JIMD Reports
DOI 10.1007/8904_2014_334

RESEARCH REPORT

Urge Incontinence and Gastrointestinal Symptoms in Adult Patients with Pompe Disease: A Cross-Sectional Survey

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Received: 31 March 2014 / Revised: 26 June 2014 / Accepted: 01 July 2014 / Published online: 26 August 2014

Abstract *Objective*: To determine the frequency and impact of gastrointestinal symptoms, and bowel and urinary incontinence, as this is currently unknown in adults with Pompe disease.

Methods: Adult German Pompe patients and age- and gender-matched controls were asked about symptoms in the upper and lower intestinal tract as well as urinary incontinence using the Gastrointestinal Symptoms Questionnaire and the International Consultation on Incontinence Questionnaires for Bowel Symptoms and Urinary Incontinence.

Results: The overall response rate was 78%; 57 patients and 57 controls participated. The mean age of the patients was 48.3 years ±14.7 (28 female, 29 male). 84% of patients were receiving enzyme replacement therapy. Stool urgency, diarrhoea, and urinary urge incontinence were reported significantly more frequently in patients compared to the age- and gender-matched controls (55%, 56%, 33% vs. 20%, 18%, 7%). 20% of Pompe patients used loperamide daily against diarrhoea. No other gastrointestinal tract-related symptoms were reported to occur more frequently in Pompe patients than in controls.

Conclusions: Compared to age- and gender-matched controls, both urinary and bowel incontinence occur in a higher frequency in adults with Pompe disease and have a major impact on daily life.

Communicated by: Daniela Karall

Competing interests: None declared

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Introduction

Pompe disease (synonyms: glycogen storage disease type II, acid maltase deficiency) is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme acid alpha-glycosidase (GAA) due to mutations in the *GAA* gene. Enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme®) for patients with classic infantile and late-onset Pompe disease has been available since 2006 (Toscano and Schoser 2013). The main clinical and prognostic features in adult patients with Pompe disease are proximal and axial paresis in the limb girdles and respiratory insufficiency due to glycogen storage in the skeletal muscles (van der Beek et al. 2012). ERT was shown to have a beneficial effect on these symptoms and to delay progression of skeletal muscle symptoms in adolescent and adult patients with Pompe disease (Regnery et al. 2012; Laforêt et al. 2013; Güngör

et al. 2013; Schneider et al. 2013; de Vries et al. 2012; Toscano and Schoser 2013).

The awareness of multisystemic symptoms as well as long-term complications and the response of signs and symptoms to ERT is currently a major issue in the follow-up of adult patients with Pompe disease. Gastrointestinal symptoms are well known in storage disorders like Fabry disease (e.g. abdominal pain, poor weight gain, chronic diarrhoea, postprandial discomfort) and Gaucher disease (weight loss, cachexia, abdominal pain) and were reported to respond well to ERT (Verderese et al. 1993; Banikazemi et al. 2005). The lysosomal accumulation of glycogen in smooth muscles in different organs was shown in a *GAA* knockout mouse model (Bijvoet et al. 1999), in infantile Pompe disease (Winkel et al. 2003) and in autopsies (including the organs of the gastrointestinal tract and the urinary tract; Swash et al. 1985; van der Walt et al. 1987; Kobayashi et al. 2010; Hobson-Webb et al. 2012), in biopsies of the arrector pili muscle (Katona et al. 2014), and in imaging studies of cerebral vessels of adult Pompe disease cases (Sacconi et al. 2010; Hobson-Webb et al. 2012).

