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

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Summary

Late-onset Pompe's 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 >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's 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's disease; glycogen storage disease type II; α-glucosidase; acid maltase; natural course

Abbreviations: ERT = enzyme replacement therapy; VSN = Vereniging Spierziekten Nederland (Dutch Neuromuscular Diseases Association)

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Introduction

Pompe's 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 intra-lysosomal accumulation of glycogen in skeletal muscle and other tissues (Hirschhorn and Reuser, 2001). The number of individuals born with the disease is predicted as 1 in 40 000 (Martiniuk *et al*., 1998; Ausems *et al*., 1999). 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 (Engel and Hirschhorn, 1994; Hirschhorn and Reuser, 2001). Classic infantile Pompe's disease presents in the first months of life and most infants die within 1 year from cardiorespiratory insufficiency (Hirschhorn and Reuser, 2001; Van den Hout

et al., 2003). Late-onset Pompe's 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 (Engel and Hirschhorn, 1994; Hirschhorn and Reuser, 2001).

A registered therapy is not yet available, but enzyme replacement therapy (ERT) for Pompe's 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 (Van den Hout *et al*., 2000, 2004). Beneficial effects of ERT were also reported for patients with late-onset Pompe's disease (Winkel *et al*., 2004). 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's disease has been reviewed (Di Sant'Agnese *et al*., 1950; Ehlers *et al*., 1962; Van den Hout *et al*., 2003), 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's 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 >100 case reports of patients with childhood, juvenile and adult forms of Pompe's disease to identify symptoms and signs possibly related to Pompe's disease. Questions were included after review and discussion by a panel of experts on Pompe's disease at Erasmus MC. This panel consisted of six senior staff members from our departments of neurology, paediatric neurology, paediatrics, internal medicine and clinical genetics, all involved in research projects on Pompe's disease. Six medical specialists (three neurologists, two paediatricians and one clinical geneticist) with experience in the field of Pompe's 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's 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's 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's 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's 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 analysing 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 0–5 years ago, 2.5 years were subtracted from the date of questionnaire completion; for 5–10 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 3.9–81.2; Fig. 1A). The 10 initial non-responders (three male, seven female) tended to be older (mean age 57.0 ± 13.7 years, range 36–72) 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's 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's 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.

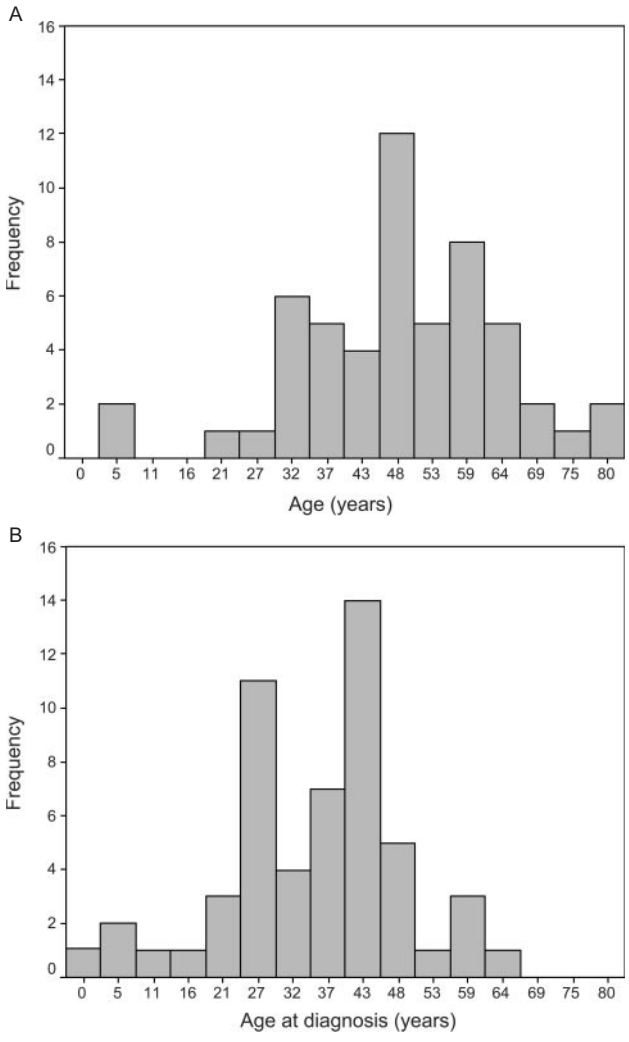


Fig. 1 Age distribution of 54 Dutch patients with late-onset Pompe's disease at the time of questionnaire completion (**A**) and at diagnosis (**B**).

Diagnosis

The mean age at diagnosis was 35.4 ± 13.9 years, ranging from shortly after birth to 63 years (Fig. 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's 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 5–30 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's 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's 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

Table 2 *Ability to perform specific movements of 51 adult patients with late-onset Pompe's 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

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.

Respiratory problems

In our study population, 20 patients (37%, Fig. 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 h per day (range 8–24 h). 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 32–81 years) and the mean age at the start of using artificial ventilation was 48.6 ± 16.3 years (range 15–78 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's 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 (Fig. 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.

