Gastrointestinal and urinary dysfunctions in late-onset Pompe disease

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INTRODUCTION

Glycogen-storage disease type II (GSD2) or Pompe disease is an hereditary metabolic myopathy caused by deficiency of the lysosomal enzyme acid α-glucosidase. The disease causes lysosomal and cytoplasmic glycogen accumulation in cardiac and skeletal muscles, as well as in various other tissues.

The classical infantile-onset Pompe disease presents with rapidly progressive cardiomyopathy, muscle weakness, and hypotonia before one year of age. Late-onset Pompe disease (LOPD) presents in juvenile or adult life and it is clinically heterogeneous. Symptoms in children and adults with a LOPD presentation are predominantly related to skeletal muscle dysfunction, resulting in both motor and respiratory deficits. LOPD clinical phenotype is heterogeneous and can vary from severe skeletal muscle weakness with respiratory involvement to asymptomatic subjects with isolated serum hyperCKemia. Low tissue levels of acid alpha-glucosidase (GAA) activity (usually in the range of 1-40% of normal) are considered the gold standard for the diagnosis, eventually confirmed by molecular analysis of GAA gene.

Several works, especially from autopsy studies, have demonstrated that glycogen accumulates also in smooth muscle: urinary and gastrointestinal tracts could be involved in this pathology but often these symptoms are not studied and they are underestimated by clinicians as they focus on the motor and respiratory involvement.

AIM OF THE STUDY

The purpose of the study was to evaluate whether LOPD patients have gastrointestinal or urinary interest, in order to assess the clinical spectrum of GSD2 and to determine intestinal and bladder dysfunctions in GSD2 patients which are currently unknown.

METHODS

Patients with LOPD were asked about their symptoms concerning the upper and lower intestinal tract as well as urinary incontinence using the Gastrointestinal Symptoms Questionnaire (GSRS) and the International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI SF). Both questionnaires are available in Italian version and have been validated. The questionnaires are given below (Fig 1 and 2).

RESULTS

Eleven patients with LOPD (6 females, 5 males), all molecular confirmed, were included in our study; the median age was 50.2 years (range 31-79 years of age). All subjects were receiving enzyme replacement therapy (ERT). Clinical features, their onset, pulmonary involvement and ambulatory status are reported in the table (Table 1). They completed GSRS and ICIQ-UI SF Italian validated questionnaires.

The most frequently mentioned symptoms were abdominal distension (81.8%), flatulence (90.9%), sensation of incomplete evacuation (72.7%). Hard stools (45.4%) and constipation (54.5%) were often reported. Diarrhoea was reported by three patients (27.2%), while nausea and vomiting by four subjects (36.3%). It seemed to emerge from the questionnaire that patients often complained about lower intestinal tract disorders than the digestive part. Two women reported severe symptoms of the digestive tract. However we think that they were more related to a psychosomatic disorder as asking patients if they took drugs regularly for these problems they have denied (Table 2).

About bladder dysfunctions, four women out of six reported mild/moderate urinary incontinence with urgency: they referred a small/moderate amount of urine, often before they get to the toilet and/or when they cough or sneeze. Three of them have had physiological pregnancies and deliveries, one female did not have children. A male patient (aged 79) suffered from a severe urinary incontinence but probably secondary to prostate surgical treatment.

DISCUSSION

Glycogen storage within the skeletal muscles as well as in the organs containing the smooth muscle (bladder, intestine, and esophagus) has been demonstrated in autopsy works (Hobson-Webb et al. 2012); these data support the clinical symptoms complained by our GSD2 population.

The GSRS and ICIQ-UI SF questionnaires are simple in compilation, translated into Italian language and can be easily used during clinical evaluation. They could be useful during follow up patients in ERT to evaluate possible beneficial effect on these problems but we cannot rule out that ERT might cause some of these symptoms (excessive intestinal air) as side effects.

Objective measurements (pelvic EMG, anorectal manometry, urodynamic tests, bladder ultrasonography) could be used to confirm these problems.

Symptoms reported by patients did not correlate with their motor deficits, age, treatment duration or with pulmonary involvement. Some Authors have demonstrated similar results in recent studies (Karabul et al 2014, Mc Namara et al 2015) .

CONCLUSION

Late-onset glycogen storage disease type 2 is characterized by motor and respiratory involvement; however GSD2 must be considered a systemic disease because accumulation of glycogen can affect other organs, in particular the smooth muscle. Other myopathies, especially muscular and myotonic dystrophy, show evidence of gastrointestinal symptoms and how they can interfere in social, professional and emotional life of the patients. These aspects could lead to disabling conditions in LOPD and their treatments may significantly improve quality of life.