With respect to gastrointestinal symptoms, the International Pompe Registry and guidelines for the treatment of Pompe disease focus mainly on the registration and management of malnutrition and dysphagia in infantile patients (https://www.registrynxt.com/Pompe/Pages/Home.aspx; Bembi et al. 2008). In adult patients, observations regarding the nutritional status only included changes of body mass index under ERT (van der Beek et al. 2009; Ravaglia et al. 2010a; Ravaglia et al. 2010b; Kobayashi et al. 2010; Papdimas et al. 2010; Bernstein et al. 2010; Regnery et al. 2012; Schüller et al. 2012). Recent reports on small cohorts addressed the issue of gastrointestinal symptoms in adults with Pompe disease as well as symptoms such as chronic diarrhoea, bowel urge incontinence, meteorism, gastrointestinal reflux, and obstipation (Bernstein et al. 2010; Sacconi et al. 2010; Remiche et al. 2012). In 20 patients with late-onset Pompe disease, 25% had incontinence definitely attributable to Pompe disease (Remiche et al. 2012). The application of ERT led to a variable reduction of lysosomal glycogen in the smooth muscles (Bijvoet et al. 1999; Winkel et al. 2003) and to a reduction of gastrointestinal symptoms including incontinence (Bernstein et al. 2010; Sacconi et al. 2010; Remiche et al. 2012). In addition, urinary incontinence was reported less frequently in patients with adult Pompe disease than bowel incontinence (Chancellor et al. 1991; Remiche et al. 2012).

In the present multicentre cross-sectional study in adults with Pompe disease, we systematically surveyed by questionnaires the occurrence of symptoms of the upper and lower gastrointestinal tract and in depth the frequency and impact of both urinary and bowel incontinence and compared this with age- and gender-matched controls from the general population.

Patients and Methods

Patients

Seventy-three patients with biochemically and genetically confirmed adult Pompe disease were recruited by the German Pompe centres. Patients were asked to complete the questionnaire when they attended the neuromuscular clinics for follow-up and/or ERT. The following German centres participated: Berlin ($n = 9/10$), Bochum ($n = 7/7$), Bonn ($n = 6/9$), Halle ($n = 13/15$), Mainz ($n = 13/20$), and Munich ($n = 10/12$) (number of participants/number of patients invited to participate). Controls were recruited in a biased manner: Controls, whose age was approximately the same as that of the patients with Pompe disease, were either accompanying acquaintances, partners, or relatives of patients with other nonhereditary neuromuscular diseases (e.g. amyotrophic lateral sclerosis, diabetic neuropathy, myasthenia gravis; exclusion criterion: history of colon cancer). All participants signed an informed consent form the Local Ethics Committee of the Martin-Luther-University Halle (Saale) and all the other participating institutions approved the study.

Questionnaires

General Information

The general information included questions about onset and severity of Pompe disease, the use and start of ERT, and age, gender, and body mass index (BMI) of each participant. Furthermore, the participants were asked whether they had ever undergone a gastroscopy or colonoscopy and whether they take drugs to relieve gastrointestinal symptoms.

Gastrointestinal Symptoms Questionnaire

The validated Gastrointestinal Symptoms Questionnaire is a standardised checklist and allows screening for the severity of both upper and lower gastrointestinal tract symptoms during the previous 4 weeks (Bovenschen et al. 2006; see also for English version). The severity was rated on a 0–6-point Likert scale, where 0 meant “no complaints” and 6 represented the worst imaginable severity of the symptom. The questionnaire has been standardised and validated in primary care patients referred for Helicobacter pylori urea breath testing and has also been used in myotonic dystrophy type 2 (Tieleman et al. 2008). We

used the German equivalent of this questionnaire (Supplementary Fig. 1), but we also added questions about the frequency of symptoms using an unstandardised method.

Since this questionnaire only rates the severity, questions about the frequency of these symptoms of the upper and lower GI tract were included (1: < two times a week, 2: 2–5 times a week, 3: > 5 times a week).

International Consultation on Incontinence Questionnaire-Bowel-Long Form (ICIQ-B-LF)

For the in-depth survey about bowel incontinence and its impact on quality of life, the validated ICIQ-B-LF was used (Cotterill et al. 2011). The self-report ICIQ-B-LF contains 21 questions arranged in five scored domains: bowel pattern, bowel control, other bowel symptoms, sexual impact, and quality of life. The German equivalent is depicted in Supplementary Fig. 2.

International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF)

The validated self-report ICIQ-UI-SF for urinary incontinence was used to score frequency and amount of urinary incontinence and its impact on the quality of life. In addition, the questionnaire asks for the situations in which incontinence occurred (Timmermans et al. 2013). A German questionnaire has been validated previously (http://www.awmf.org/uploads/tx_szleitlinien/084-001k_S2_Harninkontinenz).

