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Trunk muscle involvement in late-onset Pompe disease: Study of thirty patients

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Abstract

Late-onset Pompe disease is characterized by progressive weakness involving proximal limb and respiratory muscles. Recently, treatment with enzyme replacement therapy (ERT) has been introduced partially improving patients' prognosis, but a standard consensus on when to start ERT is still lacking. There is also a lack of biomarkers related to the clinical progression of the disease.

Here we used muscle magnetic resonance imaging (MRI) or computed tomography (CT) to study the abdominal and paravertebral muscles of 30 late-onset Pompe patients at different stages of disease.

We observed a selective pattern of muscle damage, with early involvement of the *Multifidus* muscle, followed by the *Obliquus internus abdominis* and *Longissimus* muscle. Some degree of trunk involvement on MRI occurred even in asymptomatic patients. Severity of muscle involvement in MRI correlated with patients' functional stage.

We suggest that: (a) the combination of paravertebral and abdominal muscle involvement may serve as a useful tool in the diagnostic work-up of patients with a clinical suspicion of Pompe disease; (b) trunk abnormalities appear at very early stages of disease and even in asymptomatic patients, possibly "announcing" the onset of the disease and thus the need for a closer clinical follow-up.

Keywords: Pompe disease; MRI; Paravertebral muscles; Abdominal muscles

1. Introduction

Pompe disease, also known as acid maltase deficiency (AMD) or glycogen storage disease type II (GSD II), is a rare autosomal recessive disorder due to a deficiency of the lysosomal enzyme acid alpha glycosidase (GAA). This deficiency causes intralysosomal accumulation of glycogen

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in several tissues such as skeletal muscle, cardiac muscle or liver [1]. Different clinical patterns have been described, ranging from rapidly progressive infantile forms to slowly progressive adult-onset phenotypes [2]. In general, late-onset Pompe disease is characterized by weakness of the proximal limb and axial muscles associated with respiratory muscles involvement [3]. However, many different clinical presentations have been reported, ranging from predominant respiratory involvement to exclusive limb muscles weakness.

Clinical and muscle biopsy findings can be unspecific in Pompe disease, so that muscle imaging can become a helpful diagnostic tool [1]. Computed tomography (CT) studies in adult patients have shown that the disease spreads over the years from trunk to extremities [4] with selective muscle involvement found in the thighs [5].

The most recent therapeutic progress in Pompe disease has been enzymatic replacement therapy (ERT) with recombinant human GAA (rh-GAA), which has proved to be effective in both infantile and adult forms [6,7]. Although long-term follow-up data in treated patients are still lacking, ERT seems to improve muscle weakness and to stabilize the disease. The response to rh-GAA may be less robust in more advanced phases of the disease [8] and this emphasizes the need for prompt diagnosis and early treatment initiation. Because of the high costs of the treatment there have been controversial discussions about when the therapy should be started [9].

Considering that paravertebral muscles are involved at an early disease stage, we decided: (1) to study both the posterior and anterior trunk muscles in 30 late-onset Pompe patients by muscle imaging in order to evaluate their degree of involvement in a large cohort of patients at different functional stages; (2) to investigate whether there is a correlation between our clinical and imaging data.

2. Material and methods

2.1. Clinical data

A group of 30 adult-onset Pompe patients undergoing regular follow-up assessments at our centres was recruited from April 2006 to July 2011. Pompe disease diagnosis was based on <30% reduction versus controls of GAA activity in peripheral blood lymphocytes/muscle, and was confirmed by molecular analysis of the GAA gene (Table 1).

Muscle MRI was performed as part of the assessment and patients were classified into 4 groups according to the following functional stages:

- *Asymptomatic*: no muscle weakness or respiratory involvement, the only abnormal finding was hyperCKemia.
- *Mild involvement*: patients were able to walk and climb up stairs without help, muscular weakness was detected on clinical examination.
- *Moderate involvement*: patients needed aids (banister, crutch, stick) to climb up stairs, had difficulties to stand up from a chair or required non-invasive ventilation at night.
- *Severe involvement*: patients were unable to walk more than 10 m without help or required non-invasive mechanical ventilation during the day.