This is a preliminary study which shows that patients complain gastrointestinal symptoms (abdominal distension, flatulence, feeling of incomplete emptying) and even in some females moderate urinary incontinence. These single-center data are preliminary and require a more extensive instrumental evaluation and may be expanded to Italian GSDII Group.

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APPENDIX M

Gastrointestinal Symptom Rating Scale (GSRS)

Name: _____

A rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Circle the number which best represents the current severity of the symptom.

1. Abdominal pains. Representing subjectively experienced bodily discomfort, aches and pains.

The type of pain may be classified according to the patient's description of the appearance and quality of the pain as epigastric, on the basis of typical location, association with acid-related symptoms, and relief of pain by food or antacids; as colicky when occurring in bouts, usually with a high intensity, and located in the lower abdomen; and as dull when continuous, often for several hours, with moderate intensity.

Rate according to intensity, frequency, duration, request for relief, and impact on social performance.

0 No or transient pain
1 Occasional aches and pains interfering with some social activities
2 Prolonged and troublesome aches and pains causing requests for relief and interfering with many social activities
3 Severe or crippling pains with impact on all social activities

2. Heartburn. Representing retrosternal discomfort or burning sensations. Rate according to intensity, frequency, duration, and request for relief.

0 No or transient heartburn
1 Occasional discomfort of short duration
2 Frequent episodes of prolonged discomfort; requests for relief
3 Continuous discomfort with only transient relief by antacids

3. Acid regurgitation. Representing sudden regurgitation of acid gastric content. Rate according to intensity, frequency, and request for relief.

0 No or transient regurgitation
1 Occasional troublesome regurgitation
2 Regurgitation once or twice a day; requests for relief

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4. Sucking sensations in the epigastrium. Representing a sucking sensation in the epigastrium with relief by food or antacids. If food or antacids are not available, the sucking sensations progress to ache, and pains. Rate according to intensity, frequency, duration, and request for relief.

0 No or transient sucking sensation
1 Occasional discomfort of short duration; no requests for food or antacids between meals
2 Frequent episodes of prolonged discomfort, requests for food and antacids between meals
3 Continuous discomfort; frequent requests for food or antacids between meals

5. Nausea and vomiting. Representing nausea which may increase to vomiting. Rate according to intensity, frequency, and duration.

0 No nausea
1 Occasional episodes of short duration
2 Frequent and prolonged nausea; no vomiting
3 Continuous nausea; freque nt vomiting

6. Borborygmus. Representing reports of abdominal rumbling. Rate according to intensity, frequency, duration, and impact on social performance

0 No or transient borborygmus
1 Occasional troublesome borborygmus of short duration
2 Frequent and prolonged episodes which can be mastered by moving without impairing social performance
3 Continuous borborygmus severely interfering with social performance

7. Abdominal distension. Representing bloating with abdominal gas. Rate according to intensity, frequency, duration, and impact on social performance.

0 No or transient distension
1 Occasional discomfort of short duration
2 Frequent and prolonged episodes which can be mastered by adjusting the clothing
3 Continuous discomfort seriously interfering with social performance

8. Eructation. Representing reports of belching. Rate according to intensity, frequency, and impact on social performance.

0 No or transient eructation
1 Occasional troublesome eructation
2 Frequent episodes interfering with some social activities
3 Frequent episodes seriously interfering with social performance

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9. Increased flatus. Representing reports of excessive wind. Rate according to intensity, frequency, duration, and impact on social performance

0 No increased flatus
1 Occasional discomfort of short duration
2 Frequent and prolonged episodes interfering with some social activities
3 Frequent episodes seriously interfering with social performance

10. Decreased passage of stools. Representing reported reduced defecation. Rate according to frequency. Distinguish from consistency.

0 Once a day
1 Every third day
2 Every fifth day
3 Every seventh day or less frequently

11. Increased passage of stools. Representing reported increased defecation. Rate according to frequency. Distinguish from consistency.

0 Once a day
1 Three times a day
2 Five times a day
3 Seven times a day or more frequently

12. Loose stools. Representing reported loose stools. Rate according to consistency independent of frequency and feelings of incomplete evacuation.