Statistics

Descriptive statistics are presented as mean ± 1 standard deviation. All variables were analysed to evaluate their normality using the Kolmogorov–Smirnov test. Differences between groups were analysed using unpaired Student's *t*-test or Mann–Whitney rank sum test, χ^2 test, or Fisher exact test. Spearman's rank correlation coefficient was determined to investigate correlations (SPSS 17, IBM Software Group, USA).

Results

Patient Characterisation

Out of 73 adult Pompe patients, 57 patients responded to all questionnaires (response rate 78%, 28 women, 29 men) in contrast to age- and gender-matched controls from the general population (response rate 84%). Details are given in Table 1. Forty-nine patients (84%) were currently receiving ERT. There was no difference in BMI of Pompe patients and controls (24.2 ± 4.7 vs. 25.7 ± 4.8).

Information About Endoscopy and Drugs for Gastrointestinal Symptoms

Equal numbers of patients and controls had undergone endoscopy of the upper and/or lower gastrointestinal tract in their life (20.7–26.9%). There was no statistical difference in the numbers of patients and controls who used drugs for heartburn, flatulence, and obstipation. However, statistically significant more patients than controls required drugs against diarrhoea and urge incontinence ($p < 0.01$: Table 1). This comprised loperamide 1–3 times a day in 12 patients (21%). Only one control reported taking loperamide about three times a year.

Gastrointestinal Symptoms Questionnaire

Detailed results of this questionnaire are given in Table 2. When the severity of symptoms of the upper and lower gastrointestinal tract was analysed, patients had significantly higher scores than controls in the items "diarrhoea" and "stool urgency". Diarrhoea was reported by 23 patients (14 women, 9 men, median age: 51 years, range: 23–73). Stool urgency was reported by 23 patients (10 women, 13 men, median age: 53 years, range: 23–73). Statistically significant higher numbers of controls than patients reported heartburn, bloating, postprandial fullness, and flatulence. However, when the severity of these symptoms was asked for, no statistically significant differences for these symptoms between controls and patients were found. Additionally, analysing the nonstandardised part of the questionnaire, there was no difference in the frequency of symptoms between patients and controls (data not shown).

International Consultation on Incontinence Questionnaire-Bowel-Long Form (ICIQ-B-LF)

Bowel control was analysed in detail using the ICIQ-B-LF (Table 3). The scores for both frequency and interference with daily activities for the domains "bowel pattern", "bowel control", and "quality of life" were statistically higher in patients than controls. For the domain "other bowel symptoms", only the interference with daily life but not the frequency was scored higher in patients than controls. The differences in the domain "sexual impact" did not reach statistical significance. There was a mostly high linear correlation between frequency and interference

Table 1 Demographic and clinical data, including frequency of colonoscopy and gastroscopy and frequency of drug intake for different gastrointestinal complaints in adults with Pompe disease and in age- and gender-matched controls (i.e. accompanying spouses and partners)

	Pompe patients ($n = 57$)	Age- and gender-matched controls ($n = 57$)	p
Gender (female/male)[b]	28/29	28/29	
Age at examination (years)[a]	48.3 ± 14.7 (18–73)	52.3 ± 15.8 (23–78)	n.s.
Disease duration (years)	17.1 ± 11.9 (2–50)	n.a.	
Wheelchair bound [*n* (%)]	12 (20.7)	n.a.	
Non-invasive ventilation [*n* (%)]	19 (32.8)	n.a.	
ERT [*n* (%)]			
Currently receiving [*n* (%)]	49 (84)	n.a.	
Interrupted [*n* (%)]	4 (6.7)	n.a.	
Never [*n* (%)]	4 (6.7)	n.a.	
BMI[a]	24.2 ± 4.7 (15.4–35.7)	25.7 ± 4.8 (18.0–41.0)	n.s.
Colonoscopy [*n* (%)][c]	15 (26.9)	12 (20.7)	n.s.
Gastroscopy[c]	13 (22.4)	13 (22.4)	n.s.
Drug intake for			
Gastrointestinal complaints [*n* (%)][c]	17 (29.3)	15 (26.9)	n.s.
Heartburn [*n* (%)][c]	5 (8.6)	9 (15.5)	n.s.
Flatulence [*n* (%)][c]	8 (13.8)	7 (12.1)	n.s.
Obstipation [*n* (%)][c]	3 (5.2)	3 (5.2)	n.s.
Diarrhoea/urge incontinence [*n* (%)][c]	12 (20.7)	1 (1.7)	0.0046

Data are given as mean ± 1SD (range). Groups were compared using unpaired Student's *t*-test[a] or χ^2 test[b] and Fisher exact test[c]
n.a. not applicable, *n.s.* nonsignificantly

for all five domains using the Spearmen Rank Coefficient: bowel pattern $r^2 = 0.73$, bowel control $r^2 = 0.88$, other bowel symptoms $r^2 = 0.54$, sexual impact $r^2 = 0.85$, quality of life $r^2 = 0.88$.