We collected the following data from each patient: (1) demographics (age, sex); (2) clinical features (age at onset, age at diagnosis, disease duration at the time of imaging, presence of hyperlordosis, abdominal or paravertebral muscle weakness, presence of lumbar pain, percentage of vital capacity in sitting position, and need for respiratory support); (3) therapeutic data (ERT treatment at time of MRI, time from treatment onset to MRI); (4) mutations found in the GAA gene.

2.2. Muscle MRI

Muscle MRI was performed by a 1.5T MR scanner (1.5T Philips Intera and 1.5T Philips Achieva XR Realeas) and was used to obtain T1-weighted spin-echo axial images from the mid-dorsal segment to the sacrum using the same parameters (TR = 300 ms, TE = 10 ms, thickness = 10 mm). The imaging protocol took 45 min. Five patients were investigated using muscle CT scan. They did not tolerate the MRI protocol due to severe respiratory weakness. CT axial images were performed at the same level with the same thickness. None of the patients of this series had repeated studies.

Two independent observers blind to clinical information examined all the scans and evaluated paravertebral (specifically *Multifidus*, *Longissimus*, *Iliocostal Lumborum*, *Quadratus Lumborum* and *Illiopsoas*) and abdominal (specifically *Rectus Abdominis*, *Transversus Abdominis*, *Obliquus Externus Abdominis*, *Obliquus Internus Abdominis*) muscles (Fig. 1). Muscle atrophy was evaluated by the Mercuri scale [10].

2.3. Statistics

We performed a Pearson test to correlate the functional stage (scored 1–4) in every patient with the degree of muscle involvement (scored as the average value of the Mercuri's scale of all the muscles). It was considered significant if P was lower than 0.05.

3. Results

All patients (17 women and 13 men) had a late-onset form of the disease. All but 5 were symptomatic. Mean age at MRI was 46 years (±16.7 SD); mean age at disease onset was 29 years (±12.9 SD); mean delay in diagnosis was 10 years (±8.4 SD) and average duration of the symptoms at the time of imaging was 7 years (±12).

Table 1
Clinical and genetic data of patients analyzed. Functional scale according to functional impairment (see Section 2).

Patient	Gender	Age (years)	Age at onset (years)	Age of diagnosis (years)	Time to diagnosing (years)	Functional scale at time of MRI	Mutation	Mechanical ventilation	CV%	Treatment
1	Female	20	[a]	20	[a]	Asymptomatic	IVS 13TG IVS 13 1755GA	No	100	No
2	Male	72	[a]	70	[a]	Asymptomatic	IVS 13TG 525 del T	No	95	No
3	Male	26	[a]	3	[a]	Asymptomatic	IVS 13TG not found	No	100	No
4	Male	32	[a]	29	[a]	Asymptomatic	IVS 13 TG 525 del T	No	100	No
5	Male	22	[a]	18	[a]	Asymptomatic	IVS 13 TG delTG2219-2220	No	90	No
6	Female	47	38	43	5	Mild	IVS 13 TG 525 del T	Yes	93	Yes
7	Male	43	25	42	17	Mild	IVS 13TG 875GA	Yes	82	Yes
8	Female	25	22	25	3	Mild	1655TC 1704CG	No	93	No
9	Male	29	16	16	0	Mild	IVS 13 TG 2014 CT	No	84	Yes
10	Female	38	28	36	8	Mild	IVS 13 TG 1694-1697delTCTC	No	72	Yes
11	Male	40	36	39	3	Mild	IVS 13 TG Del exon 18	No	93	Yes
12	Male	50	23	47	24	Mild	IVS 13 TG 525 del T	No	87	Yes
13	Female	56	40	55	15	Moderate	IVS 13 TG 2600_2604delTGCT	No	80	Yes
14	Female	45	36	45	9	Moderate	IVS 13 TG 2014 CT	No	71	Yes
15	Female	47	20	47	27	Moderate	IVS 13TG 236_246delCCACACAGTGC	No	69	Yes
16	Female	42	27	32	5	Moderate	IVS 13TG 1192DupC	No	82	Yes
17	Female	45	[a]	45	[a]	Moderate	IVS 13TG 875GA	No	70	No
18	Female	61	35	49	19	Moderate	IVS 13 TG 525 del T	Yes	49	Yes
19	Female	48	20	28	8	Moderate	IVS 13 TG 525 del T	Yes	32	Yes
20	Female	60	30	36	6	Moderate	IVS 13 TG 2530-41delEx18	Yes	55	Yes
21	Male	72	50	60	10	Moderate	IVS 13 TG IVS1076-1G>C	No	58	Yes
22	Male	58	42	45	3	Moderate	IVS 13 TG 2298_2301 delinsAAAGTA	No	73	Yes
23	Female	31	10	13	3	Moderate	IVS 13 TG 1297 GA	No	80	Yes
24	Male	73	52	72	20	Severe	IVS 71195GA 1856GA	No	44	Yes
25	Male	53	17	22	5	Severe	IVS 13 TG 1465 GA	Yes	15	Yes
26	Female	60	40	57	17	Severe	IVS 13 TG 2237GA	Yes	23	Yes
27	Female	61	30	33	3	Severe	IVS 13 TG 2237GA	Yes	51	Yes
28	Male	82	67	72	5	Severe	IVS 13 TG IVS1076-1G>C	Yes	43	Yes
29	Female	61	40	53	13	Severe	IVS 13 TG 1561GA	No	85	Yes
30	Female	72	30	60	30	Severe	IVS 13 TG 784 GA	No	92	No

