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

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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.

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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

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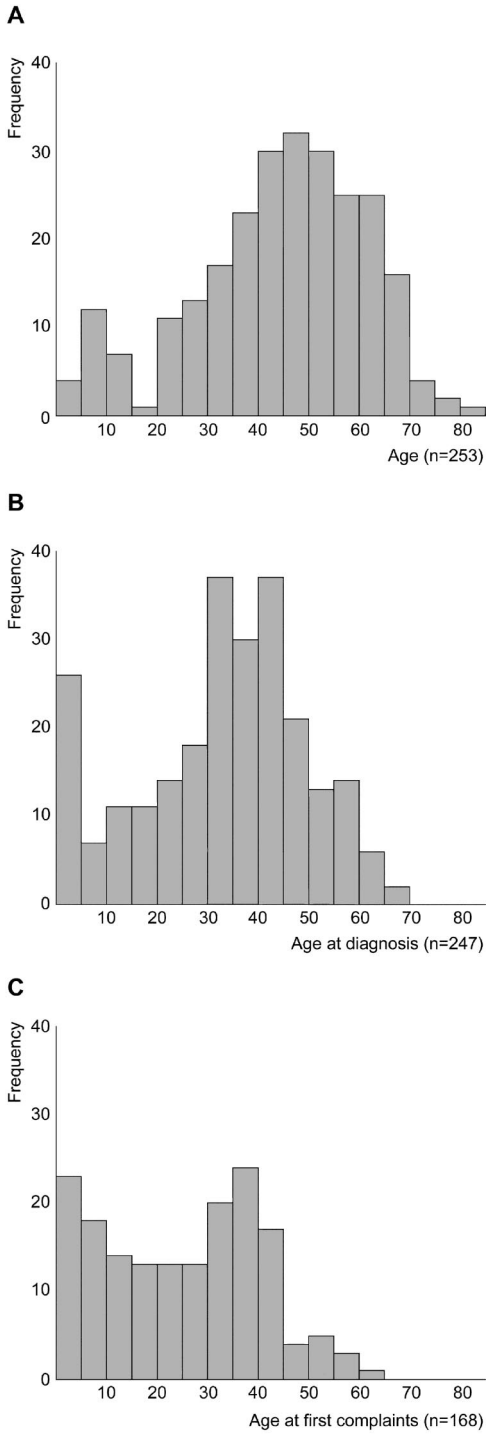

Figure 1. Distribution of age (A), age at diagnosis (B), and age at first complaints (C) in the study population. Range for age: 2.6 to 81 years; range for age at diagnosis: 0 to 66 years; range for age at first complaints: 0 to 62 years.

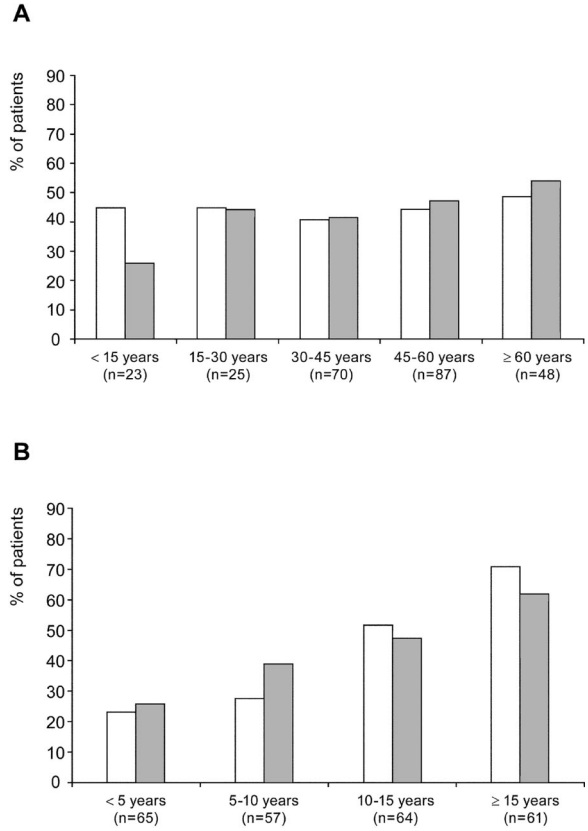

Figure 2. (A) Wheelchair use and use of respiratory support related to age in 253 children and adults with Pompe disease. (B) Wheelchair use and use of respiratory support related to disease duration in 247 children and adults with Pompe disease. White represents wheelchair use; gray shading represents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

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.

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

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.

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.

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