand, although we have shown that the average disease course is partly predicted by the time since diagnosis (disease duration), there are always exceptions to this general rule. This does not only apply to the subgroup of severely affected children described above, but also to individual adult patients who experience a period of sudden and relatively rapid decline. Therefore, one of the key topics for further research in Pompe disease is the identification of prognostic factors. This will be discussed in more detail in section 10.3.

Evaluation of assessment scales

The use of assessment scales and questionnaires is not very common in the field of inborn errors of metabolism. However, with new therapies emerging for many of these disorders, they will become increasingly important in the evaluation of the effects of treatment. For example, the evaluation of treatment effects in Fabry disease, another lysosomal storage disorder, involved the assessment of pain and quality of life scales.[12-16] In our trial with three late-onset Pompe patients, the primary outcome measures to evaluate the effect of enzyme therapy were the measurement of skeletal muscle strength and pulmonary function.[8] However, outcome was also evaluated on the level of activity limitations such as difficulties in standing, squatting, walking or climbing stairs by using the Gross Motor Function Measure.[8,17] In children and adolescents with Pompe disease, activity limitations have been assessed using an adapted version of the Pediatric Evaluation of Disability Inventory.[18,19] In adults, the Walton and Rankin scales are used.[20-22] Scales measuring participation or quality of life in Pompe disease have not been described before.

In chapter 7 to 9 of this thesis the results from the health-related quality of life questionnaire SF-36, the Fatigue Severity Scale (FSS), and the Rotterdam Handicap Scale (RHS) were presented and their applicability for patients with Pompe disease was discussed. The

results from chapter 4 to 6 already indicated the extent of disability in the study population by assessing the percentage wheelchair and ventilator use and the ability to perform specific movements. The results from the SF-36 confirm these findings in that patients with Pompe disease score markedly lower than the general population on the domains of physical functioning and role functioning-physical. The role functioning-emotional and mental health domains seem to be much less affected. The observation that patients with severe illness may maintain good quality of life equivalent to that of healthy people or less ill patients is well known in the field of cancer research[23,24] and was also described for other patient groups with severe physical limitations.[25,26] These findings have been explained by the concept of 'response shift'.[27-29] This means that when a person becomes ill he may shift his priorities and expectations in order to accommodate to the changed circumstances. Sprangers and Schwartz[27] discern three different aspects of this phenomenon: change in internal standards (e.g. a person's idea of poor functioning); change in the relative importance of different domains of quality of life (e.g. professional vs. family life); and changes in a person's definition of what quality of life is. It is likely that these processes are also present among the Pompe patients in our study population, as we suggest in chapter 7. It should be kept in mind, however, that our results are limited to health-related quality of life as measured with a generic questionnaire on a group level. To obtain more insight in the influence of the disease on the quality of life of individual patients and on mental health in particular, patient interviews held by an experienced clinical psychologist would be recommended.

The impact of the disease on daily life and level of participation, defined as the nature and extent of involvement in life situations[30] and assessed by means of the RHS, was considerable. A noteworthy finding was the large effect of Pompe disease on the ability of the patients to fulfill their work or study. The application of the third scale described in this thesis, the FSS, led to the conclusion that fatigue is a prominent symptom among adult patients with Pompe disease, even those who were less severely affected with regard to muscle and respiratory function. The underlying causes of fatigue in Pompe disease are not yet understood, but it is worthwhile to study the effects of both enzyme therapy and training programs on the prevalence and severity of this frequently occurring symptom. Further research into the causes and correlates of fatigue should include a measure of depression, as the SF-36 mental health scale gives only a rough indication. In addition to the SF-36 and FSS, the Hospital Anxiety and Depression Scale (HADS)[31,32] is currently included in the follow-up of a cohort of patients that visits our hospital every six months. Another factor that will be studied in more detail in these patients is the relationship between respiratory insufficiency, sleep disordered breathing, and daytime fatigue.

It is obvious that measurement scales like the FSS, RHS and SF-36 can not cover all aspects of a disease that are relevant for patients. Nevertheless, it seems justified to conclude that these scales turned out useful for the follow-up of adult patients with Pompe disease.

They measured relevant consequences of the disease, showed sufficient reliability and validity, and were brief and easy to complete. A point that needs some further attention is the responsiveness or 'sensitivity to change'. Responsiveness is normally assessed by the evaluation of the change in a measure over a timeframe in which the condition of the patient is known to change. For example, the measure can be applied before and after a treatment that has previously been shown to be efficacious. Different statistics can be used to indicate responsiveness, or sensitivity to change, such as the paired t-test, the effect size (ES) and the standardized response mean (SRM).[33] The ES compares the change in the measure under study to the standard deviation at baseline, while the SRM is the mean change in score divided by the standard deviation of this change. A large ES or SRM indicates a good sensitivity to change ('internal responsiveness').[33,34] It should be noted, however, that to fully evaluate the responsiveness of a scale, it should also be related to an external measure of change ('external responsiveness').[33,35]

Because we did not know beforehand whether any changes in FSS or RHS should be expected in two years time, we could not formally assess their responsiveness to change in our study population. When for example the FSS score does not change over two years, this could mean that the scale is not responsive or that there were in fact no changes in fatigue over this time period. The latter is very likely, because fatigue was shown to be present in the entire spectrum of disease and there was no correlation between disease duration and the level of fatigue as measured by the FSS (chapter 8). In patients with multiple sclerosis and Lyme disease, the responsiveness of the FSS was evaluated by comparing the change in score between 8 patients who received medication intended to reduce their fatigue and 11 patients who did not receive such medication and for whom no change in fatigue was expected. The mean FSS score showed a significant decrease from 5.7 to 3.6 points before and after treatment (paired t-test), while in the second group the difference was not significant.[36]

For the RHS, good SRM values were obtained in a group of 20 recently diagnosed patients with immune-mediated polyneuropathies, who were treated with intravenous immunoglobulin.[37] In our own study population, a significant decrease in mean score over two years was found, simultaneously with an increase in wheelchair use and in number of hours respiratory support (chapter 6). Furthermore, the test-retest reliability of the RHS in the same study population was excellent, indicating little within-person variability. These results suggest that the RHS will be able to detect a relevant change when one occurs, but this needs to be confirmed in further studies assessing the RHS over a timeframe in which the patients' condition is expected to change.

In chapter 7 it was concluded that the SF-36 seems useful for the assessment of health-related quality of life on a group level and for comparison between different groups of patients, but is not the most suitable scale for the measurement of changes over time in adults with

Pompe disease. The lack of responsiveness of generic health status questionnaires such as the SF-36 has been noted before.[38-40] If an instrument is intended for a wide range of disorders, some items may be irrelevant for one specific disease and are therefore not expected to change after treatment.[39-41] Furthermore, the presence of these non-useful items, and the need to restrict the length of the questionnaire, lead to a fewer number of relevant questions that are able to detect changes in a patient's situation.[40] For the SF-36, the presence of floor and ceiling effects in certain subscales also limits its responsiveness. This is especially true for the physical and emotional role functioning scales, as was already described by the SF-36 developers.[42] When many patients score at the 'ceiling' of a scale, further improvement cannot be measured, and when many patients score at the 'floor' detection of further deterioration is prevented.

Taking these considerations into account, the SF-36 may not be capable of measuring changes in health-related quality of life over time or as a result of treatment. Looking from the other side, the advantages of this scale are also clear: it allows comparison across different disorders, different countries and with healthy control groups, and is thoroughly evaluated with regard to reliability and validity. The question is, therefore, whether it should be included in the further follow-up of patients with Pompe disease or whether a more disease-specific scale should be used. After reviewing the literature on the comparison between generic and disease-specific scales, Streiner and Norman concluded that '... the advantages of disease specific scales may be more apparent than real; well-designed, reliable, and valid generic questionnaires appear to yield results that are comparable to disease-specific ones across a number of illnesses and instruments'.[40] Given the fact that a disease-specific instrument for Pompe disease currently does not exist, it seems sensible to continue the follow-up with the SF-36 while in the meantime identifying elements that should be included in a 'Pompe-specific' scale.

10.2 METHODOLOGICAL CONSIDERATIONS

Composition of the study population

Since this is the first study to describe such a large group of children and adults with Pompe disease, we cannot really compare the study population with data from the literature. However, some remarks can be made on the composition of our study population and the generalizability of our results. The possibility of over-representation of more severely affected patients was discussed in chapter 4, and it was concluded that although the real proportion of severely- vs. mildly affected patients cannot be known, our study population covers the entire spectrum of non-classic or late-onset Pompe disease with regard to age at onset, current age, disease severity and progression. From the studies described in chapter 7 and 9 we further learned that the patient populations from the different

countries were quite comparable, despite differences in response rate. Exceptions were a few countries with only a limited number of patients, who on average seemed to be more severely affected, but these did not influence the main conclusions for the total, international study population. However, it is to be expected that Pompe disease will receive more attention when a registered treatment becomes available, which will lead to an increase in the number of patients who are diagnosed in an early stage of the disease. Should newborn screening for Pompe disease be introduced in the future, this will further increase the proportion of late-onset patients who have only minor symptoms or who are still asymptomatic.

The number of children and adolescents in our study population was much lower than the number of adult patients. Using retrospective data on all enzymatic diagnoses of Pompe disease in the Netherlands between 1972 and 1996, Ausems et al. found a ratio infantile: juvenile: adult Pompe disease of 7:1:14.[43] In that study, the 'juvenile phenotype' was defined as patients presenting before 18 years of age and the 'adult phenotype' as patients who developed clinical signs after the age of 18. As discussed in chapter 3, using the age at onset as the criterion to assign a patient to either of the two phenotypes may lead to problems. Nevertheless, when arbitrarily defining 'juvenile' as patients under 18 years of age at the time of participation in the survey we found a ratio of 26:265= 1:10 in our total, international group of patients. When calculated for the separate countries, this ratio was in accordance with the findings of Ausems et al. for the Dutch and US subgroup. In the French, Canadian and Australian subgroups, there seemed to be an under-representation of young patients, while the number of children in the UK and German subgroups was relatively high (see also chapter 2, table 1).

Diagnostic issues

In chapter 1 we explained that the assessment of α-glucosidase activity in cultured fibroblasts or muscle tissue and DNA analysis in families at risk are the most reliable methods to confirm the diagnosis of Pompe disease. Because a muscle biopsy is more invasive, the method of choice is the assay in fibroblasts. However, the results from chapter 3 indicate that the majority of patients described in the literature were diagnosed by determination of the level of acid α-glucosidase activity in muscle. Fibroblasts were used in only a small number of patients. In contrast, the error-prone leukocyte assay was frequently used and led to false-negative results in 10% of the cases. Recently the leukocyte assay was improved by using acarbose to inhibit the interfering maltase-glucoamylase activity,[44] but this is a very new development and this assay was not yet used in the studies reviewed in chapter 3 or for the diagnosis of the participants in the IPA/ Erasmus MC Pompe survey.

As discussed in chapter 2 and illustrated in chapter 3, the diagnostic practice for the confirmation of Pompe disease varies between countries and in time. For patients

diagnosed in the past, the diagnosis is sometimes based on only a leukocyte assay or only on an increased glycogen content and/or abnormal morphology of muscle tissue (chapter 3). For the studies described in this thesis, we did not exclude any of these diagnostic methods. Patients were excluded from the analyses when they provided too little diagnostic information or when they indicated that the diagnosis was not (yet) officially confirmed. Of course, this approach does have its disadvantages. For example, the enzymatic or molecular diagnosis was checked for the Dutch subgroup of patients described in chapter 4. Nevertheless, for two patients with a decreased α-glucosidase activity initially measured in leukocytes we learned only later that this was not confirmed in muscle or fibroblasts and that in fact, the diagnosis was not conclusive. It may well be that the diagnosis was not fully conclusive for a comparable percentage (~4%) of participants from other countries. Although this percentage is relatively low and will not influence the conclusions from our group-level analyses, it is important to realize that these problems will remain present as long as the diagnostic routine for Pompe disease is not standardized between the different laboratories throughout the world.

Use of self-report questionnaires

There are many possible ways to administer a questionnaire or measurement scale, including a personal interview, a telephone interview, assessment within a clinical setting, and self-report by the patient. Each mode of administration has its advantages and disadvantages, and the choice for one of them depends on many factors, such as cost, practicality, the response rate one wishes to obtain, and the type of questions asked.[40,45] We have chosen to use a mailed self-report questionnaire. An obvious advantage of this approach is the low cost and limited timeframe needed to complete the study. Given the international character of the study, another advantage was the possibility to coordinate the survey from one central office at Erasmus MC. Streiner and Norman[40] mention as an additional advantage of mailed questionnaires that the tendency towards socially desirable answers is limited because of the absence of an interviewer (in person or on the phone).