Discussion

The direct occasion for this study was the development of ERT for Pompe's 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's 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.

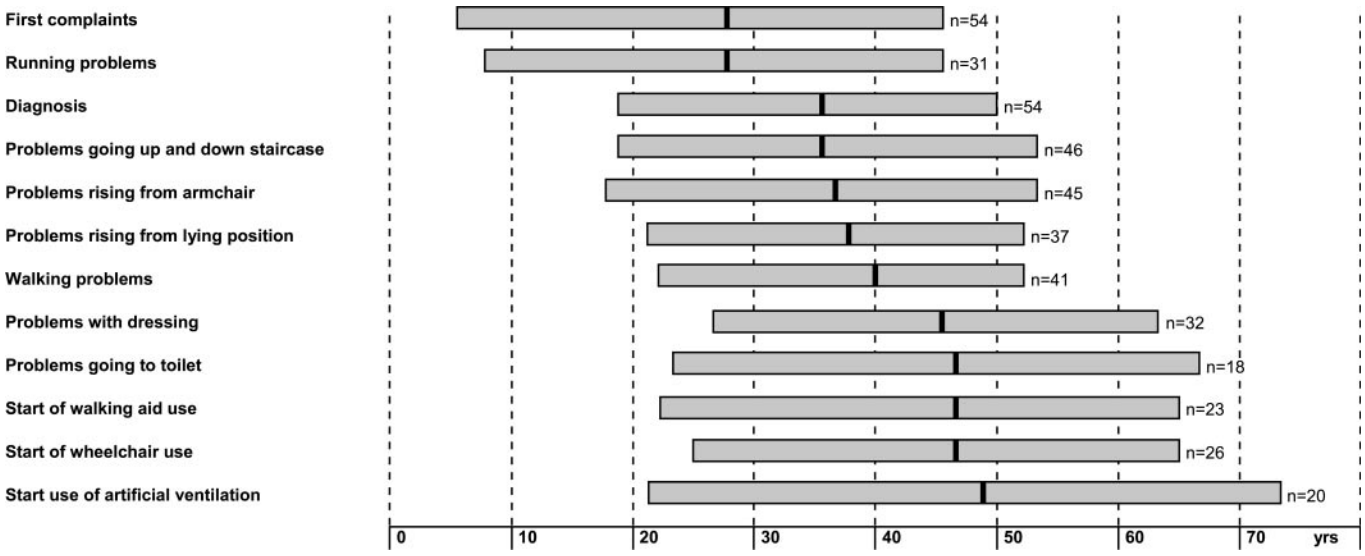
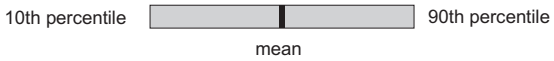


Fig. 2 Age distribution for specific events in the course of the disease for 54 late-onset Pompe patients. The number behind each bar indicates how many patients provided information on the time of these events.



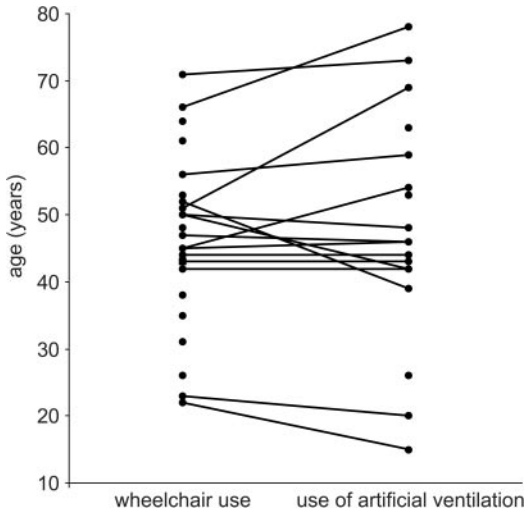


Fig. 3 Age at wheelchair use and use of artificial ventilation in 31 patients with late-onset Pompe's disease. The age at start of using a wheelchair and the age at start of using artificial ventilation are connected with lines for patients using both aids (n = 15).

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 (Engel and Hirschhorn, 1994; Kishnani and Howell, 2004). 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's 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's 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 (Laforet *et al*., 2000; Mellies *et al*., 2001). 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's disease, reporting mild muscular symptoms during childhood in 16 out of 21 patients (Laforet *et al*., 2000). 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 (Laforet *et al*., 2000; Mellies *et al*., 2001) 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 (Laforet *et al*., 2000) and the Overall Disability Sumscale (Merkies *et al*., 2002*a*). To evaluate disease severity in late-onset Pompe's 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 (Merkies *et al*., 2002*b*). 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 (Wokke *et al*., 1995). Although pain and fatigue are considered subjective and are associated with a variety of disorders, they deserve further attention in relation to Pompe's disease. The measurement of pain and fatigue could prove useful in the evaluation of treatment effects, and instruments such as the Fatigue Severity Scale (Krupp *et al*., 1989; Merkies *et al*., 1999) or the Brief Pain Inventory (Cleeland, 2002; Schiffman *et al*., 2001) 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's 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 7–20 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 (36–72 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's 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's 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.

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