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Pain in adult patients with Pompe disease
A cross-sectional survey

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ABSTRACT

Background: Pompe disease is a rare hereditary metabolic myopathy caused by a deficiency of acid-α-glucosidase. We investigated the presence and severity of pain and its interference with daily activities in a large group of adults with Pompe disease, who we compared with an age-matched control group.
Methods: Data were collected in a cross-sectional survey in Germany and The Netherlands. Pain was assessed using the short-form brief pain inventory (BPI). Patients also completed the Short Form-36 item (SF-36v2), the Hospital Anxiety and Depression Scale (HADS) and the Rotterdam Handicap Scale (RHS).
Results: Forty-five percent of the 124 adult Pompe patients reported having had pain in the previous 24 h, against 27% of the 111 controls ($p = 0.004$). The median pain severity score in Pompe patients reporting pain was 3.1 (on a scale from 0 to 10), indicating mild pain; against 2.6 amongst controls ($p = 0.06$). The median score of pain interference with daily activities in patients who reported pain was 3.3, against 1.3 in controls ($p = 0.001$). Relative to patients without pain, those with pain had lower RHS scores ($p = 0.02$), lower SF-36 Physical and Mental component summary scores ($p < 0.001$ and $p = 0.049$), and higher levels of depression and anxiety ($p = 0.005$ and $p = 0.003$).
Conclusions: To date, this is one of the largest studies on pain in a specific neuromuscular disorder. Nearly one in two Pompe patients had experienced pain in the previous 24 h. Although pain severity and its interference with daily life were mild, pain was related to a reduced quality of life, less participation in daily life, and greater depression and anxiety. Its management should therefore be seen as part of clinical practice involving Pompe patients.

1. Introduction

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

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

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is one of the dominating features [21]. In patients with Pompe disease, it may thus be an overlooked symptom.

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

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

2. Methods

2.1. Patients and controls

Patients were either recruited through the German patient organization (Selbsthilfegruppe Glykogenose Deutschland e.V., n = 110) or through Erasmus MC University Medical Center (n = 98), which is the national referral center for Pompe disease in The Netherlands. Controls, who had to be free of Pompe disease, were either partners, relatives or acquaintances of Pompe patients or of other neuromuscular patients. Their age was approximately the same as that of the Pompe patients who had been recruited. The study was approved by the Local Ethics Committees at Martin-Luther-University Halle (Saale) and Erasmus MC University Medical Center. All participants gave informed consent.

2.2. Questionnaires

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

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

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

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

All questionnaires were available in German and Dutch.

2.3. Statistical analysis

Descriptive statistics were used to summarize all variables for the patient and control groups. To assess differences in demographic characteristics and differences in the prevalence, severity, interference and treatment of pain between patients and controls, we used the Chi-square (trend) test for discrete data, or the Mann–Whitney U test for continuous data. Both tests were also used to assess differences in characteristics and quality of life, participation, depression and anxiety of patients with and without pain.

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

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

3. Results

3.1. Response and patient characteristics

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

A total of 111 controls responded out of 166 contacted (response rate 66%): 58 from Germany (response rate 89%) and 53 from The

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

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

The percentages may not always add up to 100% due to rounding. n = number; % = percentage; NA = Not Applicable; ERT = Enzyme Replacement Therapy.

[a] Difference between patients and controls assessed with the Chi-square test and the Mann–Whitney U test for discrete and continuous data, respectively.

Netherlands (response rate 52%). The median age of the controls was 53 years (range 18–78); 59% were female (Table 1). There were no significant differences between the age and gender of patients and controls, or between the German and Dutch controls.

3.2. Prevalence, severity and interference of pain

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

Table 2 shows the severity of pain and its interference with daily life in patients and controls. On a scale from 0 to 10, the median Pain Severity Score (PSS) amongst patients reporting pain in the previous 24 h was 3.1 (range 0.75–8). For controls with pain, it was 2.6 (range 0.75–5.25), and did not significantly differ from patients ($p = 0.06$).

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

3.3. Sites and type of pain, and treatment

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

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

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

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

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

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

4. Discussion

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

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

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

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

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

While the Pain Severity and Pain Interference Scores in our patient group might be seen as mild [31], and while few patients reported severe pain, some of the mildness may be attributable to the fact that two-thirds (70%) of patients with pain used pain medication — a much higher proportion than in controls (40%). Similarly, the interference of pain in patients' daily lives was higher than in controls, and Pompe patients with pain had significantly lower participation and quality of life scores and higher levels of depression and anxiety than those without. Overall, this indicates that, despite the mild severity and interference scores, pain is an important debilitating symptom in Pompe disease, and thus warrants further attention.

