Severely impaired health status at diagnosis of Pompe disease: A cross-sectional analysis to explore the potential utility of neonatal screening

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ABSTRACT

Since the introduction of enzyme replacement therapy for Pompe disease, awareness and early diagnosis have gained importance. Because the therapy is most effective when started early and methods for dried bloodspot screening for Pompe disease are currently being explored, neonatal screening is getting increased attention. The objective of this study was to investigate the gains that might be achieved with earlier diagnosis by neonatal screening. For this purpose we analyzed the health and functional status of non-screened patients with Pompe disease at the time of diagnosis.

Previously collected clinical data and results of an international patient-reported questionnaire were used. Cross-sectional data of 53 patients with Pompe disease diagnosed between 1999 and 2009 (aged 0–64 years) were analyzed. According to the World Health Organization's International Classification of Functioning, Disability and Health the following domains are described: body function, activity, participation and contextual factors.

In all patients with classic infantile Pompe disease cardiac function, hearing, muscle strength and motor development were considerably impaired at the time of clinical diagnosis. The use of oxygen and/or nasogastric tube-feeding was reported in more than 70% of these cases. Most children, adolescents and adults had advanced muscle weakness and impaired respiratory function at the time of their diagnosis, causing varying degrees of handicap. About 12% of them used a walking device and/or respiratory support at the time of diagnosis.

The severely impaired health status reported here provides a strong argument for earlier diagnosis and to further explore the potential of neonatal screening for Pompe disease.

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1. Introduction

Pompe disease, or glycogen storage disease type II [OMIM ID: 232300], is an autosomal recessive lysosomal storage disorder. It is

caused by a deficiency of acid alpha-glucosidase (GAA) [EC 3.2.1.20] which leads to glycogen accumulation in the lysosomes, predominantly resulting in progressive weakening of the muscles. The frequency of Pompe disease in the Netherlands is about 1/40,000 [1]. The genotype–phenotype correlation is largely understood in that the nature of the mutations in both GAA alleles determines the degree of enzyme deficiency, but secondary genetic factors or non-genetic factors also contribute to the broad clinical spectrum of phenotypes seen within Pompe disease [2]. Generalized hypotonia, respiratory difficulties and cardiomyopathy manifesting in the first months of life are characteristic features of the so-called classic infantile form of Pompe disease. Without treatment these patients die within the first year of life due to cardiorespiratory failure [3]. Other patients with Pompe disease have symptoms that can occur at any age, from early childhood until the sixth decade, and typically do not suffer from cardiomyopathy. In these patients the disease is characterized by a less progressive limb–girdle myopathy and decreased pulmonary function. When untreated these children, juveniles and adults with

Pompe disease may become wheelchair-dependent or in need of respiratory support. Respiratory insufficiency is the major cause of death in these patients [2,4].

Enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase (alglucosidase alfa), the first available treatment for Pompe disease, received market approval in Europe and the United States in 2006. Although not all patients respond equally well, the outcomes of treatment are promising. Previously published studies among patients with classic infantile Pompe disease ($n = 18$, aged 1–6 months) showed a prominent effect of ERT on cardiac hypertrophy and function and a substantial effect on survival. However, 4 of the 18 studied patients died before the age of 36 months and half of the studied patients required invasive ventilation at age 36 months, at the time of death or by the end of the study [5]. In children and adults with Pompe disease ($n = 60$, aged 15–70 years) treatment with ERT is associated with improved walking distance and stabilization of pulmonary function over an 18-month period [6,7]. Clinical trials indicate a better clinical outcome if ERT is started early in the course of the disease [5,8,9]. Due to rarity of the disease and the variation in disease presentation, the diagnosis of Pompe disease is often considerably delayed [2,4]. In the Netherlands, the median age of symptom onset of classic infantile Pompe disease has been earlier described as 1.6 months, whereas the median age of diagnosis was around 5 months of age [3]. For the less progressive phenotypes a median doctors' delay of 7 years has been described [4,10]. Diagnosing patients in an earlier stage of the disease, or even before onset of symptoms, enables early intervention which could prevent or postpone further health damage.