0 Normal consistency
1 Somewhat loose
2 Runny
3 Watery

13. Hard Stools. Representing reported hard stools. Rate according to consistency independent of frequency and feelings of incomplete evacuation.

0 Normal consistency
1 Somewhat hard
2 Hard
3 Hard and fragmented, sometimes in combination with diarrhea

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14. Urgent need for defecation. Representing reports of urgent need for defecation, feelings of incomplete control, and inability to control defecation. Rate according to intensity, frequency, and impact on social performance.

0 Normal control
1 Occasional feelings of urgent need for defecation
2 Frequent feelings of urgent need for defecation with sudden need for a toilet interfering with social performance
3 Inability to control defecation

15. Feeling of incomplete evacuation. Representing reports of defecation with straining and a feeling of incomplete evacuation of stools. Rate according to intensity and frequency.

0 Feeling of complete evacuation without straining
1 Defecation somewhat difficult; occasional feelings of incomplete evacuation
2 Defecation definitely difficult; often feelings of incomplete evacuation
3 Defecation extremely difficult; regular feelings of incomplete evacuation

Figure 1. The Gastrointestinal Symptom Rating Scale Questionnaire (GSRS).

ID pz	Age	Age at onset	Symptom at onset	Start ERT	NIMV	Loss of ambulation
GS	79	50	Myalgias	2006	N	N
BC	48	7	Pelvic weakness	2008	Y + MV	Y
DA	52	29	Pelvic weakness	2008	N	N
DC	52	42	Pelvic weakness	2009	Y	N
RI	42	39	HyperCKemia	2014	N	N
GE	48	42	Limb girdle weakness	2008	N	N
MV	46	34	HyperCKemia	2007 (she stopped during 2014)	N (she refused)	N
PT	57	37	Limb girdle weakness	2007	N	N
ME	59	30	Scapular weakness	2010	N	N
DeC	39	34	Pelvic weakness	2011	Y	N
DiT	31	28	Limb girdle weakness	2015	N	N

Table 1. Clinical features of our LOPD patients

ICIQ-UI Short Form

Initial number ☐☐☐☐☐☐☐☐ CONFIDENTIAL Today's date ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1 Please write in your date of birth: ☐☐ DAY ☐☐ MONTH ☐☐ YEAR

2 Are you *(tick one)*: Female ☐ Male ☐

3 How often do you leak urine? *(Tick one box)*
never ☐ 0
about once a week or less often ☐ 1
two or three times a week ☐ 2
about once a day ☐ 3
several times a day ☐ 4
all the time ☐ 5

4 We would like to know how much urine you think leaks.
How much urine do you usually leak (whether you wear protection or not)? *(Tick one box)*
none ☐ 0
a small amount ☐ 2
a moderate amount ☐ 4
a large amount ☐ 6

5 Overall, how much does leaking urine interfere with your everyday life?
Please ring a number between 0 (not at all) and 10 (a great deal)
0 1 2 3 4 5 6 7 8 9 10
not at all — a great deal

ICIQ score: sum scores 3+4+5 ☐☐

6 When does urine leak? *(Please tick all that apply to you)*
never – urine does not leak ☐
leaks before you can get to the toilet ☐
leaks when you cough or sneeze ☐
leaks when you are asleep ☐
leaks when you are physically active/exercising ☐
leaks when you have finished urinating and are dressed ☐
leaks for no obvious reason ☐
leaks all the time ☐

Thank you very much for answering these questions.

Figure 2. International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI SF)

	Absent	Mild/moderate	Severe
Abdominal pain	+++++++	++++	
Heartburn	++++++++	+++	+
Acid regurgitation	++++++++	++	+
Sucking sensation in the epigastrium	++++++++	+++	
Nausea and vomiting	+++++++	+++	+
Borborygmus	++++++	+++++	
Abdominal distension	++	+++++++	++
Eructation	+++++++	++++	
Increased flatus	+	+++++++++	+
Decreased passage of stools	+++++	++++++	
Increased passage of stools	++++++++	+++	
Loose stools	++++++++	+++	
Hard stools	++++++	++	+++
Urgent need for defecation	+++++++	++++	
Feeling of incomplete evacuation	+++	+++++++	

Table 2. Gastro-intestinal symptoms reported by GSD2 patients, according to GSRS questionnaire

References
Hobson-Webb LD, Proia AD, Thurberg BL et al. Autopsy findings in late-onset Pompe disease: a case report and systematic review of the literature. Mol Genet Metab. 2012.106:462–469
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