[a] Patients were asymptomatic or they were diagnosed due to family study; therefore age at onset and time to diagnosing were unknown.

We classified 5 patients as asymptomatic (16.6%), 7 as mildly affected (23.3%), 11 as moderately affected (36.6%), and 7 as severely affected (23.3%) (Table 1).

Eleven out of thirty (36%) patients complained of chronic lumbar pain. Thirteen (43%) patients showed trunk weakness when asked to raise the trunk from a prone position, and 14/30 (46%) patients had hyperlordosis on clinical examination. Eighteen out of thirty (60%) patients were unable to rise from the supine position, possibly indicating abdominal weakness; nine patients (30%) needed respiratory support at the time of the scan. Twenty-two (73.3%) patients were treated with ERT, with a mean time from treatment onset to MRI of 0.9 years (1.2 SD).

The group of asymptomatic patients included 4 men and 1 woman. Mean age at MRI was 30 years (21.5 SD). Only one patient complained of occasional lumbar pain. Diagnosis was reached as part of the investigation for asymptomatic hyperCKemia in 5 patients and through family screening in patient 2. MRI analysis of this group showed mild atrophy in at least one muscle (Table 2). The *Multifidus* muscle was the most frequently affected, reaching grade 2 on the Mercuri scale in 4 out of 5 patients, followed by the *Obliquus Internus Abdominis* muscle, reaching grade 2 and 3 on Mercuri scale, respectively in 2 out of 5 patients.

Mildly affected patients (4 men and 3 women) had a mean age of 37 years (9.1 SD) and a mean disease duration of 8 years (8.6 SD). 3 patients complained of chronic lumbar pain, four had trunk weakness while 6 patients had hyperlordosis. Mean vital capacity in a sitting position was $85 \pm 7.7\%$ in this group. Two patients needed nocturnal ventilation due to episodes of nocturnal apnea. Six patients are now on ERT, only in one of them the treatment had been started 3 years after performing the scan. Radiological studies showed different degrees of involvement of all paravertebral and abdominal muscles, but the *Obliquus Internus Abdominis* and *Longissimus* muscles were completely atrophic in all but one patient. The *Multifidus* muscle was involved in all these patients except in one of them. Conversely, the *Obliquus Externus Abdominis*, *Quadratus Lumborum* and *Illiopsoas* muscles were spared in most patients in this group.