The most promising option to enable earlier diagnosis is neonatal screening. It is conceivable to integrate the screening for Pompe disease into current neonatal screening programs. Recently it has been shown in Taiwan that nationwide testing of GAA-activity in dried bloodspots substantially reduced the diagnostic delay for infants with classic infantile Pompe disease [11]. This screening program confirms that early diagnosis and subsequent early treatment in babies with classic infantile Pompe disease could improve prognosis [5,12,13]. An important disadvantage of the currently available blood-spot based tests is that at present they cannot distinguish between classic infantile Pompe disease and later-onset phenotypes. This distinction can only be made by clinical follow-up and more extensive laboratory testing, which means that a positive bloodspot test could inform parents not only about the fact that their newborn child will develop classic infantile disease but also about the fact that their newborn child is likely to develop symptoms of Pompe disease at an unpredictable time-point later in life [14]. The early detection of adult-onset diseases is not a goal of current neonatal screening programs, although in the case of Pompe disease timely diagnosis could enable doctors to carefully follow their patients and install ERT promptly when indicated.

To explore the potential of a screening test, analytic validity, clinical validity, clinical utility and ethical, legal and social implications need to be reviewed [15]. It is already known that including Pompe disease in neonatal screening programs without being able to filter for classic infantile Pompe disease raises many social, ethical and legal issues [16,17]. Analytic validity of various methods is being compared elsewhere [18,19] and information on clinical utility will evolve from experiences with implemented programmes. An important step in investigating the clinical utility of neonatal screening for Pompe disease is to get better insight into the health damage which could potentially be averted or delayed by earlier diagnosis.

This report aims to quantify the health and functional status of both patients with classic infantile Pompe disease and patients with a less progressive phenotype at the time of diagnosis. It discusses to what extent patients with Pompe disease may be prone to health and functional damage for various domains (e.g. clinical parameters and limitations in activities) in order to explore the potential benefits

of neonatal screening and subsequent early interventions for future patients with Pompe disease.

2. Methods

In this study a retrospective inventory was made of the documented health and functional status of patients with Pompe disease within a year after diagnosis. Prospectively collected data from previously conducted studies on natural course and effectiveness of ERT (e.g. [4,7,20,21]) were used to select relevant information. These data include clinical data from patient records and results from the IPA/Erasmus MC Pompe survey, an international patient reported questionnaire study [4]. A confirmed diagnosis of Pompe disease by enzyme activity assay and/or DNA analysis was the main inclusion criteria. Patients with the classic infantile form characteristically had virtually no enzyme activity and completely deleterious mutations on both alleles, while children and adults with late onset variants expressed at least one milder mutation. Further inclusion criteria for the present analysis were i) date of diagnosis between 1999 and 2009 and ii) less than 1 year between date of diagnosis and date of first visit at the Erasmus MC University Medical Center. These criteria were chosen to ensure adequate availability of patient records. Data were excluded when collected or referring to a moment more than a year after the year of diagnosis (for children and adults) or a moment more than 2 weeks after start of ERT (for classic infantile patients). Outcome measures of this study were chosen on the basis of the most apparent phenotypical characteristics of Pompe disease, which lie in the physical health domains of quality of life [22]. The selected data were used to describe patients' body function and structure (impairments), activity (limitations), participation (restrictions) and some contextual factors, following the International Classification of Functioning, Disability and Health [23].

2.1. Body function and structure impairments

The cardiac function and cardiac dimension of patients with classic infantile Pompe disease were examined by 2D M-mode echocardiography according to recommendations of the American Society of Echocardiography. The left ventricular mass index (LVMI) was used as a measure for hypertrophic cardiomyopathy and was expressed as the number of standard deviations from normal mean (z-scores) [24].