International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF)

The differences in the frequency of urinary incontinence in patients compared to controls did not reach statistical significance (Table 4). However, patients were statistically more disturbed in their daily life than controls. When only those individuals who reported urinary incontinence were compared, the statistically significant difference between patients and controls was even more pronounced. Significantly, more patients than controls experienced urinary incontinence before they reached the toilet. Urinary urge incontinence was reported by 18 patients (12 women, 6 men, median age: 52 years, range: 27–73). Thirteen patients reported both urinary urge incontinence and stool urgency and/or diarrhoea (9 women, 4 men, median age: 52 years, range: 29–73). Significantly, more controls than patients reported urinary incontinence during coughing and pressure. These controls were mostly women ageing >45 years (12/15).

Symptoms in Cachectic Patients

Five out of 57 patients (8.8%, 1 woman, 4 men, age range: 23–57 years, disease duration range: 9–19 years, all received ERT for 2–7 years) had a BMI <18 (equals cachexia). All patients reported diarrhoea, three reported stool urgency, and one reported urinary urge incontinence. Three patients took regularly loperamide.

The ages of the patients with stool urgency, diarrhoea, and urinary urge incontinence were not significantly different from those patients who did not report these symptoms (age: mean 50.7 years ± 11.9 median 51 years (23–73) vs. mean 45.4 years ±17.0, median 50 years (18–74); $p = 0.21$). The duration of Pompe disease (time from the onset of the first symptoms of the skeletal muscles, i.e. pain, weakness, dyspnoea) in patients with stool urgency, diarrhoea, and urinary urge incontinence was not significantly different from those patients who did not report these symptoms (disease duration: mean 18.3 years ± 11.8, median 16 years (3–51) vs. mean 15.6 years ± 12.7, median 10 years (3–43); $p = 0.47$). Of the eight patients who had either interrupted ERT or had never been treated with ERT, two reported diarrhoea and another one urinary urge incontinence, but none stool urgency.

Table 2 Severity and frequency of abdominal and epigastric symptoms in adult patients with Pompe disease and in age- and gender-matched controls (i.e. accompanying spouses and partners) as analysed by the Gastrointestinal Symptoms Questionnaire