A generally low response rate affecting the generalizability of the results is seen as the most important drawback of mailed questionnaires.[40] This does not seem to be the case in the studies described in this thesis as the overall response rate was high (see also chapter 7). To attain this good result, we followed a number of strategies that were proposed to increase the response rate,[40] such as giving advance warning that the questionnaire was coming, adding an accompanying letter, and adding a pre-stamped, pre-addressed envelope whenever possible, in cooperation with the local patient organization. The representatives of the patient organizations in the separate countries further increased the response rate by reminding their members of the survey by mail, e-mail, or telephone or through their newsletter. Another possible drawback of a mailed questionnaire is the fact that the researcher has little control over how well the questions are understood by

the participants[45] and that the answers on many items may remain uncompleted, illegible or invalid.[40] The patients participating in this survey were always given the possibility to explain their answers, give additional information or mark questions that were not fully comprehended in blank spaces designated for that purpose and to ask questions by mail, e-mail or telephone to the researchers or the IPA representatives. Moreover, the number of missing values was low for the items of the Pompe questionnaire that were used in the analyses as well as for the scores on the Fatigue Severity Scale, the Rotterdam Handicap Scale and the SF-36 health survey.

10.3 FUTURE PERSPECTIVES

Research in the field of lysosomal storage diseases has long been directed towards unraveling the underlying molecular cause, the pathophysiological mechanisms and the development of a therapy for so far untreatable disorders. Now that enzyme replacement therapy becomes a reality other issues emerge. For Fabry disease and mucopolysaccharidosis type I[46], market authorization for enzyme replacement therapy was given 'under exceptional circumstances', meaning that additional data will have to be provided in the coming years. For Myozyme®, marketing authorization in the European Union is given under the condition that the company will continue to study the effects in late-onset patients after the approval.[47] Furthermore, several issues including the optimal time to start the treatment and the optimal dosing regimen are not solved yet. The need for continued data collection on both treated and untreated patients is evident.

The studies described in this thesis have shown that 'soft', patient-reported information can complement more traditional outcome measures such as the assessment of muscle strength, respiratory function, and endurance testing. The additional value of 'the patient's point of view' is easily understood; the ultimate goal of any treatment is that the patient feels better and is able to resume his or her previous activities. The international approach of the IPA/ Erasmus MC Pompe survey, the use of standardized self-report measurement scales, and the cooperation with patient organizations has proven its value in the collection of this type of information. Expansion of the study to a yearly follow-up of all baseline participants will provide structured, longitudinal data that may serve as reference to fully understand the effects of treatment. Over time data from both treated and untreated patients will become available and many patients will become their own reference with regard to their scores on the standardized measurement scales.

Towards a core set of measurements for Pompe disease

In rheumatology, a discipline in which longitudinal observational studies constitute the majority of scientific publications,[48] a consensus was reached on a core set of essential

outcome domains: Health status, Disease process, Damage, Mortality, and Toxicity/adverse reactions. Each domain can be divided into several subdomains, assessable by specific instruments or individual variables.[48] A similar framework could also be useful for Pompe disease, especially given the relatively small number of patients per center and per country. In order to be able to draw conclusions on the issues mentioned above it is extremely important that the data collected in the various settings are comparable.

In table 1 a first attempt to such a framework is made, that could serve as a draft for further review and discussion among experts in the field of Pompe disease. Besides the obvious differences in symptoms, and thus in the identified subdomains, between rheumatic disorders and Pompe disease, there are also a few differences in the design of the framework. The same set of five core domains is presented, but for Pompe disease 'Disease consequences' is used instead of 'Damage', because the latter term has a connotation of irreversibility. Furthermore, the core domain 'Health status' is divided according to the different levels of measurement as suggested by the WHO[30] and contains the subdomains activity limitations, participation restrictions, and quality of life. In the following paragraphs the suggested follow-up measurements in the core domains 'Health status' and 'Disease consequences' will be discussed in more detail, first for infants and children and then for adolescents and adults. Disease process markers will be described separately.

Table 1 Core domains and subdomains for longitudinal observational studies in Pompe disease

Domain	Subdomain	
		Infants
Health status	Activity limitations	Self Care and Mobility scale of Pompe PEDI
	Participation restrictions	Social function scale of Pompe PEDI
	General/ quality of life	CHQ-Toddler form*
Disease process	Routine laboratory	CK, ALAT, ASAT, LDH
	Disease markers	Muscle glycogen and morphology? Urine tetrasaccharides?
Disease consequences	Heart involvement	LVMI, LVPWd
	Psychomotor development	AIMS, BSIDII
	Muscle strength	-
	Muscle function	-
	Respiratory function	-
	Fatigue	-
Toxicity/ adverse reactions		Listing of treatment
Mortality		Number and causes

* suggested, not used in Pompe disease yet.
** currently under development.
PEDI=Pediatric Evaluation of Disability Inventory; ALDS=AMC Linear Disability Scale; RHS=Rotterdam Handicap Scale; CHQ=Child Health Questionnaire; SF-36=Short Form-36 Health Survey; CK=Creatine kinase; ALAT=Alanine aminotransferase; ASAT=Aspartate aminotransferase; LDH=Lactate dehydrogenase; LVMI=left ventricular mass index; LVPWd= left ventricular posterior wall thickness; AIMS=Alberta Infant Motor Scale; BSIDII=Bayley Scales of Infant Development; HHD=Hand Held Dynamometry; GMFM=Gross Motor Function Measure; MRC score=Medical Research Council score (manual muscle testing); PedsQL-MFS=Pediatric Quality of Life Inventory-Multidimensional Fatigue Scale; FSS=Fatigue Severity Scale.

(adapted from Wolfe et al., J Rheumatol 1999; 26:484-489).

Follow-up measurements	
Children	*Adolescents/adults*
Self Care and Mobility scale of Pompe PEDI	ALDS*
Social function scale of Pompe PEDI	RHS
CHQ*	SF-36, Pompe-specific questionnaire**
CK, ALAT, ASAT, LDH	CK, ALAT, ASAT, LDH
Muscle glycogen and morphology? Urine tetrasaccharides?	Muscle glycogen and morphology? Urine tetrasaccharides?
-	-
-	-
HHD, MRC score	HHD, MRC score
GMFM, timed tests	Adapted GMFM**, timed tests
Spirometry	Spirometry
PedsQL-MFS*?	FSS
side-effects	
of death	

Suggested follow-up measurements for infants and children

For the measurement of activity limitations and participation restrictions in infants and children the three scales of the Pompe PEDI (Self Care, Mobility and Social Function) are suggested.[18,19] This is an adapted version of the PEDI for patients with Pompe disease between 0 and 20 years of age recently constructed by Haley et al., the developers of the original PEDI.[18,19,49] They tried to lower the 'floor' of the scale, increase the 'ceiling', and increase the sensitivity to change by adding more items to the Self Care and Mobility scales, leading to a total number of 114 mobility and 90 self care items. Although the Pompe PEDI currently contains too many items and is too difficult to complete without training to use as a self-report questionnaire, in a clinical setting it can be completed by a trained physician,

nurse or researcher and used as a follow-up measure. Furthermore, a new version that uses a computer-adaptive testing approach is currently under development. In this version the number of items that have to be completed will be limited because the questions are tailored to the ability level of each patient.[50] These developments will make the Pompe PEDI much easier to complete in a clinical setting, and perhaps it may also become useful for the IPA/ Erasmus MC Pompe survey in the near future.

The Child Health Questionnaire (CHQ) is proposed for the measurement of quality of life among children with Pompe disease. Like the SF-36, the CHQ has been used in different conditions and is available in several languages.[51,52] The CHQ describes child health by both 'child-related' scales and by scales that assess the impact of the child's health on the parents and family.[53] The CHQ-parent form (CHQ-PF50; 50 items divided in 11 scales and 2 single questions) assesses physical functioning, role functioning emotional/behavior, role functioning physical, bodily pain, general behavior, mental health, self-esteem, general health perceptions, parental impact-emotional, parental impact-time, family activities, family cohesion and change in health. The CHQ-PF50 is designed for the parents of children of 4 years and older.[53] A shorter version with 28 items is also available.[51,52] For children from the age of 10 years, the child form of the CHQ[54,55] can be completed, while for children between 2 months and 4 years a CHQ-Toddler form is being developed.[52] From the age of 14 years, the SF-36 can be used.[56]

Because at this moment the IPA/ Erasmus MC Pompe survey lacks a measurement scale specific for the follow-up of children with Pompe disease, inclusion of the above-mentioned measurement scales should be considered. In addition, fatigue in children could be assessed by means of the Multidimensional Fatigue Scale of the Pediatric Quality of Life Inventory (PedsQL). This instrument consists of 3 subscales (general fatigue, sleep/rest fatigue, and cognitive fatigue) and a total of 18 items. It comprises parallel child self-report and parent-proxy report forms.[57] However, before applying the measurement of fatigue in the IPA/ Erasmus MC Pompe survey or in the regular follow-up of children with Pompe disease, it should first be investigated whether the prevalence of fatigue in children is comparable to the high prevalence found in adults (chapter 8).

For the clinical follow-up of patients with classic infantile Pompe disease the measurements as performed by Van den Hout et al. are recommended, including cardiac evaluations, the Alberta Infant Motor Scale and the Bayley Scales of Infant Development.[5,7] For older children muscle strength can be measured by means of Hand Held Dynamometry and MRC score as described by Winkel et al.,[8] and muscle function by the Gross Motor Function Measure supplemented with timed tests. Examples of such timed tests are walking 10 meters, rising from a chair and rising from the floor. As indicated before, respiratory function tests should also be performed regularly.

Suggested follow-up measurements for adolescents and adults

Besides the scales described in chapter 7 to 9 of this thesis, the AMC Linear Disability Score (ALDS) might be considered for the measurement of functional status in adolescent and adult patients with Pompe disease. In the ALDS project, an item bank of activities of daily living (ADL) has been developed using item response theory. Items were obtained from a systematic review of neurologic ADL scales.[58] The basic assumption of item response theory is that severely affected patients have a lower probability of being able to perform a certain activity than healthy persons or less severely affected patients. Based on the responses of more than 1000 patients with a variety of chronic disorders, the items were calibrated along a linear scale and a probability value ('logit') was calculated for each separate item. The disability estimate of a patient is expressed on the same logit scale and does not depend on which items are used. In this way, for each patient a set of items can be presented that is tailored to his or her level of ability. Because all items were calibrated along the same 'line of difficulty' the scores obtained with different sets of items remain comparable and a change of one logit has the same meaning both at the lower and the upper end of the scale.[59-62] The applicability of the ALDS for use in Pompe disease is currently investigated.

Furthermore, a scale specific for Pompe disease covering all topics relevant for patients of approximately 16 years and older is under development. The items included in this scale are based on an inventory of the 4 most important complaints reported by the patients in the IPA/ Erasmus MC Pompe survey. The draft version is currently tested in the Netherlands, the United Kingdom and the United States and will be further validated in the cohort of patients that visits our hospital every six months.

As for older children, the clinical follow-up of adolescents and adults with Pompe disease should include Hand Held Dynamometry and MRC score for the measurement of muscle strength as well as respiratory function testing. The Gross Motor Function Measure is less suitable for the assessment of muscle function in adults, because many items are too much oriented towards a pediatric patient population. A shorter version including the items considered most relevant for (older) children, adolescents and adults with Pompe disease is currently under evaluation in our hospital.

Disease process markers

The core domain 'Disease process' contains routine laboratory assessments and suggested disease markers such as muscle glycogen content, muscle morphology and urinary tetrasaccharides. A disease marker (also called biomarker or surrogate marker) is an indicator of a biological process, demonstrable in readily accessible tissues or body fluids, and directly linked to the clinical manifestations and outcome of a particular disease.[63,64] For Pompe disease a good biomarker should reflect the current state of the muscles, which are the target organs with respect to progression of the disease and response to

treatment. Creatine kinase (CK) in plasma is routinely measured in patients with Pompe disease and seems a suitable candidate at first sight, because the enzyme is present in large quantities in muscle and the plasma level is raised when muscle fibers are damaged.[65] However, its relation to the clinical condition of the patient and the response to treatment are not specific enough. Muscle glycogen content and morphology have also been proposed as markers for the progression of Pompe disease, but it was also noted that muscle pathology often varies substantially between different muscle bundles and fibers of the same patient.[8,66] In practice, muscle morphology cannot be used as a regular follow-up measurement, because the procedure of taking a muscle biopsy is rather invasive. Urinary glucose tetrasaccharides have been suggested as a non-invasive marker to monitor the therapeutic response.[67] The concentration of these tetrasaccharides is elevated in both infantile and late-onset patients as compared to age-matched controls.[68] In a study on 11 severely affected infants on enzyme replacement therapy, an association was found between improvement in muscle function and decreased tetrasaccharide levels. It is hypothesized that these tetrasaccharides result from the degradation of accumulated glycogen that is released into the circulation. In two patients with an unfavorable therapeutic response, a peak of urinary and plasma glucose tetrasaccharides was found around the same time that respiratory insufficiency developed.[67] However, it was not clear whether the decrease or increase in glucose tetrasaccharides preceded these clinical events or vice versa. All taken together there still is a need for a reliable biomarker to monitor the disease process in Pompe disease.