The hearing loss of patients with the classic infantile variant was evaluated by auditory brainstem-evoked responses, oto-acoustic emissions, and impedance audiometry as previously described [21].

To determine the degree of glycogen accumulation in the muscles and muscle damage of patients with classic infantile Pompe disease muscle biopsies from the M. quadriceps were used. Semi-quantitative data were obtained by histological examination with PAS-staining and evaluating the muscle fibers for their number of contractile elements. Muscle fibers were considered normal when surface area contained more than 75% contractile elements (see also [25]).

Skeletal muscle strength of children and adults was measured by manual muscle testing using the Medical Research Council (MRC) grading scale (range 0–5, 20 muscle groups tested (see for details Fig. 3)) [26] and Hand-Held Dynamometry (HHD) (13 muscle groups tested (see for details Fig. 2)) (Cytec dynamometer, CIT Technics, Haren, the Netherlands). The value measured by HHD (Newton) of each muscle group was expressed as percentage of the age- and sex-matched reference values (for children no reference value available for neck extensors) [27–29].

The pulmonary function at the time of diagnosis was assessed by analysing data on forced vital capacity (FVC). FVC was measured in upright seated and supine position using a Lilly type pneumograph (Viasys Healthcare, Würzburg, Germany) or the KoKo spirometry

system (Ferraris Respiratory, Louisville, CO, USA). Measurements were performed according to ATS/ERS standards [30] and reference values were derived from published data [31]. Results were expressed as percentage of the predicted normal value.

2.2. Activity limitation

Activity limitation of classic infantile patients was assessed by the Alberta Infant Motor development Scale (AIMS) [32]. The AIMS score is a percentile score of the gross motor development, which depicts the child's development.

To assess the muscle function of older children and adults, the Quick Motor Function Test (QMFT) was used. This test describes to what extent patients experience difficulty with sixteen different actions (e.g. sit-ups, jumping etc.). Scores per action can range from 0 (not possible, or not executed for other reason) to 4 (completed action) [33].

2.3. Participation restriction

The Rotterdam Nine Items Handicap Scale (RHS) is used to assess the self-perceived ability to perform certain everyday tasks. Scores per task can range from 0 (not applicable) or 1 (not able to perform task) to 4 (perceiving no difficulty with task). When calculating the percentage of patients having problems with a certain task, scores of zero are excluded [34].

2.4. Contextual factors

Information on the use of walking devices, ventilators, or feeding support was collected from the patients' medical files and the IPA/Erasmus MC Pompe survey [4].

2.5. Statistical analysis

Data were analyzed using descriptive statistics in SPSS for Windows (version 15.0, SPSS inc., Chicago, IL, USA).

3. Results

Data of 11 patients with classic infantile Pompe disease (median age at diagnosis: 1 month, range: 3–180 days), 13 affected children (median age at diagnosis: 10 years, range 0–16 years) and 29 adult patients (median age at diagnosis: 43 years, range: 24–68 years) met the inclusion criteria (see Table 1). There was an even gender distribution in this study population (not shown). Median time between diagnosis and date of collection of the data of patients with classic infantile Pompe disease was 12 days. Median time between first symptoms and diagnosis of the children in this study was 1 year (range 0–13) and in the adult patient group 8 years (range 0–43). Not all the selected parameters were available for all patients. Table 1 provides an overview of the age of the patients and number of patients included per test.

3.1. Classic infantile patients (n = 11)

At the time of diagnosis the left ventricular mass index (LVMI) of the 11 patients with classic infantile Pompe disease ranged from 98 to 599 g/m² with a median of 231 g/m², with reference values of 59.2 g/m² (normal mean), SD 7.9 [24]. This shows that even the lowest LVMI found in the study population already deviates 4.9 times the standard deviation from normal mean. Systolic function was depressed in four patients.

