Molecular Genetics and Metabolism 109 (2013) 371–376

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

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

D. Güngör [a,b,*], A.K. Schober [c], M.E. Kruijshaar [a,b], I. Plug [a,b], N. Karabul [d], M. Deschauer [c], P.A. van Doorn [a,e], A.T. van der Ploeg [a,b], B. Schoser [f], F. Hanisch [c]

[a] Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[b] Department of Pediatrics, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[c] Department of Neurology, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
[d] Department of Pediatrics, University of Mainz, Mainz, Germany
[e] Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[f] Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich, Germany

ARTICLE INFO

Article history:
Received 4 April 2013
Received in revised form 31 May 2013
Accepted 31 May 2013
Available online 7 June 2013

Keywords:
Pompe disease
Glycogen storage disease type 2
Acid maltase deficiency
Acid α-glucosidase
Lysosomal storage disorders
Pain

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

* Corresponding author at: Department of Pediatrics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, PO BOX 2060, 3000 CB Rotterdam, The Netherlands. Fax: +31 10 703 6800.
E-mail addresses: d.gungor@erasmusmc.nl (D. Güngör), agnes.piechaczek@student.uni-halle.de (A.K. Schober), m.kruijshaar@erasmusmc.nl (M.E. Kruijshaar), i.plug@erasmusmc.nl (I. Plug), Nesrin.Karabul@unimedizin-mainz.de (N. Karabul), marcus.deschauer@uk-halle.de (M. Deschauer), p.a.vandoorn@erasmusmc.nl (P.A. van Doorn), a.vanderploeg@erasmusmc.nl (A.T. van der Ploeg), Benedikt.Schoser@med.uni-muenchen.de (B. Schoser), Frank.hanisch@medizin.uni-halle (F. Hanisch).

1096-7192/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ymgme.2013.05.021

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.