Linking different databases

The large number of patients identified through the IPA/ Erasmus MC Pompe survey can be considered as a pool of patients in which specific questions can be further addressed. In the coming years we will work step by step towards complete linkage of all mutational, enzymatic, clinical and survey data that have been collected in the past 30 years at Erasmus MC, enabling detailed study of genotype-phenotype correlations and identification of possible prognostic information and 'disease-modifying factors'. The study of patients with the same combination of mutant alleles but varying age at onset and progression of disease will be particularly important.

The first step we made was to identify the patients with the c.-32-13T>G mutation, which is common among late-onset Caucasian patients, and a known fully deleterious mutation in the other allele. The aim was to delineate the disease variation among patients with this genotype and to define the c.-32-13T>G haplotypes. Fifty-six patients were selected from the mutation database maintained at the department of Clinical Genetics. For 27 of these patients information from the IPA/ Erasmus MC Pompe survey was also available. The age of the patients known to be still alive at the time of the study ranged from 3 to 69 years, and the age at diagnosis ranged from <1 to 78 years. Ten out of 56 patients were

under 18 years at the time of the study. One of them was ventilator dependent and none were wheelchair bound. Thus, c.-13-32T>G combined with a fully deleterious second mutation is mostly associated with an attenuated course, but can also lead to serious disease before adulthood. Because patients were selected with a known fully deleterious second mutation, this clinical diversity is either caused by micro-heterogeneity of the c.-13-32T>G allele, or by genetic background variation potentially combined with epigenetic and environmental factors. In a subset of 17 patients with this genotype, acid α-glucosidase activities between 3 and 20% were measured. There was no clear correlation between the level of residual acid α-glucosidase activity and the clinical course of the disease. The variation in residual activity might be caused by true differences between patients, but may also be partly related to uncontrollable experimental procedures (such as the growth rate of the cultured fibroblasts).

Haplotype analysis of the c.-32-13T>G alleles was performed in a subset of 29 of the 56 patients and an additional 42 patients who participated in a study on the clinical course of Pompe disease in adults (called LOPOS; Late-Onset Prospective Observational Study, sponsored by Genzyme Corp., Boston, USA). Twelve different haplotypes of c.-32-13T>G were found. There was no clear correlation between the haplotypes, the level of residual acid α-glucosidase activity, and the severity of disease, but the number of patients per specific haplotype was small. On the basis of these findings, it is considered unlikely that the clinical heterogeneity among patients with c.-32-13T>G is caused by haplotype diversity or by patient-specific variation in allele expression. A possible model to explain the clinical diversity among patients with c.-32-13T>G and a fully deleterious second mutation could be that other genes and factors have a chance to modulate the disease severity when the mutations in the GAA gene allow some level of residual acid α-glucosidase activity.[69]

Towards an expert center for Pompe disease

Throughout this thesis the problems associated with investigating a rare disorder have come into prominence. More in general it can be postulated that small numbers are not only a problem for research, but also affect the care for patients who suffer from these diseases. Much still has to be learned, even when a registered treatment has become available. For example, as long as the factors that influence the natural course of the disease in late-onset Pompe disease are not fully known, probably the best strategy to determine the optimal time to start treatment is to follow the patients closely using a standardized set of outcome measures, so that any change in the patient's condition is noticed as early as possible. This strategy obviously leaves much to the clinical judgment and experience of the physician. When enzyme therapy could be freely prescribed once it is available on the market, this would lead to scattering of patients to many different centers and physicians. In this scenario it is almost impossible to build up experience with the treatment and to address issues such as dosing, frequency, infusion regimen, infusion-associated reactions, the timing of the treatment and the overall judgment of clinical effects.

Because of the still limited experience with enzyme replacement therapy for Pompe disease and the many remaining uncertainties with regard to natural course and treatment, the establishment of an expert center for Pompe disease in the Netherlands seems indicated. Erasmus MC has a long-standing history of preclinical and clinical research into Pompe disease (for review see Reuser et al.[70]). Basic processes observed in cultured fibroblasts and muscle cells[e.g.71-74], as well as the increasing knowledge on the structure and function of acid α-glucosidase,[e.g.75-77] were translated to the experimental treatment of animals[e.g.78,79] and thereafter to the first clinical trial in patients with Pompe disease.[e.g.5,7] The close collaboration between departments makes it possible to return to preclinical studies when new questions arise from clinical observations. For example, when it was noticed that the four classic infantile patients in the initial clinical trial all had a hearing loss,[7] insight in the pathogenic process was obtained by studying the cochlear pathology in a knock-out mouse model for Pompe disease.[80] Issues to be addressed in future that will benefit from input from both basic science and clinical research are, amongst others, the development of methods to improve the uptake of α-glucosidase, the search for biomarkers to follow the disease process, and the exploration of new therapeutic options besides or in addition to enzyme therapy.

Furthermore, it is important to realize that enzyme replacement therapy profoundly alters the natural course of the disease, most notably for classic infantile patients, who otherwise would have died within the first year of life. The classic infantile patients from the first clinical trial are now 7 years old. However, they all have residual disease of varying severity and it is still uncertain how they will develop in the future. For infants as well as children and adults with Pompe disease, enzyme therapy will be a life-long treatment. Follow-up of patients who started enzyme replacement therapy as a child will need to be continued throughout adulthood to learn the full effects and side-effects of this treatment. The framework suggested in the previous paragraph could be used for the further development of a set of outcome measures to follow those patients from child- through adulthood. Clearly, collaboration and interaction between those involved in the care and research of pediatric and adult patients is required.

Concluding remarks

At the advent of a registered treatment for Pompe disease it is realized that continued and structured follow-up of patients throughout child- and adulthood is necessary to advance our knowledge of the natural course of the disease, to identify prognostic factors, and to fully evaluate long-term effects of enzyme therapy. This requires close collaboration between basic and applied science, between pediatric and adult disciplines, and between research centers, patient organizations and industry worldwide. The studies described in this thesis on the natural course of Pompe disease and the use of selected measurement scales illustrate the advantages of combining the efforts of patient organizations and academic hospitals on an international level.

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Appendix

Erasmus | **Clinical condition of late onset Pompe patients** | Case Number

A. DIAGNOSIS.

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

1. What were your first four complaints that had to do with Pompe's disease?

1. ☐ *difficulty in walking (taking steps)*
2. ☐ *difficulty in running*
3. ☐ *difficulty in doing a sport*
4. ☐ *difficulty in going up and down a staircase*
5. ☐ *difficulty in rising from an armchair*
6. ☐ *difficulty in rising from a lying position*
7. ☐ *difficulty in lifting my head*
8. ☐ *difficulty in acquiring my swimming certificate*
9. ☐ *breathing problems*
10. ☐ *sleeping problems*
11. ☐ *tiredness / sleepiness*
12. ☐ *muscle spasms / cramps, mainly in* _____
13. ☐ *muscle pain, mainly in* _____
14. ☐ *other, namely:* _____

2. During which years did these first four complaints occur for the first time?

A. Complaint number *B. Please, fill in year **or** indicate how many years ago*

		○ *<5 years ago*	○ *5-10 yrs*	○ *11-15 yrs*	○ *>15 yrs*	○ *do not remember*
		○ *<5 years ago*	○ *5-10 yrs*	○ *11-15 yrs*	○ *>15 yrs*	○ *do not remember*
		○ *<5 years ago*	○ *5-10 yrs*	○ *11-15 yrs*	○ *>15 yrs*	○ *do not remember*
		○ *<5 years ago*	○ *5-10 yrs*	○ *11-15 yrs*	○ *>15 yrs*	○ *do not remember*

3. Which complaints 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.*** ☐

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

other, namely:

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4. When was the diagnosis "Pompe's disease" (also called: "glycogen storage disease type 2" or "acid maltase deficiency" or "alpha glucosidase deficiency") made with respect to you?

A. year

Please fill in year, ***or*** tick box.

- ○ <5 years ago
- ○ 5-10 years ago
- ○ 11-15 years ago
- ○ >15 years ago
- ○ I do not remember

5. Do you remember who made this diagnosis? ○ Yes ○ No

Name physician: _____

Specialism: _____

Name and town hospital: _____

6. Which of the following (diagnostic) tests have been carried out with respect to you? More than one answer is possible.

A. muscle biopsy	○ Yes	○ No	○ I do not know
B. fibroblasts (skin biopsy)	○ Yes	○ No	○ I do not know
C. leukocytes (blood)	○ Yes	○ No	○ I do not know
D. DNA analysis	○ Yes	○ No	○ I do not know
E. other, namely:	○ Yes	○ No	

_____

7. How long did it take before the diagnosis was made, since you have visited a physician for your first complaints?

year and months ☐ I do not remember

8. How many different physicians (inclusive of your general practitioner) did you visit before the diagnosis of "Pompe's disease" was made?

physicians ☐ I do not remember

9. Space for remarks/additions:

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B. HISTORY OF RELATIVES. ***The following questions concern the history of your relatives. Since Pompe's disease is a genetic disorder, it is very important to know which diseases or disease profiles occur amongst your relatives.***

1. Are your parents related by blood?

- ○ *No*
- ○ *I do not know*
- ○ *Yes, their blood relationship is the following:* _____

2. How many brothers and sisters do (did) you have? ☐☐ *brothers and* ☐☐ *sisters*

3. Which number are you in the row (the oldest one is number 1)? *I am number* ☐☐ *in the row*

4. How many brothers and/or sisters have been subjected to diagnostic testing for Pompe's disease? (do not count yourself) ☐☐ *brothers and sisters* ☐ *I do not know*

5. With respect to how many brothers and/or sisters was the diagnosis "Pompe's disease" made? (do not count yourself) ☐☐ *brothers and sisters* ☐ *I do not know*

date of birth (day-month-year) ☐☐ - ☐☐ - ☐☐☐☐ ○ *Brother* ○ *Sister*

date of birth (day-month-year) ☐☐ - ☐☐ - ☐☐☐☐ ○ *Brother* ○ *Sister*

date of birth (day-month-year) ☐☐ - ☐☐ - ☐☐☐☐ ○ *Brother* ○ *Sister*

date of birth (day-month-year) ☐☐ - ☐☐ - ☐☐☐☐ ○ *Brother* ○ *Sister*

6. Do you have other blood relations (no brothers and sisters) that suffer from Pompe's disease? Can you indicate your relationship to these relatives (for instance niece, grandfather etc.)?

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C. CHILDHOOD.

We are interested in possible complaints and disorders you had as a child, since this can give us many indications about the course of Pompe's disease. If this questionnaire is completed by or on behalf of young patients, section C (Childhood) and section D (Current situation) will partly overlap.

1. Looking back, did you already have problems as a child that may be related to Pompe's disease?

○ *Yes, namely:* ○ *No* ○ *I do not know*

2. What was your heigth as child, compared to other children?

- ○ *shorter than other children*
- ○ *about as tall as other children were*
- ○ *taller than other children*
- ○ *I do not know*

3. As a child, were you

- ○ *slimmer than other children*
- ○ *not slimmer nor fatter than other children*
- ○ *fatter than other children*
- ○ *I do not know*

4. Development.

4a. When were you able to sit without any support?

- ○ *early*
- ○ *normal age*
- ○ *late*
- ○ *I do not remember*

Do you remember which age you had? ☐☐ *months*

4b. When were you able to stand in an upright position without any support?

- ○ *early*
- ○ *normal age*
- ○ *late*
- ○ *I do not remember*

Do you remember which age you had? ☐☐ *months*

4c. When were you able to walk (take steps) without any support?

- ○ *early*
- ○ *normal age*
- ○ *late*
- ○ *I do not remember*

Do you remember which age you had? ☐☐ *months*

4d. As a child, were you able to raise your head when lying on your back?

- ○ *without any problems*
- ○ *with difficulty*
- ○ *hardly at all*
- ○ *I do not remember*

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Erasmus | **Clinical condition of late onset Pompe patients** | Case Number

5. Sports and games.

5a. How well were you able to run as a child?

- ○ *less well than other children*
- ○ *as well as other children*
- ○ *better than other children*
- ○ *I do not know*

5b. As a child, did you fall down more often than other children?

- ○ *Yes*
- ○ *No*
- ○ *I do not know*

5c. Were you able to keep up with the other children during physical exercise at school?