Data on hearing from before or within a maximum of 10 days after start of ERT were available for all eleven patients with classic infantile Pompe disease. Nine out of the 11 patients described around

Table 1
Available patient records: number and age of patients per test.

Patient group	Classic infantile	Affected children	Affected adults
n	**11**	**13**	**29**
Age: median (range)[a]	1 (0.1–6.0) m	10 (0–16) y	43 (24–68) y
Test			
Heart dimension (LVMI)	**11** 1 (0.1–6.0)		
Hearing loss (BERA)	**11** 1 (0.1–6.0)		
Muscle condition (biopsy)	**9** 1 (0.3–6.0)		
Motor development (AIMS)	**11** 1 (0.1–6.0)		
Muscle strength (HHD)		**8** 13 (8–16)	**29** 43 (24–68)
Muscle strength (MMT)		**5** 12 (4–14)	**29** 43 (24–68)
Pulmonary function (FVC)		**8**[b] 14 (10–16)	**29** 43 (24–68)
Muscle function (QMFT)		**8** 13 (4–16)	**29** 43 (24–68)
Handicaps (RHS)			**22** 44 (34–64)

[a] For classic infantile patients the median age and age range in the group is described in months (m), for children and adults in years (y).
[b] FVC in sitting position. In supine position FVC was measured of 7 children (mean age: 13 years, range: 7–16).

diagnosis had sensoneural hearing loss, with estimated hearing thresholds ranging from 10–90 dB. The nature of the hearing loss was mainly cochlear, although some patients also showed impaired middle-ear function, resulting in variable degrees of conductive hearing loss [21].

Muscle biopsies of nine infants with classic infantile Pompe disease were taken at the time of diagnosis. Analysis of the biopsies revealed that the samples contained 3%–77% normal fibers when evaluated for the preservation of contractile elements, with a median of 49%. Fig. 1A depicts the percentage-wise distribution of normal muscle fibers in the biopsies.

Motor development of all 11 infants was assessed at the time of diagnosis and all of them showed severe hypotonia and head lag. The percentile scores of the AIMS of the patients ranged from <1 to 50, with a median percentile score of 2. Five patients showed severe motor development delay (percentile score ≤5). The distribution of the percentile scores is depicted in Fig. 1B.

At the time of diagnosis 4 of the 11 infants required supplemental oxygen and 7 required (partial) nasogastric tubefeeding.
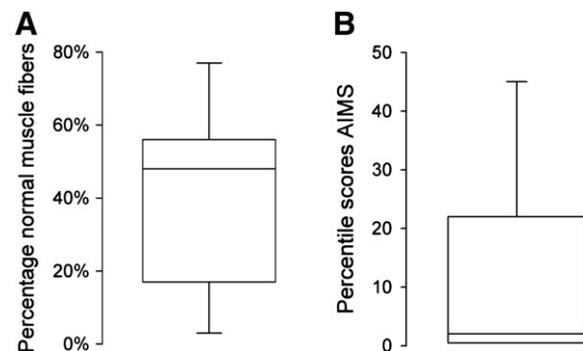

Fig. 1. Percentage normal muscle fibers in biopsies (A) (n = 11)* and AIMS percentile scores (B) (n = 11) of patients with classic infantile Pompe disease at the time of diagnosis. *Fibers with more than 75% surface area covered by contractile elements are considered normal.

3.2. Children (n = 13) and adults (n = 29)

The youngest child with Pompe disease without cardiac involvement was diagnosed directly after birth, due to an affected sibling. Of this patient only an AIMS-score (at the age of 3 months) was available from the tests selected for this research. The percentile score of this child was 5, which indicates a delay in motor development.