Symptom	Pompe patients reporting symptoms [*n* (%)]	Controls reporting symptoms [*n* (%)]	p^b	Severity Pompe patients ($n = 58$)	Severity Age- and gender-matched controls ($n = 58$)[a]	p^a
Abdominal pain						
General	2/41 (4.5)	2/49 (4.1)	n.s.	0.22 ± 0.88	0.06 ± 0.32	n.s.
Postprandial	8/41 (20)	8/43 (19)	n.s.	0.34 ± 0.73	0.23 ± 0.52	n.s.
Fasting	2/39 (6.9)	1/40 (2.5)	n.s.	0.18 ± 0.72	0.03 ± 0.16	n.s.
Persistent after stools	3/38 (7.9)	0/41 (0)	n.s.	0.26 ± 0.72	0	n.s.
Epigastric pain						
General	1/39 (2.6)	1/49 (2.0)	n.s.	0.13 ± 0.66	0.02 ± 0.14	n.s.
During daytime	7/39 (18)	6/43 (14)	n.s.	0.28 ± 0.79	0.19 ± 0.55	n.s.
At night/asleep	2/37 (5.4)	2/41 (4.8)	n.s.	0.14 ± 0.48	0.12 ± 0.56	n.s.
Heartburn	5/49 (10)	14/51 (27)	0.04	0.30 ± 0.71	0.37 ± 0.69	n.s.
Regurgitation	4/48 (8.3)	10/50 (20)	n.s.	0.20 ± 0.61	0.24 ± 0.52	n.s.
Abdominal rumbling	14/51 (27)	23/50 (46)	n.s.	0.84 ± 1.05	0.58 ± 0.70	n.s.
Bloating	17/52 (1.9)	36/53 (68)	0.04	1.32 ± 1.24	1.04 ± 0.91	n.s.
Empty feeling	7/48 (15)	5/50 (10)	n.s.	0.40 ± 0.79	0.16 ± 0.55	n.s.
Nausea	7/46 (15)	3/51 (5.9)	n.s.	0.20 ± 0.50	0.19 ± 0.71	n.s.
Vomiting	4/48 (8.3)	3/51 (5.9)	n.s.	0.06 ± 0.24	0.16 ± 0.70	n.s.
Loss of appetite	4/48 (8.3)	2/51 (3.9)	n.s.	0.23 ± 0.66	0.12 ± 0.71	n.s.
Postprandial fullness	8/46 (17)	20/53 (38)	0.03	0.80 ± 1.13	0.58 ± 0.95	n.s.
Belching	4/45 (8.9)	18/51 (35)	0.003	0.51 ± 0.76	0.41 ± 0.61	n.s.
Flatulence	6/43 (14)	30/51 (59)	0.01	1.07 ± 1.24	0.83 ± 0.79	n.s.
Hematemesis	1/44 (2.3)	1/50 (2.0)	n.s.	0	0.02 ± 0.14	n.s.
Dysphagia						
Liquid food	7/44 (16)	5/51 (9.8)	n.s.	0.39 ± 0.84	0.21 ± 0.63	n.s.
Solid food	6/46 (13)	6/51	n.s.	0.23 ± 0.67	0.23 ± 0.67	n.s.
Stools						
Melaena	1/37 (2.7)	0/41 (0)	n.s.	0	0	n.s.
Bloody	1/39 (2.6)	2/41 (4.5)	n.s.	0.05 ± 0.22	0.05 + 0.22	n.s.
Mucous	2/38 (5.2)	2/41 (4.5)	n.s.	0.15 ± 0.57	0.15 + 0.57	n.s.
Frequent hard	2/39 (5.1)	12/43 (28)	n.s.	0.34 ± 0.62	0.35 + 0.65	n.s.
Diarrhea	26/41 (63)	7/40 (18)	<0.001	0.93 ± 1.21	0.28 + 0.64	0.02
Alternately solid or loose	10/44 (23)	28/48 (58)	n.s.	0.95 ± 0.93	0.83 + 0.81	n.s.
Constipation	4/40 (10)	10/41 (24)	n.s.	0.35 ± 0.70	0.34 + 0.76	n.s.
Frequently with pain	1/39 (2.6)	6/40 (15)	n.s.	0.26 ± 0.59	0.25 + 0.74	n.s.
Stool urgency	23/42 (55)	8/41 (20)	0.0014	1.26 ± 1.50	0.29 + 0.68	<0.01
Incomplete	6/39 (15)	2/40 (5.0)	n.s.	0.38 ± 0.85	0.08 + 0.35	n.s.
Steatorrhea	2/38 (5.2)	1/40 (2.5)	n.s.	0.11 ± 0.39	0.03 + 0.16	n.s.

Data are given as mean ± 1SD. Groups were compared using Mann–Whitney rank sum test[a] and Fisher exact test[b]
Frequencies were compared using Mann–Whitney rank sum test
n.s. nonsignificantly

Table 3 Bowel pattern questionnaire in adult patients with Pompe disease and in age- and gender-matched controls (i.e. accompanying spouses and partners) as analysed by ICIQ-B-LF

	Pompe patients ($n = 57$)	Age- and gender-matched controls ($n = 57$)	p
Bowel pattern			
Frequency	6.2 ± 3.5	4.2 ± 2.4	<0.001
Interference	7.5 ± 9.0	2.5 ± 4.4	<0.001
Bowel control			
Frequency	5.6 ± 5.6	1.5 ± 2.0	<0.001
Interference	13.5 ± 16.2	1.9 ± 3.1	<0.001
Other bowel symptoms			
Frequency	4.4 ± 2.3	3.8 ± 1.4	n.s.
Interference	5.0 ± 7.1	1.3 ± 2.7	<0.01
Sexual impact			
Frequency	0.3 ± 1.1	0.02 ± 0.13	n.s.
Interference	0.4 ± 1.6	0.02 ± 0.13	n.s.
Quality of life			
Frequency	3.7 ± 4.3	1.5 ± 2.2	0.02
Interference	11.5 ± 15.4	1.9 ± 5.0	<0.001