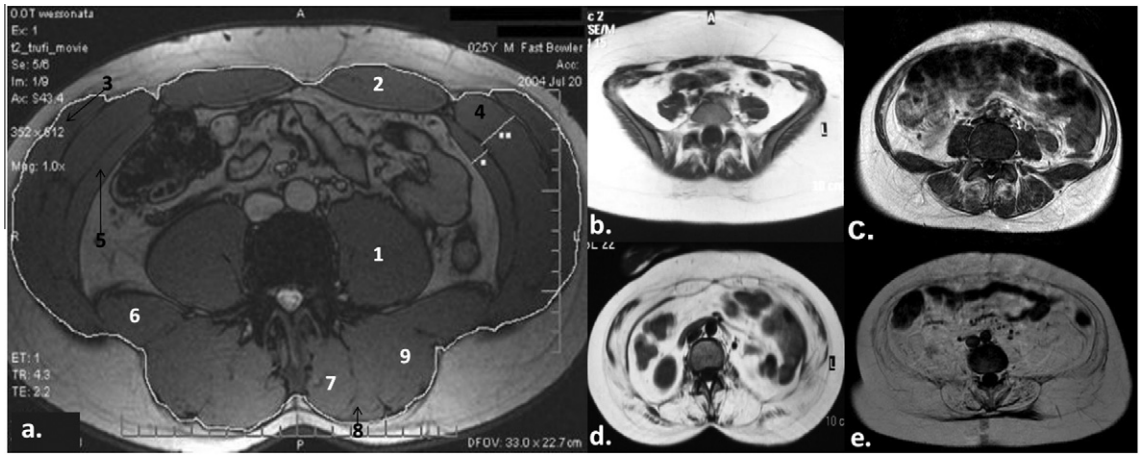

Fig. 1. MRI involvement of trunk muscles. Normal abdominal and paravertebral muscles slice (a): *Psoas* muscle (1), *Rectus Abdominis* (2), *Obliquus Externus Abdominis* (3), *Obliquus Internal Abdominis* (4), *Transversus Abdominis* (5), *Quadratus Lumborum* (6), *Multifidus* muscle (7), *Longissimus* muscle (8), *Iliocostal Lumborum* (9). Asymptomatic. patient number 1 (b). Mild clinical stage patient number 10 (c). Moderate clinical satge patient number 13 (d). Severe clinical stage patient number 27 (e).

The group with moderate disease severity included 2 men and 9 women with a mean age of 50 years (11.2 SD) and a mean duration of disease of 19 years (7.3 SD). Five patients complained of lumbar pain, 5 had trunk weakness while 5 other patients had hyperlordosis. Mean vital capacity in a sitting position was 62% (16.1 SD) and 3 patients needed respiratory support. Nine patients were on ERT treatment (mean treatment duration to MR time was 1.2 years). Imaging showed involvement of all paravertebral and abdominal muscles. Specifically, at this stage the *Transversus Abdominis*, *Obliquus Internus Abdominis*, *Rectus Abdominis, Ilicostal, Iliopsoas* and *Longissimus* muscles were completely atrophic. The *Obliquus Externus Abdominis, Multifidus* and *Illiopsoas* muscles were less atrophic.

Finally, 3 men and 4 women were classified as severely affected. The mean age was 65 years (9.9 SD) and mean duration of disease was 28 years (13.3 SD). Three patients complained of lumbar pain, five had trunk weakness and one had hyperlordosis. The mean vital capacity in a sitting position was 42% (28.9 SD) and 4 patients needed non-invasive mechanical ventilation. Six patients were on ERT treatment (time from treatment start to MRI was 1.1 years (0.9 SD). Imaging studies showed complete atrophy of all muscles.

We analysed if any correlation could be established between the functional stage and the degree of muscle involvement using the Pearson test. We found a positive significant correlation ($p < 0.001$) showing that with a worse functional stage there was a greater degree of muscle involvement on MRI.

4. Discussion

Pompe disease as a metabolic muscle disease has received a lot of radiologic attention in the last few years, especially in relation to the recent ERT introduction [4,5,8,11,12]. Muscular imaging, especially muscle MRI, has proved to be reliable in assessing both the pattern and the severity of muscle damage in several different muscle disorders [13–16].

In particular, CT studies demonstrated that Pompe disease in adult patients spreads over the years from trunk to extremities with axial and thigh muscles being more severely affected than lower leg and shoulder girdle muscles [4]. Specifically, posterior lumbar paraspinal and *Psoas* muscles were demonstrated to be severely atrophic in all patients [4,11] so that it was suggested to consider Pompe disease in any case of otherwise unexplained paraspinal muscle atrophy [11]. A study in 11 patients showed selective damage in different thigh muscles over time [5], while another study performed with whole-body MRI in 20 patients also observed involvement of the subscapular and tongue muscles [17] .