Data on hand-held dynamometry (HHD) around the time of diagnosis were available for 8 children (age 7–16 years) and all 29 adults (age 24–68 years). In 2 children the first HHD was performed more than 1 year after diagnosis and these data were therefore excluded. For 3 children (aged 0–2 years) no HHD data were available because they were too young to perform the test. The median HHD scores per muscle group were ≤80% of the reference value for 4 muscle groups (hip abductor, knee flexor, hip flexor and shoulder abductor). The HHD scores for the individual muscle groups are depicted in Fig. 2 as percentages of age- and sex-matched reference values (100%).

The manual muscle test (MMT) was performed in 29 adult patients and 5 affected children (age 4–14 years) at the time of diagnosis. Using the MRC scale, more than 50% of the patients had lost strength in the shoulder abductors, adductors and exorotators as well as the hip abductors, adductors and extensors (Fig. 3). The lowest MRC score that was reported for a muscle group in our study population was 2 (only horizontal movement possible).

Data on the forced vital capacity (FVC) in both sitting and supine position at the time of diagnosis were available of 7 children and all 29 adults. FVC of one additional child was measured only in sitting position. Data of 2 children were excluded because pulmonary function was measured more than 1 year after diagnosis. No data were available on the pulmonary function of five children for various reasons, mainly because they were too young to perform the test. In sitting position the median FVC at diagnosis was 92% of normal (range 16%–140%), while the median FVC in supine position was 77% (range 20%–124%). In supine position the FVC was 80% or below (pathological threshold) for 18 adults and 3 children (58.3% of the tested patients).

Data from the Quick Motor Function Test (QMFT) performed at the time of diagnosis of 8 children and all 29 affected adults with Pompe disease were available. Not included were data of 3 children (aged, 2, 5 and 8 years) because the QMFT was only documented from measurements more than 1 year after diagnosis. Of two children with Pompe disease no data on the QMFT were available. The data show

that at diagnosis more than 80% of them had difficulty with executing a sit-up from lying position or succeeded only partly. More than 50% of them had difficulties with or could only partly execute the following actions (scores under 4): getting up from a squat, or from one knee, squatting, jumping, stretching the legs in supine position, getting up from a chair, raising the torso from prone position, walking ten meters, picking up an object from the ground when standing or flexing the hip or knee in supine position. More than 40% of the patients described had difficulty with or could not stand on one leg and/or walk stairs. An overview of the results of the QMFT is depicted in Fig. 4.

Data of 22 adults on the Rotterdam Handicap Scale were available and met the inclusion criteria (Fig. 5). More than 70% of them at least sometimes needed help with domestic tasks indoors and outdoors. More than 40% reported that they had difficulty with driving a car, traveling by bus and/or riding a bicycle and/or needed help with leisure activities outdoors; 15.8% of the patients (aged 34–64 years, median 44) reported that they were unable to fulfil their work or study at the time of diagnosis.

At time of diagnosis two adult patients (aged 43 and 64 years) were using a wheelchair and four adult patients (aged 36–64 years) were using non-invasive ventilation.

4. Discussion

The delay in diagnosing Pompe disease was until now only described in terms of time i.e. number of years [3,4,10]. Our study reporting on the condition of the patients at the time of diagnosis provides insight into the damage, which might be averted by early diagnosis and effective intervention. The data presented in this report reveal that patients with Pompe disease are significantly impaired in body function and structure, limited in activities, restricted in participation and in some cases dependent on respiratory, walking and/or feeding support already at the time of diagnosis.