Data are given as mean ± 1SD. Groups were compared using Mann–Whitney rank sum test
n.s. nonsignificantly

Table 4 Urinary incontinence in adult patients with Pompe disease and in age- and gender-matched controls (i.e. accompanying spouses and partners) as analysed by ICIQ-UI-SF

	Pompe patients ($n = 58$)	Age- and gender-matched controls ($n = 58$)	p
People reporting urinary incontinence [n (%)][b]	23/55 (42)	14/56 (25)	n.s.
Frequency of urinary incontinence[a]	0.98 ± 1.45	0.43 ± 0.93	n.s.
Quantity of urinary incontinence[a]	1.15 ± 1.58	0.57 ± 1.06	n.s.
Interference with daily life[a]	2.09 ± 3.15	0.48 ± 1.33	0.01
Interference with daily life in those patients reporting urinary incontinence[a]	5.00 ± 2.95	2.14 ± 2.07	0.004
Situations in which urinary incontinence occurs [n (%)][b,c]			
Never	32 (58)	37 (66)	n.s.
Before the toilet is reached	18 (33)	4 (7.1)	0.002
During coughing and pressure	3 (5.5)	15 (27)	0.0021
During sleeping	2 (3.6)	0	n.s.
During physical exertion	4 (7.3)	4 (7.1)	n.s.
After urinating and dressing	4 (7.3)	2 (3.6)	n.s.
Without explicable cause	3 (5.5)	2 (3.6)	n.s.
Permanently	0 (0)	0 (0)	n.s.

Data are given as mean ± 1SD. Groups were compared using Mann–Whitney rank sum test[a] and Fisher exact test[b]. [c] More than one answer possible
n.s. nonsignificantly

Discussion

This is the first multicenter cross-sectional study which systematically analysed symptoms of the upper and lower gastrointestinal tract as well as bowel and urinary incontinence using validated questionnaires in a large representative cohort of adult patients with Pompe disease.

The comparison with a population-based age- and gender-matched control group revealed that stool urgency and diarrhoea did occur more frequently in Pompe patients than in controls. These symptoms/signs were present in more than half of the Pompe patients. Twenty percent of the patients self-treated these symptoms/signs with loperamide indicating that they have an impact on the activities of daily living in Pompe patients. Stool urgency and diarrhoea were reported in equal frequencies in men and women. Other signs and symptoms of the upper and lower gastrointestinal tract did not occur more frequently in Pompe patients than in controls. Some symptoms of the GI tract (heartburn, bloating, postprandial fullness, flatulence) were reported statistically more significantly in controls than in patients. However, a statistically significant difference was not found, when we asked for the severity of these symptoms. The frequency of these symptoms in both our Pompe patient group and our control group is within the reported range (Bovenschen et al. 2006; Hollenz et al. 2002). Our controls were recruited in a slightly biased manner, but we think that they represent a sound population-based control group. The nonstandardised part of the "Gastrointestinal Symptoms Questionnaire" we had added to analyse the frequency of the symptoms should be omitted in future studies.

Urinary urge incontinence was present in one third of the Pompe patients, statistically more often in Pompe patients than in matched controls. Twenty-three percent of patients reported both symptoms of urinary and stool urge incontinence. This symptom was reported twice as frequently in women than men. Functional bladder tests in those Pompe patients reporting urinary urge incontinence are warranted.

Most of our patients had a disease course much longer than the duration of their individual period of ERT. Therefore, we do not know whether and how frequently urge symptoms occur as initial disease symptoms.

Bowel and urinary incontinence has probably been an under-reported symptom in Pompe patients. However, our study shows that these symptoms are physically disabling and have an important impact on the patients' daily life.