A recent report has suggested that routine EMG assessment of these patients should include a lumbar paravertebral examination, which is affected at early stages of the disease [12,18]. Recent reports about atypical cases of Pompe disease revealed by a “rigid spine syndrome” have raised further interest in trying to elucidate the pattern and extent of trunk involvement in these patients [19,20]. However, clinical symptoms and signs of trunk involvement are often vague and unspecific (pain, subtle postural changes) and may be easily overlooked. Moreover, these muscles are difficult to assess clinically. A rough clinical evaluation may be based on the ability to rise from the supine position or to raise the trunk from the prone position, but these are complex movements involving several muscle groups and their clinical assessment may be further hampered in the presence of concomitant respiratory dysfunction.

Taking into account the early involvement of trunk muscles, we decided to carefully study both paravertebral

Table 2
MRI analysis and quantification of trunk muscle involvement.

Patient	MRI date	Time onset-MRI yrs	Time treatment-MRI	*Transversus Abdominis*	*Obliquus Internal Abdominis*	*Obliquus External Abdominis*	*Rectus Abdominis*	*Multifidus* muscle	*Longissimus* muscle	*Ilio-costal lumborum*	*Quadratus lumborum*	*Psoas* muscle
1	2008–2009	[a]	[b]	1	1	1	1	2	1	1	1	1
2	2011/06/27	[a]	[b]	1	3	1	NA	2	2	1	1	1
3	2010/02/18	[a]	[b]	1	1	1	1	2	2	1	1	1
4	2010/03/16	[a]	[b]	1	2	1	1	1	1	1	1	1
5	2008/12/10	[a]	[b]	1	1	1	1	2	1	1	1	1
6	2011/07/06	9	3	NA	NA	NA	NA	4	4	4	4	1
7	2010/09/14	17	0	4	4	3	4	3	4	4	2	3
8	2009/02/06	1	[b]	1	1	1	2	1	1	1	1	1
9	2007/08/27	13	0	4	4	4	NA	3	4	2	1	1
10	2008/12/17	10	0	1	3	1	NA	2	2	1	1	1
11	2009/05/07	4	0	1	4	1	1	4	4	3	1	1
12	2006/10/25	27	0	3	4	4	3	4	4	4	4	4
13	2007/06/01	16	0	3	4	4	4	3	4	4	4	2
14	2008/12/31	9	0	NA	NA	NA	NA	3	4	3	4	2
15	2010/06/17	27	0	4	4	3	4	3	4	4	4	3
16	2010/02/18	11	3	NA	NA	NA	NA	4	4	3	3	3
17	2011/06/01	[a]	[b]	4	3	2	4	4	4	4	1	4
18	2007/01/08	26	1	2	4	2	NA	4	4	4	4	3
19	2009/05/19	28	3	4	4	4	4	4	4	4	4	4
20	2006/08/08	30	0	3	NA	NA	3	3	3	3	3	1
21	2006/08/21 TC	22	0	3	2	1	3	3	3	3	2	3
22	2010/01/13	16	3	4	4	4	4	4	4	4	4	4
23	2008/09/16 TC	21	1	NA	NA	NA	NA	2	2	2	1	1
24	2011/06/20	52	1	4	4	4	4	4	4	4	4	3
25	2006/04/12 TC	36	1	NA	NA	NA	NA	4	4	3	3	4
26	2006/04/21 TC	20	1	NA	NA	NA	NA	3	4	2	4	4
27	2007/04/05	31	1	4	NA	NA	4	4	4	4	4	4
28	2006/08/21 TC	15	0	1	NA	NA	1	3	3	3	2	2
29	2009/06/23	21	3	NA	4	3	NA	4	4	4	4	4
30	2008/05/29	42	[b]	4	4	4	4	3	4	4	4	4

[a] Age at onset is unknown because patients were asymptomatic or diagnosed due to family study.
[b] These patients were not under treatment with ERT. NA: not accessible. CT: computerized tomography.

and abdominal muscles in 30 late-onset Pompe patients, evaluating nine muscles of the lumbar paravertebral area and the anterior abdominal muscles. We found that all our patients, including asymptomatic ones, had some degree of trunk muscle atrophy, suggesting that MRI is able to find muscle changes in trunk muscles before patients notice any symptom (Fig. 2). Although a clear pattern of involvement could not be found, a distribution of the damage in different muscles over time was observed. Specifically, the *Multifidus* and the *Obliquus Internus Abdominis* muscles were commonly the first muscles affected, followed by the *Longissimus,* the *Transversus Abdominis* and the *Rectus Abdominis* muscles and eventually the *Iliocostal Lumborum*, *Quadratus Lumborum*, *Illiopsoas* and *Obliquus Externus Abdominis* muscles.