- ○ *well*
- ○ *averagely well*
- ○ *not so well*
- ○ *I do not remember*

5d. As a child, did you engage in any sports outside school hours? ○ *Yes* ○ *No* ○ *I do not remember*

Which sport?

1. _____ *during* ____ *year(s)*
2. _____ *during* ____ *year(s)*
3. _____ *during* ____ *year(s)*

6. Complaints.

6a. As a child, did you experience any problems concerning your respiratory tracts?

- ○ *often*
- ○ *sometimes*
- ○ *never/hardly ever*
- ○ *I do not remember*

6b. What kind of problems? You may tick more than one box.

- ☐ *1. bronchitis*
- ☐ *2. shortness of breath*
- ☐ *3. asthma*
- ☐ *4. pneumonia*
- ☐ *5. often having a cold*
- ☐ *6. I do not know*
- ☐ *7. other, namely:* _____

6c. As a baby, did you experience any problems with drinking?

- ○ *often*
- ○ *sometimes*
- ○ *never/hardly ever*
- ○ *I do not remember*

6d. How was your appetite as a child?

- ○ *less good than that of other children*
- ○ *as good as that of other children*
- ○ *greater than that of other children*
- ○ *I do not remember*

7. Space for remarks / additions:

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Erasmus | **Clinical condition of late onset Pompe patients** | Case Number

D. CURRENT SITUATION. **This section of the questionnaire concerns your current situation, complaints and disorders.**

1. Heigth: feet and inches **Weight:** kgs

2. Can you indicate which complaints are most uncomfortable for you and/or restricting you the most? Please rank them from 1 to 4, as being the most uncomfortable or restricting complaint.

1.
2.
3.
4.

Walking, doing a sport.

3. Do you experience any problems in walking (taking steps, a walk) at this moment? ○ Yes ○ No **continue with question 6**

3a. Can you describe your problems in walking?

3b. Since when have you been experiencing such problems?

year

Please fill in year **or** tick box

○ <5 years ago
○ 5-10 years ago
○ 11-15 years ago
○ >15 years ago
○ I do not know

4. Do you make use of a wheelchair?

○ no
○ yes, a wheelchair that must be pushed
○ yes, an electric wheelchair
○ yes, both a wheelchair that must be pushed and an electric wheelchair

4a. Since when have you been using a wheelchair?

year

Please fill in year **or** tick box

○ <5 years ago
○ 5-10 years ago
○ 11-15 years ago
○ >15 years ago
○ I do not know

4b. Where do you use your wheelchair mainly?

○ inside my house
○ outside my house
○ both

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5.a. Do you use aids for walking?

○ No
○ No, I only use my wheelchair
○ Yes

5b. Which of the following aids do you use? (You may tick more than one box)

☐ 1. crutches
☐ 2. walking cane
☐ 3. triple stool
☐ 4. walking frame
☐ 5. rollator
☐ 6. other, namely: _____

5c. Since when have you been using such aids?

year ☐☐☐☐ Please fill in year **or** tick box

○ <5 years ago
○ 5-10 years ago
○ 11-15 years ago
○ >15 years ago
○ I do not know

5d. How often do you use such aids?

○ less than half the time during which I am walking
○ about half of the time during which I am walking
○ more than half of the time during which I am walking
○ always

5e. Which distance are you able to cover using a walking aid?

○ an unlimited distance
○ a few miles
○ a few hundred feet about ☐☐☐ miles/ feet
○ a few feet
○ I do not know

6. Which distance are you able to cover without assistance?

○ an unlimited distance
○ a few miles
○ a few hundred feet about ☐☐☐ miles/ feet
○ a few feet
○ I am no longer capable of walking without assistance
○ I do not know

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7. Do you fall down or stumble while walking?

- ○ *often*
- ○ *sometimes*
- ○ *never/hardly ever*
- ○ *not applicable*

8.a. Are you able to run?

- ○ *yes, without any problems*
- ○ *yes, but with difficulty*
- ○ *no*
- ○ *I do not know*

b. When did the problems with running occur for the first time?

year ☐☐☐☐ *Please fill in year* ***or*** *tick box*

- ○ *<5 years ago*
- ○ *5-10 years ago*
- ○ *11-15 years ago*
- ○ *>15 years ago*
- ○ *I do not know*

9. Are you able to ride a bicycle?

- ○ *yes, without any problems*
- ○ *yes, but with difficulty*
- ○ *yes, on an adjusted bicycle*
- ○ *no, I have not (yet) learned to ride a bicycle*
- ○ *no, I did learn to ride a bicycle at some point of time, but now I am no longer able to ride it*
- ○ *I do not know*

10. Are you able to swim?

- ○ *yes, without any problems*
- ○ *yes, but with difficulty*
- ○ *no, I have not (yet) learned to swim*
- ○ *no, I did learn to swim at some point of time, but now I am no longer able to*
- ○ *I do not know*

11. Do you do any sports?

○ *Yes, namely:* ○ *No*

12. Are you feeling better when moving more?

- ○ *yes*
- ○ *no, that makes no difference*
- ○ *no, to the contrary, I feel worse*
- ○ *I do not know*

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MOVING.

13. Are you able to go up and down a staircase?

- ○ without any problems
- ○ I do not know, I never have to deal with staircases
- ○ with the support of banisters
- ○ with the assistance of other people
- ○ with the support of banisters ánd with the assistance of other people
- ○ no, I am no longer able to go up or down a staircase.

b. When did the first problems with going up and down a staircase occur?

year ☐☐☐☐ Please fill in year **or** tick box

- ○ <5 years ago
- ○ 5-10 years ago
- ○ 11-15 years ago
- ○ >15 years ago
- ○ I do not know

14. Are you able to rise from an armchair by yourself?

- ○ without any problems
- ○ with difficulty
- ○ no

b. When did the first problems with rising from an armchair occur?

year ☐☐☐☐ Please fill in year **or** tick box

- ○ <5 years ago
- ○ 5-10 years ago
- ○ 11-15 years ago
- ○ >15 years ago
- ○ I do not know

15. Are you able to rise from a lying position on the ground all by yourself?

- ○ without any problems
- ○ with difficulty
- ○ no

b. When did the first problems with rising from a lying position on the ground occur?

year ☐☐☐☐ Please fill in year **or** tick box

- ○ <5 years ago
- ○ 5-10 years ago
- ○ 11-15 years ago
- ○ >15 years ago
- ○ I do not know

16. Are you able, when lying on your back, to raise your legs from the surface?

- ○ without any problems
- ○ with difficulty
- ○ no

b. When did the first problems with moving in this way occur?

year ☐☐☐☐ Please fill in year **or** tick box

- ○ <5 years ago
- ○ 5-10 years ago
- ○ 11-15 years ago
- ○ >15 years ago
- ○ I do not know

17. Are you able to raise your arms above your head?

- ○ without any problems
- ○ with difficulty
- ○ no

18. Are you able to rise from a squatting position without any assistance?

- ○ without any problems
- ○ with difficulty
- ○ no

19. Are you able to jump?

- ○ without any problems
- ○ with difficulty
- ○ no

20. Are you able to come into an upright position after bending over without any assistance?

- ○ without any problems
- ○ with difficulty
- ○ no

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Clinical condition of late onset Pompe patients

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BREATHING.

21. Can you indicate whether you are (have been) experiencing the following breathing problems?

			since (year)		number of years ago		
a) asthma	○ No	○ Yes		OR			
b) shortness of breath while not moving	○ No	○ Yes		OR			
c) shortness of breath after a small amount of exercise	○ No	○ Yes		OR			
d) shortness of breath after heavy exercise	○ No	○ Yes		OR			
e) shortness of breath in a lying position	○ No	○ Yes		OR			number of times
f) pneumonia	○ No	○ Yes		OR			
g) bronchitis	○ No	○ Yes		OR			
h) often having a cold	○ No	○ Yes		OR			
i) other, namely: _____	○ No	○ Yes		OR			

22. a. Do you use any help for breathing? ○ No ○ Yes

b.Do you use such help through a

○ nose hood

○ trachea canulla

○ other, namely: _____

c. When do you use this help? You may tick more than one box.

☐ when sleeping

☐ during the daytime

☐ after exercise

d. How may hours per day (in total: adding daytime and night time) do you use a breathing help? hours per day.

e. Since when have you been using a breathing help?

year

Please fill in year **or** tick box

○ <5 years ago
○ 5-10 years ago
○ 11-15 years ago
○ >15 years ago
○ I do not know

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Erasmus MC | **Clinical condition of late onset Pompe patients** | Case Number

SLEEPING.

23. a. Do you have any problems with sleeping? ○ never/hardly ever ○ occasionally ○ often

23.b. What kind of sleeping problems do you have (you may tick more than one box)?

☐ 1. nightmares
☐ 2. waking up often
☐ 3. sweating during the night
☐ 4. other, namely:_____

24. When rising in the morning, do you have a headache or do you feel light-headed? ○ never/hardly ever ○ sometimes ○ often

25. Do you experience nausea in the morning? ○ never/hardly ever ○ occasionally ○ often

26. Are you able to lie flat on your back while sleeping? ○ No ○ Yes

EATING.

27.a. Do you have any chewing problems while eating?

○ not applicable
○ never/hardly ever
○ occasionally
○ often
○ always

b. Since when have you been experiencing chewing problems while eating?

year ☐☐☐☐ Please fill in year **or** tick box

○ <5 years ago
○ 5-10 years ago
○ 11-15 years ago
○ >15 years ago
○ I do not know

28.a. Do you have any problems with swallowing while eating?

○ not applicable
○ never/hardly ever
○ occasionly
○ often
○ always

b. Since when have you been experiencing problems with swallowing while eating?

year ☐☐☐☐ Please fill in year **or** tick box

○ <5 years ago
○ 5-10 years ago
○ 11-15 years ago
○ >15 years ago
○ I do not know

29. Are you able to eat by yourself?

○ not applicable
○ no
○ with difficulty
○ without any problems

30.a. Is there any food that you can not eat?

○ not applicable
○ no
○ yes, namely:

30.b. Why are you unable to eat such food?

31. How is your appetite?

○ not applicable
○ bad
○ moderate
○ fair
○ good

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Clinical condition of late onset Pompe patients

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32. Are you on a special diet?

○ No

○ Yes, namely: _____

33.a. Do you use a PEG tube to take in food?

○ No

○ Yes

b. Since when have you been using a PEG tube?

year

Please fill in year **or** tick box

○ <5 years ago
○ 5-10 years ago
○ 11-15 years ago
○ >15 years ago
○ I do not know

c. Which part of your food do you take in through the PEG tube?

○ less than 25%
○ 25 - 50%
○ 50 - 75%
○ more than 75%

34.a. Do you use a naso-gastric (NG) tube to take in food through your nose?

○ No

○ Yes

b. Since when have you been using this NG tube?

year

Please fill in year **or** tick box

○ <5 years ago
○ 5-10 years ago
○ 11-15 years ago
○ >15 years ago
○ I do not know

c. Which part of your food do you take in through this tube?

○ less than 25%
○ 25 - 50%
○ 50 - 75%
○ more than 75%

OTHER COMPLAINTS

35.a. Are you suffering from a restriction in movement with respect to one or more joints (contractures)?

○ No

○ Yes

35.b. At what spot in your body are you suffering from a restriction in movement with respect to joints (contractures)? You may tick more than one box.

☐ 1. ankles ☐ 2. neck ☐ 3. hands ☐ 4. hips

☐ 5. knees ☐ 6. elbow ☐ 7. shoulders

☐ 8. other, namely: _____

36. Are you suffering from muscle cramps?

○ always
○ often
○ occasionally
○ never/hardly ever

At what spot in your body are you suffering from muscle cramps?

37. Are you suffering from muscle pains?

○ always
○ often
○ occasionally
○ never/hardly ever

At what spot in your body are you suffering from muscle pains?

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38. Are you suffering from pain in your back?
○ always ○ often ○ occasionally ○ never/hardly ever
When, after which activity or at which point of time, do you have a pain in your back?

39. Are you suffering from pain in your neck?
○ always ○ often ○ occasionally ○ never/hardly ever
When, after which activity or at which point of time, do you have a pain in your neck?

40. Are you suffering from pain in your legs?
○ always ○ often ○ occasionally ○ never/hardly ever
When, after which activity or at which point of time, do you have a pain in your legs?