The reported substantial loss of muscle fibers retaining normal contractile elements in classic infantile patients and low AIMS scores are particularly noteworthy, because the effect of ERT depends on preservation of intact muscle fibers and consequently residual muscle function at the start of treatment [8,24,35]. Also the life-threatening cardiomyopathy found in these patients at diagnosis, which is known to normalize when treated promptly [13] and the
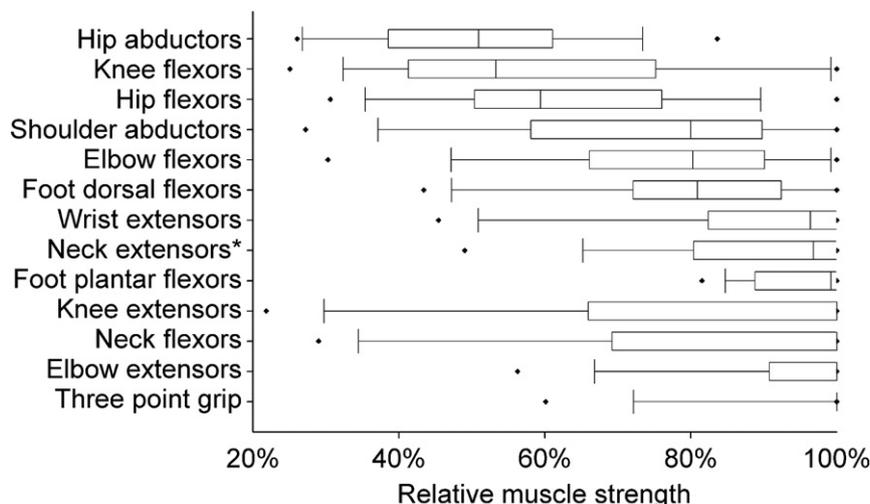

Fig. 2. HHD scores per muscle group of 8 children and 29 adults with Pompe disease at the time of diagnosis. Percentage of normal value of age- and sex-matched normal population. (Dots depict minimum and maximum percentages). * For children no reference value for neck extensors was available.
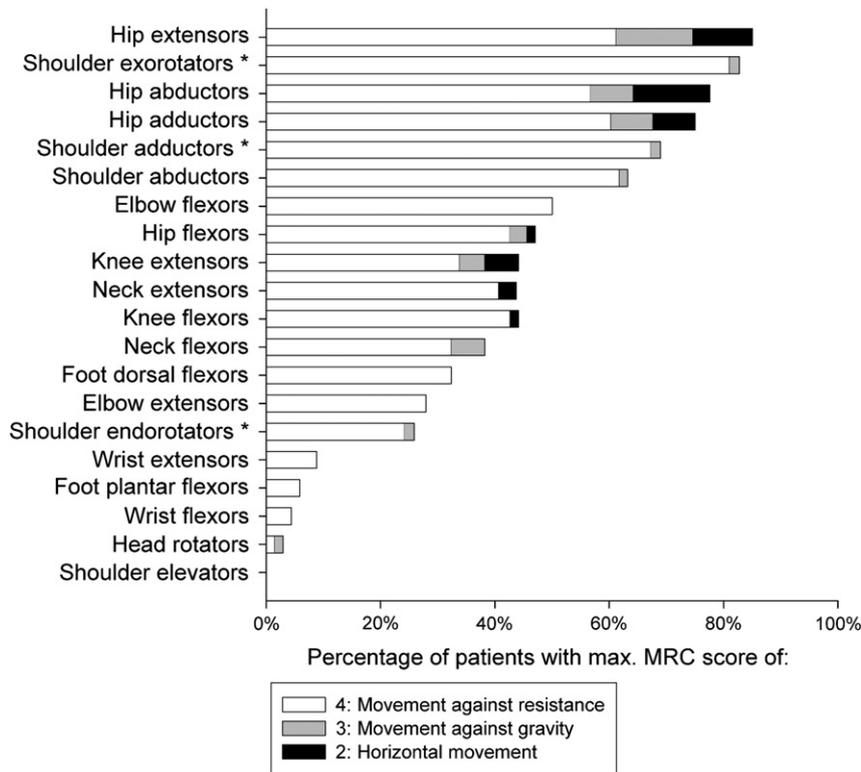
Fig. 3. Percentage of patients with loss of strength in different muscle groups at the time of diagnosis. MRC was measured in 20 muscle groups in adults and in 17 muscle groups in children. * Shoulder adductors and shoulder endo- and exorotators have not been evaluated in children.