To avoid a recall bias, we have not asked for the onset of both urinary and bowel incontinence. Therefore we cannot judge how these symptoms are related and whether the symptoms responded to ERT. Forty-nine out of 57 of our Pompe patients were regularly treated with ERT. Thus, we cannot rule out that alglucosidase alfa might cause diarrhoea and stool urgency as a side effect. However, intravenously administered alglucosidase alfa (ERT) did not seem to be associated with any other gastrointestinal symptoms in the present study. Follow-up studies with ERT naïve patients are required in the future to clarify this issue. The frequent occurrence of both urinary and bowel incontinence suggests that these symptoms are due to smooth muscle dysfunction related to Pompe disease and not side effects of the ERT. Nevertheless, in most patients, urge symptoms persisted and did not seem to respond to ERT. An accumulation of glycogen in the smooth muscles of the lamina muscularis in all parts of the gastrointestinal tract but also in the urinary bladder has been frequently demonstrated in the mice models of glycogen storage disease type II and also in autopsies of patients with infantile and adult Pompe disease (Van der Walt et al. 1987; Bijvoet et al. 1999; Winkel et al. 2003; Kobayashi et al. 2010; Hobson-Webb et al. 2012). Therefore, evidence suggests that disturbed smooth muscles cause the symptoms of bowel and urinary incontinence. Gastrointestinal symptoms, such as diarrhoea and abdominal pain, are even more prevalent in Fabry disease (alpha-galactosidase A deficiency), another storage disorder, but were reported to be ameliorated by ERT (Keshav 2006; Hoffmann et al. 2007). Pathophysiologically, in contrast to Pompe disease, these symptoms may be caused by a combination of enteric neuropathy and a myopathy of the intestinal smooth muscle (Keshav 2006). Lipid accumulation in the smooth gastrointestinal muscles occurs in the lipid storage disorder Gaucher disease type 1. Gastrointestinal symptoms were reported to improve upon ERT (Verderese et al. 1993). Other myopathies with multisystemic involvement including gastrointestinal symptoms include myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2) due to a myopathy of the intestinal smooth muscles causing dysphagia, delayed gastric emptying, obstipation, and other gastrointestinal motility problems (Tieleman et al. 2008; Tanaka et al. 2013). In mitochondrial myopathies (another group of diseases with multisystemic affection), gastrointestinal symptoms have been less well studied, but it has been suggested that they are due to autonomous neuropathy (Chinnery et al. 2001; Pfeffer et al. 2011).

In conclusion, urinary and bowel incontinence are frequent symptoms in adults with Pompe disease and are often socially disabling.

Acknowledgment We thank Kathryn Birch for copy-editing and all patients who participated in the study.

Synopsis

In adults with Pompe disease, urinary and bowel incontinence are frequent symptoms and are often socially disabling.

Compliance with Ethical Guidelines

Conflict of Interest

Nesrin Karabul, Cornelia Kornblum, Rudolf A. Kley, Eugen Mengel, Matthias Vorgerd, Marcus Deschauer, Benedikt Schoser, and Frank Hanisch have received lecturer honoraria and travel fees from Genzyme, a Sanofi company. Frank Hanisch has also received lecturer honoraria and travel fees from Astellas and Biomarin Incorp.

Anika Skudlarek, Janine Berndt, Stephan Wenninger, Nikolaus Tiling, and Ursula Plöckinger declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all patients included in the study.

Statement About the Contribution of Every Co-author

Nesrin Karabul – principal investigator, participated in the design of the study, recruited patients, contributed to data analysis, major participation in drafting the manuscript

Anika Skudlarek – major participation in collection and analysis of data, participation in drafting the manuscript

Janine Berndt – participation in statistical analysis

Cornelia Kornblum – recruited patients, participation in drafting the manuscript

Rudolf A. Kley – recruited patients, participation in drafting the manuscript

Stephan Wenninger – recruited patients

Nikolaus Tiling – recruited patients, participation in drafting the manuscript

Eugen Mengel – participation in drafting the manuscript

Ursula Plöckinger – participation in drafting the manuscript

Matthias Vorgerd – participation in drafting the manuscript

Marcus Deschauer – participation in drafting the manuscript

Benedikt Schoser – participation in drafting the manuscript

Frank Hanisch – principal investigator, designed the study, recruited patients, performed statistical analysis, major participation in drafting the manuscript

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