41. Do you have any problems with raising your head? ○ yes ○ no ○ a little bit

42. Do you have any problems in keeping your head upright (head balance)? ○ yes ○ no ○ a little bit

43. Do you have any skin problems? ○ yes ○ no
What is the exact problem?

44. Do you have any problems with hearing? ○ yes ○ no
What is the exact problem?

45. Do you have any problems with your eyes? ○ yes ○ no
What is the exact problem?

46. Do you have any problems with speaking? ○ yes ○ no
What is the exact problem?

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47. Can you indicate in the following list which complaints you are suffering (you have ever been suffering) from?

			since (year)		number of years ago		number of times
a)	suspended eyelid	○ No	○ Yes	OR			
b)	flatfeet	○ No	○ Yes	OR			
c)	concave feet (pes cavus)	○ No	○ Yes	OR			
d)	concave back (lordosis)	○ No	○ Yes	OR			
e)	sideways curvature of the spine (scoliosis)	○ No	○ Yes	OR			
f)	difficulty with holding your faeces	○ No	○ Yes	OR			
g)	difficulty with holding your water	○ No	○ Yes	OR			
h)	diarrhoea	○ No	○ Yes	OR			
i)	obstipation	○ No	○ Yes	OR			
j)	urinary tract infections	○ No	○ Yes	OR			
k)	widened blood vessel (aneurysm)	○ No	○ Yes	OR			
l)	thrombosis	○ No	○ Yes	OR			
m)	cerebral haemorrhage	○ No	○ Yes	OR			
n)	epileptic fits	○ No	○ Yes	OR			
o)	heart complaints	○ No	○ Yes	OR			
p)	ringing in the ears	○ No	○ Yes	OR			
q)	quickly tired	○ No	○ Yes	OR			
r)	sleepiness	○ No	○ Yes	OR			
s)	cold feet and/or hands	○ No	○ Yes	OR			
t)	salivation, sialorrhea	○ No	○ Yes	OR			
u)	other, namely: _____	○ No	○ Yes	OR			

Space for remarks:

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DAILY ACTIVITIES.

48. Are you able to do your shopping yourself?
- ○ *no*
- ○ *with difficulty*
- ○ *without any problems*
- ○ *I do not know, I never go shopping*

49. Do you have any problems with carrying out certain household chores?
- ○ *no*
- ○ *I do not know, I don't carry out any household chores*
- ○ *yes, namely with:*

50. Are you able to drive a car?
- ○ *yes*
- ○ *yes, with adjustments to my car*
- ○ *no, I have learned to drive at some point of time, but are no longer able to drive*
- ○ *no, I have not yet / never obtained my driver's license*

51. Are you able to comb your hair yourself?
- ○ *without any problems*
- ○ *with difficulty*
- ○ *no*

52. Are you able to wash yourself?
- ○ *without any problems*
- ○ *with difficulty*
- ○ *no*

53.a. Are you able to dress and undress?
- ○ *without any problems*
- ○ *with difficulty*
- ○ *no*

b. When did the first problems with dressing /undressing occur?

year ☐☐☐☐ *Please fill in year **or** tick box*
- ○ *<5 years ago*
- ○ *5-10 years ago*
- ○ *11-15 years ago*
- ○ *>15 years ago*
- ○ *I do not know*

54.a. Are you able to go to the toilet by yourself (possibly with a raised lavatory bowl or aids)?
- ○ *without any problems*
- ○ *with difficulty*
- ○ *no*

b. When did the first problems with going to the toilet by yourself occur?

year ☐☐☐☐ *Please fill in year **or** tick box*
- ○ *<5 years ago*
- ○ *5-10 years ago*
- ○ *11-15 years ago*
- ○ *>15 years ago*
- ○ *I do not know*

4768015663

Erasmus | **Clinical condition of late onset Pompe patients** | Case number

55.a. Do you make use of an aid to pee?

- ○ *no*
- ○ *yes, I use an urinal*
- ○ *yes, differently, namely:* _____

b. Since when have you been using this aid for peeing?

year ☐☐☐☐ *Please fill in year **or** tick box*

- ○ *<5 years ago*
- ○ *5-10 years ago*
- ○ *11-15 years ago*
- ○ *>15 years ago*
- ○ *I do not know*

JOB, STUDY, ETC.

56. What is the highest type of education that you have completed?

57. Did your disease in your opinion have any impact on your choice of education?

- ○ *very much so*
- ○ *to some extent*
- ○ *hardly at all*
- ○ *not at all*
- ○ *not applicable*

58. Which of the following characteristics do apply to you? You may tick more than one box.

- ☐ *a. I do paid work*
- ☐ *b. I am active as a volunteer*
- ☐ *c. I go to school/ university*
- ☐ *d. I am looking for a job*
- ☐ *e. I used to have a job, but now I do not*
- ☐ *f. I take care of the household*
- ☐ *g. other, namely:* _____

59. How may hours per week do you work/study?

hrs / wk ☐☐

60. What kind of work do you do?

61.a. In your opinion does your disease have any impact on the choice of the work you do?

- ○ *very much so*
- ○ *to some extent*
- ○ *hardly at all*
- ○ *not at all*
- ○ *not applicable*

61.b. Did you change jobs as a consequence of your disease?

- ○ *no*
- ○ *yes*
- ○ *not applicable*

61.c. Did you change the number of hours that you spend on working as a consequence of your disease?

- ○ *yes, I used to work* ☐☐ *hours per week and now* ☐☐ *hours per week.*
- ○ *no, I still work as many hours as I used to*
- ○ *no, I have already started with a limited number of hours on account of my disease*
- ○ *not applicable*

5857015663

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62. Do you receive a state benefit on account of occupation disability at this moment?

- ○ not applicable
- ○ no
- ○ yes

62.a. If so, for what percentage? ☐☐☐ %

63. Did you have a job in the past, but at this moment not any longer?

- ○ not applicable
- ○ no
- ○ yes

63.a. When did you stop working?

year ☐☐☐☐ *Please fill in year* ***or*** *tick box*

- ○ <5 years ago
- ○ 5-10 years ago
- ○ 11-15 years ago
- ○ >15 years ago
- ○ I do not know

63.b. For what reason did you stop working?

- ○ occupational disability
- ○ early retirement
- ○ pension
- ○ children
- ○ other, namely: _____

64. Do you have problems concentrating on your work, study, school or other activities?

- ○ often
- ○ occasionally
- ○ never/ hardly ever

MODIFICATIONS TO YOUR HOME AND USE OF CARE.

65.a. Where do you live?

- ○ in a nursing home
- ○ in a rehabilitation centre
- ○ at my parents' place, at the place of care providers, at the place of another relative
- ○ on my own
- ○ together with my partner
- ○ together with my partner and children
- ○ another type of housing, namely: _____

65.b. Has your home (or that of your parents / care providers/ other relatives) been modified on account of your disease?

- ○ no
- ○ yes

65.c. Where has your home been modified? You may tick more than one box.

- ☐ 1. kitchen
- ☐ 2. bedroom
- ☐ 3. bathroom
- ☐ 4. toilet
- ☐ 5. tresholds
- ☐ 6. everything is on the ground floor
- ☐ 7. elevator
- ☐ 8. other, namely: _____

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66. Can you indicate which of the following aids you are using? You may tick more than one box.

- ☐ a. raising lift
- ☐ b. robot arm
- ☐ c. arm supporter
- ☐ d. adjusted bicycle
- ☐ e. adjusted chair (not a wheelchair)
- ☐ f. adjusted bed
- ☐ g. none of the aforementioned aids

67.a. Do you have an adjusted bed? ○ no ○ yes

67.b. Which are the adjustments to your bed? You may tick more than one box.

- ☐ 1. the height can be adjusted
- ☐ 2. adjusted foot
- ☐ 3. adjusted head
- ☐ 4. more than one cushion
- ☐ 5. electronic turn around system
- ☐ 6. waterbed
- ☐ 7. adjusted mattress
- ☐ 8. adjusted cushion
- ☐ 9. bed has been made to measure
- ☐ 10. other, namely: _____

68. Can you indicate if and to what extent you are making use of paid assistance for the following activities in relation to your disease?

a. Household activities	○ no	○ yes	for	☐☐	hrs per week
b. Catering	○ no	○ yes	for	☐☐	days per week
c. Bodily care	○ no	○ yes	for	☐☐	hrs per week
d. Family care	○ no	○ yes	for	☐☐	hrs per week
e. Nursing	○ no	○ yes	for	☐☐	hrs per week

ADMISSIONS TO HOSPITAL AND TREATMENTS .

69. a. How often have you been treated in hospital? ☐☐ times

69.b. For what reason(s) were you in hospital?

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70.a. Did you ever have surgery for scoliosis (sideways curvature of the spine)?

- ○ *yes*
- ○ *no*
- ○ *I do not know*

70.b. When did you have surgery for scoliosis?

year ☐☐☐☐ *Please fill in year* ***or*** *tick box*

- ○ *<5 years ago*
- ○ *5-10 years ago*
- ○ *11-15 years ago*
- ○ *>15 years ago*
- ○ *I do not know*

71.a. Have you ever been subjected to a lung function examination?

- ○ *yes*
- ○ *no*
- ○ *I do not know*

71.b. Is your lung function tested regularly?

○ *yes* ○ *no*

71.c. When was your most recent lung function examination?

year ☐☐☐☐ *Please fill in year* ***or*** *tick box*

- ○ *<5 years ago*
- ○ *5-10 years ago*
- ○ *11-15 years ago*
- ○ *>15 years ago*
- ○ *I do not know*

71.d. Was the lung function most recently tested normal?

○ *yes* ○ *no* ○ *I do not know*

71.e. Do you remember what the lung function value was that was measured most recently?

○ *no* ○ *yes* ☐☐☐ *[normal=100%]*

71.f. If you had more than one lung function examination, do you remember when your lung function was abnormal for the first time?

year ☐☐☐☐ *Please fill in year* ***or*** *tick box*

- ○ *<5 years ago*
- ○ *5-10 years ago*
- ○ *11-15 years ago*
- ○ *>15 years ago*
- ○ *I do not know*

72.a. Are you treated by a home ventilation team? ○ *yes* ○ *no*

72.b. Have you been subjected to oxygen/CO2 measuring ?

- ○ *I do not know*
- ○ *no*
- ○ *yes*

72.c. How often is (has) this measuring (been) done? ☐☐ *times per year* ***or*** ☐☐ *times in total*

72.d. Where is this measuring carried out?

- ○ *at home*
- ○ *I am admitted to hospital for this*
- ○ *other, namely:*

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73. Do you take any medicines? ○ yes ○ no

name medicine	dose

74. Do you make use of any food supplements (for instance, certain vitamins)? ○ yes ○ no

name supplement	dose (where applicable)

75. Do you participate in any training programme? ○ yes ○ no

description:

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Erasmus | **Clinical condition of late onset Pompe patients** | Case number

76. How often during the past year did you visit your general practitioner or did your general practitioner make a home call? ☐☐ *times*

77.a. By which of the following specialists have you ever been treated in relation with Pompe's disease?

☐ *1. cardiologist*
☐ *2. surgeon*
☐ *3. dermatologist*
☐ *4. gastroenterologist*
☐ *5. internist*
☐ *6. E.N.T. specialist*
☐ *7. clinical geneticist / genetic counsellor*
☐ *8. paediatrician*
☐ *9. lung specialist*
☐ *10. neurologist*
☐ *11. ophthalmologist*
☐ *12. orthopaedist*
☐ *13. psychiatrist*
☐ *14. rheumatologist*
☐ *15. rehabilitation specialist*
☐ *16. urologist*
☐ *17. other specialist, namely:* _____

77.b. By which of the following specialists have you been treated in relation to Pompe's disease during the past two years?

☐ *1. cardiologist*
☐ *2. surgeon*
☐ *3. dermatologist*
☐ *4. gastroenterologist*
☐ *5. internist*
☐ *6. E.N.T. specialist*
☐ *7. clinical geneticist/ genetic counsellor*
☐ *8. paediatrician*
☐ *9. lung specialist*
☐ *10. neurologist*
☐ *11. ophthalmologist*
☐ *12. orthopaedist*
☐ *13. psychiatrist*
☐ *14. rheumatologist*
☐ *15. rehabilitation specialist*
☐ *16. urologist*
☐ *17. other specialist, namely:* _____

78.a. By which of the following paramedics have you ever been treated in relation to Pompe's disease?

☐ *1. dietician*
☐ *2. occupational therapist*
☐ *3. physiotherapist*
☐ *4. speech therapist*
☐ *5. exercise therapist Cesar / Mensendieck*
☐ *6. psychologist*
☐ *7. other paramedic, namely:* _____

78.b. By which of the following paramedics have you been treated in relation to Pompe's disease during the past two years?

☐ *1. dietician*
☐ *2. occupational therapist*
☐ *3. physiotherapist*
☐ *4. speech therapist*
☐ *5. exercise therapist Cesar / Mensendieck*
☐ *6. psychologist*
☐ *7. other paramedic, namely:* _____

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E. Conclusion.

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

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

By way of conclusion of 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?