hearing loss which is irreversible [21] emphasize the need for earlier diagnosis in patients with classic infantile Pompe disease. This study however also shows significant loss of muscle strength at the time of diagnosis of children and adults with Pompe disease and consequently the loss of muscle function. Eighty percent of the patients had problems with executing a sit-up, 50% with getting up from a chair and 40% had difficulty with walking stairs at the time of diagnosis. The functional limitations had also significant consequences for daily functioning. At the time of diagnosis 80% experienced problems with domestic tasks outdoors, while almost 50% experienced limitations in performing their work or study. The fact that more then 20% of the adult patients were already either wheelchair bound
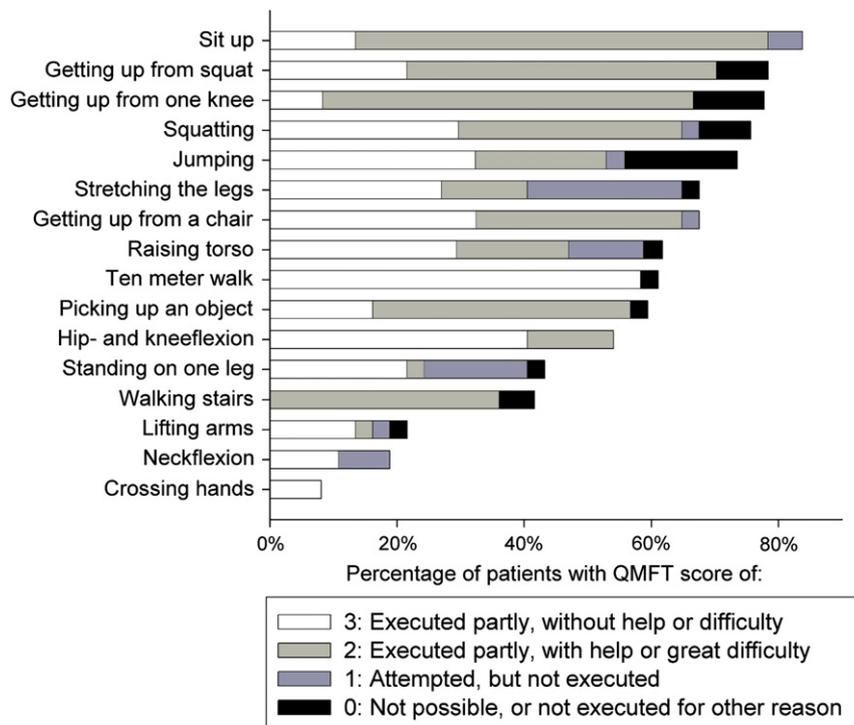
Fig. 4. Percentage of affected children and adult patients with any difficulty executing different tasks at the time of diagnosis.
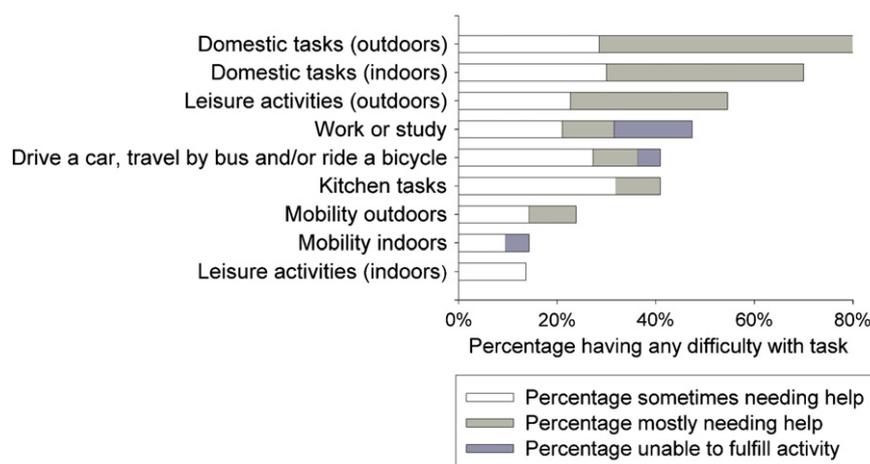
Fig. 5. Rotterdam Handicap Scale results of adults at the time of diagnosis.