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

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

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

While the exact mechanisms that cause pain in Pompe disease require further investigation, each mechanism may require a different therapeutic approach. Most patients in our study used some kind of treatment for pain, mainly over-the-counter drugs, but they also used other drugs and physical therapy. Without these measures, the prevalence of pain might have been even higher. Patients reported a subjective average pain relief of about 50%, indicating that their current pain management did not suffice.

Whether ERT can itself help to reduce pain requires further research. In our study the use of ERT was similar between patients who reported pain and those who did not, while ERT duration was related to pain in

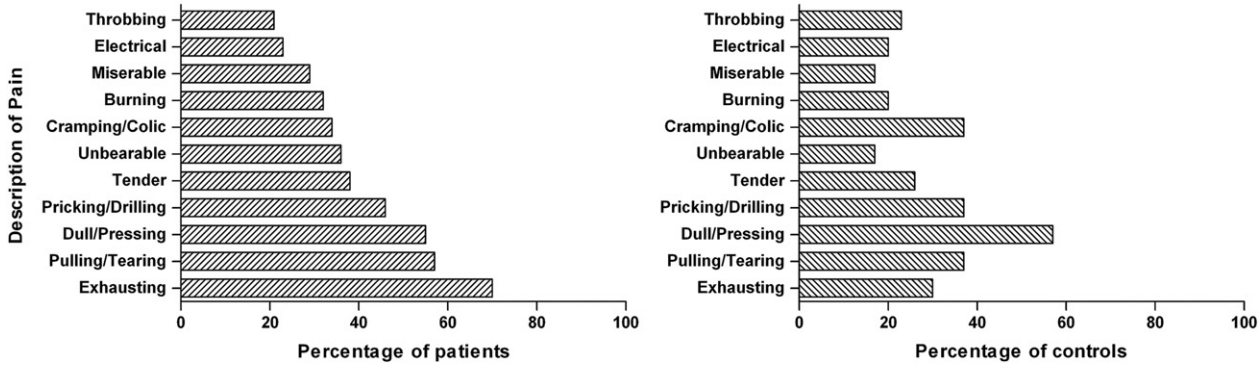

Fig. 2. Description of the type of pain by 56 Pompe patients and 30 controls reporting pain in the last 24 h.

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

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

Percentages may not always add up to 100% due to rounding. n = number; % = percentage, ERT = Enzyme Replacement Therapy; SF-36v2 = Short Form Health Survey 36 version 2; PCS = Physical Component Summary; MCS = Mental Component Summary; HADS = Hospital Anxiety and Depression Scale; RHS = Rotterdam Handicap Scale.

[a] Difference between patients with and those without pain assessed with the Chi-square test and the Mann–Whitney U test for discrete and continuous data, respectively.

[b] Chi-square trend test.

those patients who did receive ERT. We were prevented from drawing any conclusions on this by the cross-sectional design and the small percentage of patients who were not on ERT.

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

5. Conclusions

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

Conflicts of interest and funding

FH and MD have received lecturers' fees from the Genzyme Corporation, a Sanofi Company. BS has received lecturer's fees from the Genzyme Corporation, a Sanofi Company, and is a member of the global advisory board for Pompe disease at the Genzyme Corporation. Research on Pompe disease at Erasmus MC is financially supported by the following parties: ZonMw — The Netherlands Organisation for Health Research and Development [project no. 152001005]; the Dutch TI Pharma initiative "Sustainable Orphan Drug Development through Registries and Monitoring" (T6-208); "EUCLYD — a European Consortium for Lysosomal Storage Diseases" (health F2/2008 grant agreement 201678); the Prinses Beatrix Fonds [project no. OP07-08]; and Genzyme Corporation, Cambridge, MA, USA. Since August 2004, ATvdP and AJJR have provided consulting services for Genzyme Corporation, under an agreement between Genzyme Corporation and Erasmus MC, Rotterdam, The Netherlands. This agreement also covers financial support for Erasmus MC to pursue research in the field of Pompe disease. Erasmus MC and the inventors of the method for treating Pompe disease by enzyme replacement therapy receive royalty payments pursuant to Erasmus MC policy on inventions, patents and technology transfer. None of the other authors report conflicts of interest. The funders of the study had no role in the design and conduct of the study, data collection, data management, data analysis, data interpretation, or preparation, review, or approval of the manuscript.

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