6173015665

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Fatigue Severity Scale

We are interested in the role of fatigue on your everyday life. Please read the following statements, then tick 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

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

1820550315

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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 = moves between rooms mostly with help of another person*
   - ○ *3 = moves between rooms most of the time independent; sometimes needing help of another person*
   - ○ *4 = moves 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 = moves outdoors mostly with help of another person*
   - ○ *3 = moves outdoors most of the time independent; sometimes needing help of another person*
   - ○ *4 = moves 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*

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*

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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. Able to 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*

3566550314

Erasmus | **Clinical condition of late onset Pompe patients** | Case number

SF-36 health survey

This questionnaire concerns your attitude towards your health, now and during the past 4 weeks. We wish to get a better impression of how you and other Pompe patients feel, how well you are able to carry out your normal activities and what your opinion is about your own health.

In this questionnaire "health" refers to your health in general. It therefore not only concerns things that have to do specifically with Pompe's disease, but your general well-being.

Please answer all questions, and only choose one single answer per question. Please choose the answer that corresponds best with how you yourself are feeling. If you are not sure which answer you should give, please give the best possible answer. For example: in the case of question 3 you may choose between "yes, limited a lot", "yes, limited a little", and "no, not limited at all". But there may be activities that you can not carry out at all (any longer). In such cases you should tick the figure in the column "yes, limited a lot".

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

- ○ *1 = Excellent*
- ○ *2 = Very good*
- ○ *3 = Good*
- ○ *4 = Fair*
- ○ *5 = Poor*

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

- ○ *1 = Much better now than one year ago*
- ○ *2 = Somewhat better now than one year ago*
- ○ *3 = About the same as one year ago*
- ○ *4 = Somewhat worse now than one year ago*
- ○ *5 = Much worse now than one year ago*

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activites? 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*	○	○	○
*b. **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf*	○	○	○
c. Lifting or carrying groceries	○	○	○
*d. Climbing **several** flights of stairs*	○	○	○
*e. Climbing **one** flight of stairs*	○	○	○
f. Bending, kneeling, or stooping	○	○	○
*g. Walking **more than a mile***	○	○	○
*h. Walking **half a mile***	○	○	○
*i. Walking **one hundred yards***	○	○	○
j. Bathing or dressing yourself	○	○	○

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

a. Cut down on the **amount of time** you spent on work or other activities	○ Yes	○ No
b. **Accomplished less** than you would like	○ Yes	○ No
c. Were limited in the **kind** of work or other activities	○ Yes	○ No
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ Yes	○ No

5. During the past 4 weeks, 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)?

a. Cut down on the **amount of time** you spent on work or other activities	○ Yes	○ No
b. **Accomplished less** than you would like	○ Yes	○ No
c. Didn't do work or other activities as **carefully** as usual	○ Yes	○ No

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?

- ○ 1 = Not at all
- ○ 2 = Slightly
- ○ 3 = Moderately
- ○ 4 = Quite a bit
- ○ 5 = Extremely

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

- ○ 1 = None
- ○ 2 = Very mild
- ○ 3 = Mild
- ○ 4 = Moderate
- ○ 5 = Severe
- ○ 6 = Very severe

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

- ○ 1 = Not at all
- ○ 2 = A little bit
- ○ 3 = Moderately
- ○ 4 = Quite a bit
- ○ 5 = Extremely

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9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks.</u>
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 <u>past 4 weeks</u> -

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

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

- ○ 1 = All of the time
- ○ 2 = Most of the time
- ○ 3 = Some of the time
- ○ 4 = A little of the time
- ○ 5 = None of the time

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	○	○	○	○	○
b. I am as healthy as anybody I know	○	○	○	○	○
c. I expect my health to get worse	○	○	○	○	○
d. My health is excellent	○	○	○	○	○

Space for remarks:

5269550316

Summary

Samenvatting

SUMMARY

Pompe disease is an inherited metabolic disorder, caused by deficiency of the enzyme acid α-glucosidase. This enzyme is needed to break down glycogen in the lysosomes. Lysosomes are cytoplasmic organelles involved in the removal and recycling of cellular materials. Deficiency of acid α-glucosidase leads to accumulation of glycogen in the lysosomes of virtually all cells of the body, but the effects are most notable in muscle. The nature of the mutations in the acid α-glucosidase gene largely determines the level of the residual acid α-glucosidase activity and the clinical phenotype of Pompe disease. Patients with classic, infantile Pompe disease have virtually no residual activity. They present shortly after birth with generalized muscle weakness and cardiac hypertrophy, and usually die within the first year of life. Non-classic or late-onset Pompe disease presents as a slowly progressive proximal myopathy without cardiac involvement, eventually leading to wheelchair dependency and use of respiratory support. These patients have a certain amount of residual α-glucosidase activity, leading to a milder disease course. The course of the disease can vary substantially between patients and the onset of symptoms may vary between the first and sixth decade of life. The main cause of death is respiratory failure.

Pompe disease is a rare disorder with an estimated frequency of 1 in 40,000 births. It has long been an untreatable disease, for which only supportive care was available. Research on enzyme replacement therapy is performed at Erasmus MC since many years, starting with preclinical experiments on the uptake of α-glucosidase in cultured fibroblasts and muscle tissue, followed by animal studies, and in 1999 by the first clinical trial on enzyme replacement therapy for Pompe disease. Currently more than 250 patients worldwide are treated with enzyme therapy in clinical studies or on a 'compassionate use' basis. In March 2006 recombinant human acid α-glucosidase for the treatment of Pompe disease (Myozyme®) has received marketing authorization in the European Union.

The development of new therapies for rare diseases is full of challenges, such as the limited number of patients and the often variable expression of the disease. A good overview of the natural course of a disease is important to fully evaluate the effects of new therapeutic options, especially for rare disorders like Pompe disease. In 2002, the need to improve the understanding of the variability, progression and natural history of the heterogeneous group of patients with non-classic or late-onset Pompe disease was recognized by Erasmus MC and the International Pompe Association (IPA), a worldwide federation of patient groups. This led to the initiation of the IPA/ Erasmus MC Pompe survey, an ongoing international study in which data are collected from children and adults with Pompe disease by means of self-report questionnaires. The goal of this survey is to gather as much information as possible on the natural course of the disease, the severity of the disease in the patient population, and the impact on the daily life of the patients. A second objective is to test a

number of measurement scales for their usefulness in the assessment of disease severity and changes over time. At this moment approximately 300 Pompe patients have participated in the survey through the IPA-affiliated patient organizations in the United States, the United Kingdom, the Netherlands, Germany, France, Canada and Australia. This thesis describes the results of the baseline survey in the international patient population and the first two years of follow-up in the Dutch subgroup.

In **chapter 1**, some background information is given on the cause, epidemiology, clinical manifestations, diagnosis and treatment of Pompe disease and on the development of medicinal products for rare disorders ('orphan drugs'). In **chapter 2** the design of the IPA/ Erasmus MC Pompe survey, the recruitment of participants, and the included measurement scales are discussed. Before describing the results from the survey, information on the natural course obtained in a review of 225 published cases is presented in **chapter 3**. This review illustrates the continuous spectrum of phenotypes in non-classic or late-onset Pompe disease. The ranges in age at onset, age at diagnosis, and age at which artificial ventilation or a wheelchair become necessary were wide. Subdivision of the patients based on age at onset did not identify specific symptoms or differences in disease course that could serve as criteria for further subtyping. The findings in this review confirmed the importance of the measurement of acid α-glucosidase activity in cultured fibroblasts or muscle tissue to establish the diagnosis of Pompe disease. Data on skeletal muscle strength and function, pulmonary function, handicap and quality of life were only scarcely reported in the literature.

Chapter 4 describes the first results from the IPA/ Erasmus MC Pompe survey in the subgroup of 54 Dutch participants. An important message from this analysis is that almost 60% of the adult patients indicated the presence of mild muscular symptoms already during childhood. The study also clearly shows that Pompe disease is a genuine spectrum. First symptoms may occur at any age and the sequence of respiratory and skeletal muscle involvement varied substantially between the patients. Periodic measurement of respiratory function is therefore important, no matter how old a patient is and whether skeletal muscle problems are present or not. Other observations from this study were that pain and fatigue are more frequent symptoms in Pompe disease than previously thought.

In the much larger, international group of 255 patients described in **chapter 5** it was possible to make a division into groups based on age and duration of disease, and to link these two variables to the severity of disease. It was concluded that disease severity depended on disease duration and not on age. Mildly and severely affected patients were present in every age group, and an early manifestation of Pompe disease generally implied earlier wheelchair or ventilator dependency. Specific attention was drawn to a subset of patients under 15 years with a more rapidly progressive course. These patients all used respiratory support, were all wheelchair dependent, required nutritional support, and experienced first complaints before 2 years of age.

As a pilot study, the Dutch participants in the baseline survey were asked to complete a short follow-up questionnaire after one and after two years. The results are presented in **chapter 6**. Already in this relatively small group of patients, changes were recorded in mobility, functional activities and respiration and in the scores on the Rotterdam Handicap Scale. These results illustrate the progressiveness of late-onset Pompe disease and indicate the need for close clinical follow-up of both children and adults with this disorder. It also illustrates the usefulness of this type of information, which has led to the current expansion of the follow-up study to all patients who previously participated in the baseline survey.

In **chapter 7**, data on health-related quality of life were collected among 210 adult patients from different countries. Health-related quality of life was assessed with the 'Short Form-36 health survey' (SF-36). This questionnaire measures quality of life on 8 health domains (physical functioning, physical role-functioning, bodily pain, general health, vitality, social functioning, emotional role-functioning, and mental health). In general, patients with Pompe disease had a low score on the physical health domains, but did not differ from the general population on the mental health domains. There were no clear differences between patients from different countries. The usefulness of the SF-36 health survey for the assessment of changes over time remains questionable.

In **chapter 8**, the prevalence and severity of fatigue is further investigated in the international patient group, using the Fatigue Severity Scale (FSS). This is a brief and simple questionnaire with 9 statements on fatigue and its impact on the patients' lives. The mean score among adult Pompe patients was significantly higher than that of healthy controls. Fatigue was an important symptom in the entire clinical spectrum, also among patients who had very little other complaints. The FSS appeared to be a useful tool for the assessment of fatigue among patients with Pompe disease.

With the prospect of enzyme replacement therapy, insight into the social consequences of the disease becomes even more relevant. In **chapter 9** it is investigated whether the Rotterdam Handicap Scale (RHS) could be a good instrument to assess these consequences. The RHS assesses the level of participation in life situations, a concept formerly referred to as 'handicap', by means of 9 questions on the topics mobility indoors, mobility outdoors, kitchen tasks, domestic tasks indoors, domestic tasks outdoors, leisure activities indoors, leisure activities outdoors, traveling and work or study. The results from this study indicate that the RHS seems suitable for use in Pompe disease. The mean RHS score in our international group of patients was clearly reduced, and in particular the ability of the patients to fulfill their work or study is affected.

In **chapter 10** the main findings are discussed, some methodological issues are addressed, and suggestions for future research are made. A core set of measurements for the follow-up of patients with Pompe disease is proposed. Such standardized data collection

is important, especially for rare diseases, because it ensures that the data collected in different centers and different countries are comparable. To answer the many remaining questions on pathology, natural course and treatment, close collaboration between basic and applied science and pediatric and adult disciplines is required, preferably in the setting of an expert center for Pompe disease.

The IPA/ Erasmus MC Pompe survey is an example of the successful international collaboration between patient organizations and academic hospitals, and has shown that patient-reported information can complement more traditional outcome measures such as the assessment of muscle strength and respiratory function.

SAMENVATTING

De ziekte van Pompe is een erfelijke stofwisselingsziekte die veroorzaakt wordt door een tekort aan het enzym zure α-glucosidase. Normaal gesproken zorgt dit enzym ervoor dat glycogeen (suikerketens) in de lysosomen afgebroken wordt. Lysosomen zijn kleine 'blaasjes' in de cel die betrokken zijn bij het verwijderen en hergebruiken van verschillende stoffen. Wanneer er een tekort is aan α-glucosidase kan het glycogeen niet afgebroken worden en stapelt het zich op in het lysosoom. Dit gebeurt in vrijwel alle lichaamscellen, maar de effecten zijn het duidelijkst zichtbaar in de spieren. De hoeveelheid enzym die nog over is (de 'restactiviteit') bepaalt in grote lijnen het klinische beeld van de ziekte. De restactiviteit wordt op zijn beurt weer grotendeels bepaald door de soort mutaties in het gen dat codeert voor zure α-glucosidase. Patiëntjes met de klassiek infantiele vorm van de ziekte van Pompe hebben van zichzelf vrijwel geen restactiviteit. De eerste symptomen, algehele spierzwakte en een vergroot hart, zijn vaak al vlak na de geboorte zichtbaar. Deze kinderen worden meestal niet ouder dan 1 jaar. De niet-klassieke of 'late-onset' vorm van de ziekte van Pompe is een langzaam voortschrijdende spierziekte, waarbij voornamelijk de skeletspieren zijn betrokken en niet het hart. De spieren die het dichtst bij de romp liggen zijn het meest aangedaan. Deze patiënten hebben wel een bepaalde hoeveelheid restactiviteit, wat leidt tot het langzamere beloop. Er zijn grote verschillen tussen patiënten onderling. De eerste symptomen treden bij sommigen al als kind op, terwijl er ook patiënten zijn die pas rond het zestigste levensjaar klachten krijgen. Uiteindelijk zijn vaak een rolstoel en (nachtelijke) beademing nodig.