Our results suggest that the presence of both paravertebral and abdominal muscle atrophy on muscle MRI of patients with prominent weakness of the pelvic girdle muscles or asymptomatic hyperCKemia could be suggestive of late-onset Pompe disease and potentially shorten the well known problem of the diagnostic delay.

Paravertebral atrophy is not uncommon and may be seen in other metabolic myopathies (i.e. glycogenosis V), in muscular dystrophies (e.g. facio-scapulo-humeral muscular dystrophy -FSHD-, laminopathies), in mitochondrial myopathies (e.g. NADH-CoQ reductase deficiency), in congenital myopathies, as for example in SEPN-1 or dynamin-2 related myopathies or in a substantial percentage of patients with low back pain as well [11,21–25]. However, their association with abdominal muscle atrophy, as we observed in our cohort of patients, is not commonly seen in other diseases, as far as we know. The association of abdominal and paravertebral weakness is a clinical characteristic feature of FSHD, where it is frequent to find hyperlordosis, lumbar pain and prominent asymmetric abdomen [26]. However, the presence of facial weakness, clear

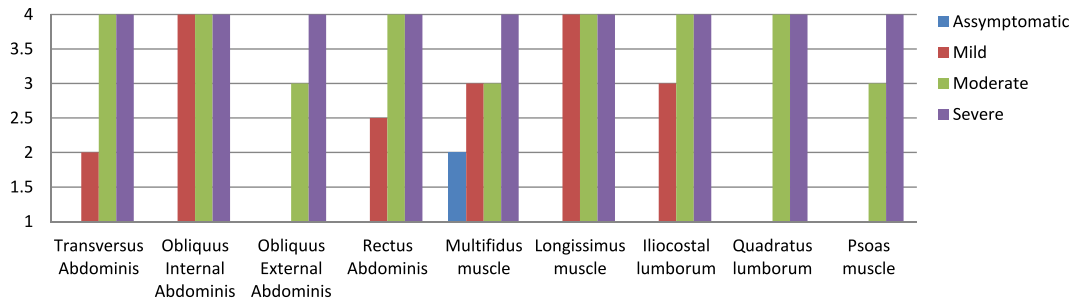

Fig. 2. Schematic representation of median MRI or CT muscle score according to Mercuri scale of each functional group of patients.

asymmetric muscle involvement and distal anterior weakness distinguishes Pompe from FSHD phenotypes.

It is relevant to note that from the imaging point of view trunk atrophy should be associated with other radiologic features suggestive of late-onset Pompe disease, such as the selective location of thigh muscles' deterioration of great adductor muscle and posterior compartment muscles and the characteristic sparing of lower leg muscles [5], in order to strengthen the diagnostic suspect.

Clinically, we observed that only one third of our Pompe patients complained of lumbar pain that could be permanent or fluctuating, especially related to walking or standing up for hours, and did not seem to correlate with disease severity nor with the severity of trunk involvement on imaging. Rather, we found a good correlation between motor functional stage and trunk muscle atrophy, with the exception of the early stages of disease, when the sensitivity of muscle imaging seems to overtake the limits of the clinical evaluation. We did not find significant differences in the pattern of muscle involvement between ERT treated and untreated patients. However we did not conduct follow-up studies to determine changes in the progression of the disease. A prospective study is needed to investigate how ERT affects MRI changes in Pompe disease.

This may be important from a therapeutic perspective. In fact, due to its high cost, there is controversy about when ERT should be initiated [9]. Whether trunk involvement may serve as an indicator of the proper time to start ERT is not the aim of this study, as follow-up and efficacy data are needed. However, detection of trunk abnormalities may help to reduce the time between first subtle clinical symptoms accompanying the onset of the disease and the diagnosis. They may warn the clinician about disease onset and thus the need for a stricter clinical follow-up.

In conclusion, our study demonstrated that MRI study of trunk muscles in late-onset Pompe patients can be useful in the diagnostic work-up and a potential good tool to gauge the rate of disease progression and monitor response to therapy. Further studies will demonstrate whether MRI could also be used as a helpful biomarker in order to decide when ERT treatment has to be started.

5. Conflict of interest

None.

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