and/or required respiratory support stresses the consequences of the delayed diagnosis. Part of these problems might have been prevented if patients were diagnosed and treated with ERT earlier [7,20]. Given the progressive nature of Pompe disease, rapid in patients with classic infantile Pompe disease and slower in other patients, early diagnosis is in all cases expected to be associated with less tissue pathology, better preserved muscle function and fewer limitations in daily life at the start of treatment. Altogether the results of this study form a strong argument to advocate for earlier diagnosis for the whole spectrum of Pompe disease.

The patients described in this study include all patients seen in the Erasmus MC University Medical Center diagnosed between 1999 and 2009 who met the inclusion criteria. The median age at diagnosis of patients with classic infantile Pompe disease in this study was 30 days (range: 3–180 days). Since the literature [3] describes a longer diagnostic delay than in our study-group this may mean that awareness has been raised during recent years resulting in earlier diagnosis or that our results may not be representative for all patients with classic infantile Pompe disease at diagnosis. However, because the reason for the earlier diagnosis in the current group is unknown, our results could be an under- or overestimate of the health and functional status of patients with classic infantile Pompe disease in general. Six children in our study group did not perceive any neuromuscular symptoms before being diagnosed. They were tested for Pompe disease following the diagnosis of a sibling or acting on findings from tests for other purposes indicating muscle or liver pathology. Therefore the time between first symptoms and diagnosis in this group (of 13 children) is rather broad and ranges between 0 and 13 years, with a median of 1 and a mean of 2.5 years. The diagnostic delay in our adult patient group (median delay 8 years, range 0–43 years) is similar to what has been described in the literature [4,10]. Most missing data are assumed to be missing at random, so we presume they do not bias our conclusions. Unfortunately data on pulmonary and muscle function and muscle strength are missing for three of the five affected children under 5 years of age without cardiomyopathy, due to their inability to adequately perform the selected tests at a young age.

Neonatal screening seems an obvious choice to ensure the earliest diagnosis, mainly because of the bloodspot screening system that is already in place for other diseases in most developed countries. However, the currently available screening techniques for Pompe disease on blood spots do not discriminate between patients with classic infantile Pompe disease and less progressive variants of the disease [14,19]. Consequently, not only babies who need immediate treatment will be identified, but also seemingly healthy infants who will manifest symptoms at unpredictable age. For the latter

patients and their parents this implies a constant awareness of a pre-symptomatic stage of the disease, while some cases may remain asymptomatic until the age of 70. Possible consequences for these so-called "patients in waiting" [36] have been discussed elsewhere [16,17] as well as views of the public on this dilemma [37]. Most of the current neonatal screening programs are aimed at detecting conditions that require immediate treatment. In this respect finding late-onset cases would be an unsought effect of the screening. This study, however, suggests that not only future patients with disease manifestations at very young age but also patients who would experience the first signs of disease much later in life might benefit from earlier diagnosis, as it allows for earlier intervention and presumably better treatment results. Consequences of early diagnosis for patients at the opposite ends of the clinical spectrum clearly need to be further explored.

5. Conclusion

This study quantifies the health and functional status of patients with Pompe disease and clearly shows that this is already severely impaired at the time of diagnosis. This is a strong argument to advocate for earlier diagnosis and to further explore the potential of neonatal screening.

Sources of funding and competing interests

Details of ethics approval

The study was approved by the institutional review boards of the Erasmus MC University Medical Center (MEC2007-103, addendum 3) and the VU University Medical Center (letter 2010/104).

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