De ziekte van Pompe komt naar schatting 1 keer per 40.000 geboorten voor en is daarmee een zeldzame ziekte. Het was ook lang een ongeneeslijke ziekte, waarvoor alleen ondersteunende behandelingen zoals kunstmatige beademing mogelijk waren. In het Erasmus MC wordt al sinds lange tijd onderzoek gedaan naar enzymtherapie voor de ziekte van Pompe. Bij enzymtherapie wordt het ontbrekende enzym, dat niet door het eigen lichaam aangemaakt wordt, van buitenaf toegediend via een infuus. Eerst werden proeven gedaan waarin de opname van het enzym bestudeerd werd in gekweekte huidcellen en spierweefsel. Daarna werd het uitgetest bij dieren en uiteindelijk ging in 1999 de eerste klinische studie (onderzoek bij mensen) van start. Op dit moment worden er wereldwijd al meer dan 250 patiënten met enzymtherapie behandeld in klinische studies en op basis van 'compassionate use', dat wil zeggen dat ernstig zieke patiënten het middel al voordat het officieel op de markt is kunnen ontvangen. Sinds maart 2006 is in de Europese Unie enzymtherapie met recombinant humaan α-glucosidase (Myozyme®) officieel geregistreerd voor de behandeling van de ziekte van Pompe.

De ontwikkeling van nieuwe medicijnen voor zeldzame ziekten kent specifieke problemen, zoals het geringe aantal patiënten en de vaak grote verschillen in ziektebeloop tussen

patiënten. Een goed overzicht van het natuurlijke beloop van een ziekte is belangrijk om de effecten van een nieuwe behandeling op waarde te kunnen schatten, met name voor zeldzame aandoeningen zoals de ziekte van Pompe.

De behoefte aan meer inzicht in het natuurlijk beloop en in de verschillen tussen patiënten onderling was duidelijk aanwezig voor de niet-klassieke of 'late-onset' vorm van de ziekte van Pompe. In 2002 werd daarom in een samenwerking tussen Erasmus MC en de International Pompe Association (IPA), een overkoepelende organisatie van patiëntengroepen, begonnen met de IPA/ Erasmus MC Pompe survey. Dit is een doorlopende internationale studie waarin door middel van vragenlijsten gegevens verzameld worden van kinderen en volwassenen met de ziekte van Pompe. Het doel van dit onderzoek is om uiteindelijk een goede beschrijving te kunnen geven van het natuurlijk beloop, de ernst van de ziekte en de invloed op het dagelijks leven. Een tweede doel was het ontwikkelen en testen van meetschalen voor het vastleggen van de ernst van de ziekte en het meten van veranderingen in de tijd. Op dit moment hebben ongeveer 300 Pompe-patiënten aan het onderzoek deelgenomen via de bij de IPA aangesloten patiëntenverenigingen in Nederland, Duitsland, Groot-Brittannië, Frankrijk, de Verenigde Staten, Australië en Canada. Dit proefschrift beschrijft de resultaten van de eerste 'meetronde' in de totale groep patiënten en de eerste twee jaren van de vervolgstudie in de Nederlandse subgroep.

In **hoofdstuk 1** wordt achtergrondinformatie gegeven over de ziekte van Pompe: oorzaak, epidemiologie (het vóórkomen van de ziekte), het klinische beeld, de testen die nodig zijn om de diagnose te stellen en de (toekomstige) behandelingsmogelijkheden. Ook wordt stilgestaan bij de ontwikkeling van medicijnen voor zeldzame ziekten, de zogenaamde 'weesgeneesmiddelen'. In **hoofdstuk 2** worden de opzet van de IPA/ Erasmus MC Pompe survey, het werven van de deelnemers en de gebruikte meetschalen besproken. Voordat overgegaan wordt op het bespreken van de resultaten van de survey, geeft **hoofdstuk 3** eerst een overzicht van de informatie die verkregen werd uit een overzichtsstudie van 225 patiënten met de niet-klassieke vorm van de ziekte van Pompe, die eerder in de literatuur beschreven werden. Hieruit komt het continue spectrum van de ziekte duidelijk naar voren. Zo werden er grote verschillen gevonden in de leeftijd waarop de eerste klachten optraden, de leeftijd waarop de diagnose gesteld werd en de leeftijd waarop beademing of rolstoelgebruik noodzakelijk werden. Op basis van de 225 patiëntenbeschrijvingen konden we geen duidelijke criteria ontdekken voor het verder opdelen van de niet-klassieke vorm in verschillende subtypen met een specifiek beloop. Verder bevestigden de resultaten van deze literatuurstudie nog eens dat het belangrijk is om de diagnose te stellen door het meten van de zure α-glucosidase activiteit in gekweekte huidcellen of spierweefsel, omdat andere methoden niet altijd de juiste uitslag geven. Gegevens over spierkracht en spierfunctie, longfunctiewaarden, de mate van handicap en kwaliteit van leven werden in de literatuur nauwelijks beschreven.

In **hoofdstuk 4** zijn de eerste resultaten van de IPA/ Erasmus MC Pompe survey in de groep van 54 Nederlandse patiënten uitgewerkt. Een belangrijk punt dat hieruit naar voren kwam was dat bijna 60% van de volwassen deelnemers als kind al milde klachten had die gerelateerd waren aan de ziekte van Pompe. Ook werd uit dit onderzoek duidelijk dat de ziekte van Pompe een echt spectrum is, waarbij de eerste symptomen op elke leeftijd mogelijk zijn en waarbij de volgorde van mobiliteits- en ademhalingsproblemen niet vast ligt. Daarom is het volgen van de longfunctie belangrijk, hoe oud een patiënt ook is en of hij nu loopproblemen heeft of niet. Een andere observatie uit dit onderzoek was dat vermoeidheids- en pijnklachten bij de ziekte van Pompe veel vaker voorkomen dan werd aangenomen.

De internationale groep van 255 patiënten beschreven in **hoofdstuk 5** was groot genoeg om een indeling te kunnen maken op basis van leeftijd en ziekteduur en om deze twee variabelen te relateren aan de ernst van de ziekte. Hieruit werd duidelijk dat de ernst van de ziekte samenhangt met de ziekteduur, maar los staat van de leeftijd van de patiënt. Dat wil zeggen dat in het algemeen patiënten met vroege symptomen ook eerder een rolstoel en/of beademing nodig hebben, maar dat de tijd tussen aanvang van de klachten en het gebruik van deze hulpmiddelen gemiddeld gelijk is. We zagen echter ook dat van de patiënten onder de 15 jaar ongeveer een kwart een duidelijk sneller en ernstiger ziektebeloop had. Deze kinderen hadden allemaal zowel beademing als een rolstoel nodig en kregen aanvullende sondevoeding. De eerste klachten traden op voor het tweede levensjaar.

Van de Nederlandse groep patiënten zijn ook gegevens na een en na twee jaar verzameld. De resultaten van dit vervolgonderzoek zijn te lezen in **hoofdstuk 6.** Zelfs in deze relatief kleine patiëntengroep was een duidelijke achteruitgang te meten in mobiliteit, ademhaling en in de score op de Rotterdam Handicap Scale. Deze resultaten zeggen iets over de mate waarin de niet-klassieke of 'late-onset' vorm van de ziekte van Pompe voortschrijdt en geven aan dat het nodig is om zowel kinderen als volwassenen met deze ziekte regelmatig te onderzoeken. Op basis van de bruikbare resultaten uit de Nederlandse groep is besloten om de vervolgstudie uit te breiden naar alle patiënten die in de eerste ronde ook meededen aan de survey.

In **hoofdstuk 7** werd onder 210 volwassen patiënten uit verschillende landen de gezondheidsgerelateerde kwaliteit van leven gemeten. Dit gebeurde met een specifiek meetinstrument, de SF-36. Deze vragenlijst meet kwaliteit van leven op 8 gebieden: fysiek functioneren, rolbeperkingen door fysieke gezondheidsproblemen, lichamelijke pijn, ervaren gezondheid, vitaliteit, sociaal functioneren, rolbeperkingen door emotionele problemen en geestelijke gezondheid. In het algemeen scoorden patiënten met de ziekte van Pompe erg laag op het gebied van lichamelijke gezondheid, maar verschilden ze nauwelijks van de algemene bevolking op het gebied van geestelijke gezondheid. Er waren

geen duidelijke verschillen tussen patiënten uit de verschillende landen. De geschiktheid van de SF-36 voor het meten van veranderingen was twijfelachtig.

In **hoofdstuk 8** werd met de 'Fatigue Severity Scale' (FSS) vermoeidheid in meer detail bestudeerd in de internationale patiëntengroep. De FSS is een korte en eenvoudige vragenlijst met 9 uitspraken over vermoeidheid en de invloed van vermoeidheid op het dagelijks leven. De gemiddelde score van patiënten met de ziekte van Pompe lag veel hoger dan die van gezonde controlepersonen. Vermoeidheid blijkt een belangrijk symptoom van de ziekte van Pompe te zijn dat voorkomt bij zowel milde als ernstig aangedane patiënten. De FSS lijkt een goed instrument te zijn om vermoeidheid bij patiënten met de ziekte van Pompe te meten.

Het vooruitzicht van een behandeling maakt het (nog) belangrijker om ook de sociale gevolgen van de ziekte in kaart te brengen. In **hoofdstuk 9** hebben we onderzocht of de 'Rotterdam Handicap Scale' (RHS) een goede meetschaal is om deze gevolgen vast te leggen. De RHS meet de mate van participatie in het dagelijks leven, een begrip dat ook bekend is onder de naam 'handicap'. Dit gebeurt door middel van 9 vragen over de volgende onderwerpen: mobiliteit binnenshuis, mobiliteit buitenshuis, keukentaken, huishoudelijk werk binnenshuis, huishoudelijk werk buitenshuis, ontspanning binnenshuis, ontspanning buitenshuis, reizen en werk of studie. Op basis van de resultaten in de internationale groep lijkt de RHS heel geschikt voor patiënten met de ziekte van Pompe. De gemiddelde RHS score was duidelijk verlaagd, en het bleek dat de ziekte met name van invloed was op de mogelijkheid van de patiënten om hun werk of studie uit te voeren.

Tenslotte worden in **hoofdstuk 10** de belangrijkste bevindingen op een rijtje gezet, enkele beperkingen besproken en worden suggesties gedaan voor toekomstig onderzoek. Een voorstel wordt gedaan voor een 'basis-set' van metingen voor het volgen van patiënten met de ziekte van Pompe in de tijd. Zo'n gestandaardiseerde verzameling van gegevens is belangrijk, met name voor zeldzame ziekten, omdat alleen zo de gegevens die in de verschillende centra en verschillende landen verzameld worden met elkaar kunnen worden vergeleken en samengevoegd. Om de vele nog openstaande vragen met betrekking tot de precieze oorzaak van de spierzwakte, het natuurlijk beloop en de behandeling van de ziekte van Pompe te kunnen beantwoorden is een nauwe samenwerking tussen basaal en klinisch onderzoek en tussen kindergeneeskunde en 'volwassen' specialismen nodig, het liefst in de vorm van een expertisecentrum.

De IPA/ Erasmus MC Pompe survey is een voorbeeld van de succesvolle internationale samenwerking tussen patiëntenorganisaties en academische ziekenhuizen en heeft laten zien dat informatie die rechtstreeks van de patiënt afkomstig is een nuttige aanvulling kan zijn op meer traditionele uitkomstmaten zoals het meten van spierkracht en longfunctie.

Curriculum vitae

List of publications

List of abbreviations

CURRICULUM VITAE

Marloes Hagemans was born on November 18, 1977 in Terneuzen, the Netherlands. She passed her secondary school exam (Atheneum) at the Zeldenrustcollege in Terneuzen in 1995 and went on to study Nutrition and Health at Wageningen University. Her training included a 6-month research period at the Julius Center for Health Sciences and Primary Care (University Medical Center Utrecht) on the relationship between estrogen exposure and bone mineral density, and a 6-month research period at the ICDDR,B Centre for Health and Population Research in Dhaka on the food and nutrient intake of pregnant women in a rural area of Bangladesh. She obtained her MSc degree in 2001 (cum laude). In October 2001 she joined the Pompe-research team of dr. A.T. van der Ploeg (department of Pediatrics) and dr. A.J.J. Reuser (department of Clinical Genetics) at the department of Pediatrics, Metabolic Diseases and Genetics of Erasmus MC Rotterdam, where the studies described in this thesis were performed. Marloes lives in Breda and is married to Lennart Nicolai.

Marloes Hagemans werd op 18 november 1977 geboren te Terneuzen. In 1995 behaalde zij het Atheneumdiploma aan het Zeldenrustcollege in Terneuzen en begon aan de studie Voeding en Gezondheid aan de Wageningen Universiteit. Tijdens haar studie deed zij gedurende 6 maanden onderzoek naar de relatie tussen oestrogenen en botmineraaldichtheid bij het Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde (Universitair Medisch Centrum Utrecht). Een tweede periode van 6 maanden werd doorgebracht aan het ICDDR,B Centre for Health and Population Research in Dhaka, waar zij de voedsel- en nutriëntinname van zwangere vrouwen op het platteland van Bangladesh bestudeerde. In 2001 studeerde zij cum laude af. In oktober van hetzelfde jaar begon zij als wetenschappelijk onderzoeker in het Pompe-onderzoeksteam van dr. A.T. van der Ploeg (afdeling Kindergeneeskunde) en dr. A.J.J. Reuser (afdeling Klinische Genetica) op de afdeling Kindergeneeskunde, Metabole Ziekten en Genetica van het Erasmus MC in Rotterdam, waar het in dit proefschrift beschreven onderzoek uitgevoerd werd. Marloes woont in Breda en is getrouwd met Lennart Nicolai.

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LIST OF ABBREVIATIONS

AAV	Adeno-associated virus
Ad	Adenovirus
ADL	Activities of daily living
AGLU	Acid α-glucosidase
AIMS	Alberta Infant Motor Scale
ALAT	Alanine aminotransferase
ALDS	Academic Medical Center Linear Disability Scale
ANOVA	Analysis of variance
ASAT	Aspartate aminotransferase
BSIDII	Bayley Scales of Infant Development II
CHMP	Committee for medicinal products for human use
CHO-cells	Chinese hamster ovary cells
CHQ	Child Health Questionnaire
CI	Confidence interval
CK	Creatine kinase
DNA	Deoxyribonucleic acid
EMEA	European Medicines Agency
ERT	Enzyme replacement therapy
ES	Effect size
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
GAA	Acid α-glucosidase gene
GMFM	Gross Motor Function Measure
HADS	Hospital Anxiety and Depression Scale
ICC	Intraclass correlation coefficient
ICF	International classification of functioning, disability and health
ICIDH	International classification of impairments, disabilities, and handicaps
IPA	International Pompe Association
IQR	Interquartile range
kDA	Kilo dalton
LDH	Lactate dehydrogenase
LSD	Lysosomal storage disorder
LVMI	Left ventricular mass indexed by body surface area
LVPWd	Left ventricular posterior wall thickness measured at diastole
MOS	Medical Outcomes Study
MRC	Medical Research Council
mRNA	Messenger ribonucleic acid
4-MU	4-methylumbelliferyl-α-D-glucopyranoside
OMIM	Online Mendelian Inheritance in Man
PAS	Periodic acid Schiff reagent
PEDI	Pediatric Evaluation of Disability Inventory
PEG	Percutaneous endoscopic gastrostomy
PedsQL-MFS	Pediatric Quality of life Inventory-Multidimensional Fatigue Scale
RHS	Rotterdam Handicap Scale
SD	Standard deviation
SEM	Standard error of the mean
SF-36	Medical Outcomes Study short-form 36 health survey
SRM	Standardized response mean
VSN	Vereniging Spierziekten Nederland
WHO	World Health Organization

Dankwoord

DANKWOORD!

Allereerst dank aan alle patiënten die hebben deelgenomen aan dit onderzoek; many thanks to all patients who participated in this study. I sometimes felt I was asking too much of you, but you kept answering all my questions and completing my questionnaires. Without you, this study would not have been possible. Thank you very much, danke schön, merci beaucoup, dank jullie wel!

Ook dank aan de patiënten, ouders en partners die ik in de loop van dit onderzoek persoonlijk heb leren kennen, in het ziekenhuis en via de patiëntenvereniging. Door jullie kreeg ik inzicht in wat het betekent te leven met de ziekte van Pompe en hoe het is om in afwachting te zijn van een nieuw medicijn. Ik heb veel bewondering voor de manier waarop jullie je leven inrichten en hoop dat de toekomst veel goeds mag brengen.

Dr. van der Ploeg, beste Ans, ik heb ontzettend veel van je geleerd. Jij gaat altijd door, ook als het tegenzit, en blijft geloven in jezelf, het team en het project. Jouw enorme inzet en betrokkenheid zijn bewonderenswaardig. 'Never a dull moment' in de af en toe chaotische wereld van het Pompe-onderzoek, en temidden van dat alles ben ik erg blij met je steun en vertrouwen.

Dr. Reuser, beste Arnold, ook jij bedankt voor alle hulp en steun de afgelopen jaren. Met je kritische blik op manuscripten en je vermogen om gewoon erg goed na te denken over hoe iets daadwerkelijk in elkaar zit werd het er altijd weer beter van. Jij en Ans vormen samen een geweldig team dat aan de basis stond en staat van de enzymtherapie voor de ziekte van Pompe.

Prof. van der Heijden, fijn dat u mijn promotor wilde zijn. Dank voor uw interesse in dit onderzoek en het Pompe-onderzoek in het algemeen. Prof. van Doorn, beste Pieter, dank voor de prettige samenwerking bij de verschillende artikelen in dit proefschrift. Jouw nadruk op het helder en leesbaar houden van de tekst en het altijd in gedachten houden voor wie je het schrijft heb ik goed onthouden! Fijn ook dat je plaats wilde nemen in de kleine commissie. Ook prof. Niermeijer en prof. van Duijn wil ik hartelijk danken voor het vlot lezen van het manuscript en voor het nuttige commentaar.

Dr. Winkel en dr. Hoving, ik ben blij dat jullie mijn zeergeleerde paranimfen zijn. Léon, het is alweer even geleden, maar we waren toch wel een goed team samen! Bedankt voor de goede samenwerking, de gezelligheid en de discussies, over het onderzoek maar ook over alles daarbuiten. Saske, jij werkte al in het Erasmus MC toen ik hier kwam en eigenlijk ben ik zelfs mede dankzij jou hier terechtgekomen. Het was ontzettend leuk om een vriendin uit Wageningen zo dicht in de buurt te hebben, jammer dat je nu helemaal in Amsterdam zit!

Dr. Kamphoven en dr. van den Hout, samen met Léon zijn jullie mijn voorgangers op het promotietraject. Hannerieke, je weet het misschien zelf niet meer maar ik herinner me nog heel goed de 'spoedcursus Pompe en alles wat eromheen gebeurt' op mijn eerste werkdag hier. Joep, de 'muizenman' die inmiddels via de Klinische Genetica bij de Huisartsgeneeskunde (èn in Breda) terecht is gekomen. Bedankt voor de gezelligheid, o.a. tijdens het 10-uur-heen-12-uur-terug-uitstapje naar Praag!

Nadine, na een flitsend begin in Boston zijn we ook nog samen naar Athene, Londen en Berlijn geweest. Dat was elke keer weer erg gezellig, vooral het in elkaar zetten van onze presentatie op een belachelijk vroeg tijdstip op het vliegveld in Brussel…Jouw studie is in anderhalf jaar tijd behoorlijk van karakter veranderd en je hebt het er nu heel erg druk mee, maar het gaat zeker iets moois opleveren! Jacqueline, je bent een erg plezierige kamergenoot en een heel betrokken researchverpleegkundige. Knap hoe jij het overzicht weet te houden in die ongelooflijke wirwar aan studies, afspraken en protocollen. Rineke en Anna Karina, ik ben heel blij dat jullie sinds kort aan het 'survey-team' toegevoegd zijn. Tot nu toe loopt het heel goed en nu ik weer meer tijd heb kunnen we er samen nog wat dieper induiken. Carine, jij kwam vorig jaar zomer ons team versterken en werd meteen in het diepe gegooid. Maar het zwemmen gaat je erg goed af en je enthousiasme werkt aanstekelijk!

Marian, jij blijft altijd rustig temidden van alle verwikkelingen en werkt gestaag door aan alles wat er in het lab moet gebeuren. Bedankt voor de goede samenwerking met de databases, hopelijk zetten we die nog even voort! Sabine, jij kwam als student bij ons onderzoek doen en bleef daarna ook nog om te helpen met het opstarten van een nieuwe trial. Bedankt voor al het werk dat je voor het Fatigue Scale-artikel hebt gedaan. Christa Loonen, jij bent al heel lang betrokken bij het onderzoek naar de ziekte van Pompe en ik vond het ontzettend leuk dat je ook aan een aantal van mijn manuscripten mee hebt willen werken. Marianne van Elck, zonder jou zou het Pompe-team behoorlijk in de soep lopen. Bedankt voor al je hulp! Ook Hans de Klerk, Otto van Diggelen, Laura, Remco, Ralph, en de vele, vele anderen die in meer of mindere mate bij het Pompe-onderzoek betrokken zijn of zijn geweest wil ik hartelijk danken.

Wim Hop, jij zorgde ervoor dat mijn manuscripten statistisch verantwoord waren, hartelijk dank hiervoor! Ingemar Merkies, ik heb veel van je geleerd over onderzoek doen met meetschalen, bedankt voor de stevige discussies! Dr. Pascal Laforêt, thank you for your help in the initiation of the IPA/ Erasmus MC Pompe survey in France and for the pleasant collaboration on the Rotterdam Handicap Scale manuscript. Cecile Janssens, dankjewel voor je hulp bij de kwaliteit-van-leven en vermoeidheidsdata, je heldere kijk en vooral voor de prettige samenwerking.

De beste koffie in het Erasmus MC was altijd te vinden bij Kris Sieradzan. Kris, ik kwam

bij jou voor wat in eerste instantie een ‘tussendoorprojectje’ van een week of drie zou worden... het werd ietsje langer. Dank voor het ontwerpen van de Teleform-formulieren en voor je hulp bij het verwerken van alle gegevens! Tom de Vries Lentsch, heel, heel hartelijk bedankt voor het vele werk dat je in de lay-out van dit proefschrift hebt gestopt en voor het bewerken van de figuren voor de verschillende publicaties. Ook Anneke Hoekzema wil ik graag bedanken, voor de hulp bij al het regel- en papierwerk dat bij promoveren komt kijken.

Also many thanks to the contact persons of the International Pompe Association and the patient organizations in the different countries: Ria Broekgaarden, Thomas Schaller, Randall and Marylyn House, Bob Morrison, Helen Walker, Allan and Barbara Muir, Kathy McPherson, and Christelle and Florence Fauré.

De lunches, borrels, kerstdiners en weekenden met de vele collega-onderzoekers vond ik altijd ontzettend leuk. Met name wil ik graag bedanken mijn voormalige kamergenoten Sophie en Marieke (koffie, thee, choco-de-luxe, dubbele cup-a-soups...) en mijn hardloopmaatje Maaike (met z’n tweeën rennen is echt leuker!). Floor, het was erg leuk om nòg een vriendin in Rotterdam te hebben om mee thee te drinken, te lunchen en af en toe te borrelen. Jij en Saske waren altijd op de hoogte van de ups en downs van mijn onderzoek, en andersom. Marleen, jij zat behoorlijk ver uit de buurt de afgelopen tijd, maar onze Breda-Hanoi msn en skype gesprekken maakten veel goed. Nu je terug bent in dit kikkerlandje en dit proefschrift af is kunnen we weer vaker afspreken!

Natuurlijk mogen ook mijn ouders, Pim en Els, hier niet ontbreken. Jullie hebben mij altijd het gevoel gegeven dat ik bij jullie terechtkan, wat er ook gebeurt, en daar ben ik heel blij mee. Papa, jij zag ons altijd al wel eens promoveren, het duurde even voor ik daar zelf ook de lol van inzag. Heb je toch gelijk gekregen;-). Rob, bij je afstuderen in de natuurkunde snapte ik maar de helft van alle praatjes, hopelijk kun jij hier meer van maken. Volgend jaar (?) ben jij aan de beurt! Ook dank aan mijn schoonouders Peter en Anneke, voor jullie interesse in mijn werk en voor de gezellige weekenden aan de Zeeuwse kust.

Lieve Lennart, alle punten en komma’s in dit proefschrift zijn door jou op de juiste plek gezet, maar dat is natuurlijk niet het enige…Wat is het leuk samen met jou! Bedankt voor je liefde, steun en al onze discussies over leven, werk, geloof en de toekomst. Laat die maar komen, samen maken we er iets moois van!