CORRELATION BETWEEN QUANTITATIVE WHOLE-BODY MUSCLE MAGNETIC RESONANCE IMAGING AND CLINICAL MUSCLE WEAKNESS IN POMPE DISEASE

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ABSTRACT: *Introduction:* Previous examination of whole-body muscle involvement in Pompe disease has been limited to physical examination and/or qualitative magnetic resonance imaging (MRI). In this study we assess the feasibility of quantitative proton-density fat-fraction (PDFF) whole-body MRI in late-onset Pompe disease (LOPD) and compare the results with manual muscle testing. *Methods:* Seven LOPD patients and 11 disease-free controls underwent whole-body PDFF MRI. Quantitative MR muscle group assessments were compared with physical testing of muscle groups. *Results:* The 95% upper limits of confidence intervals for muscle groups were 4.9–12.6% in controls and 6.8–76.4% in LOPD patients. LOPD patients showed severe and consistent tongue and axial muscle group involvement, with less marked involvement of peripheral musculature. MRI was more sensitive than physical examination for detection of abnormality in multiple muscle groups. *Conclusion:* This integrated, quantitative approach to muscle assessment provides more detailed data than physical examination and may have clinical utility for monitoring disease progression and treatment response.

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Pompe disease (glycogen storage disease type II; GSD II) is a rare autosomal recessive neuromuscular disease that occurs due to deficiency of acid α-glucosidase (GAA), a lysosomal enzyme.[1] The infantile form of Pompe disease, which results from a complete lack of GAA, is severe and rapidly progressive. Patients with late-onset Pompe disease (LOPD), however, have incomplete GAA deficiency and may present with symptoms from early childhood to as late as the sixth decade of life. LOPD typically results in skeletal and respiratory muscle involvement leading to fatigue, exercise intolerance, proximal muscle weakness, and dyspnea.[2–4]

The natural course of LOPD is highly variable.[5] Enzyme replacement therapy (ERT) trials using alglucosidase alfa have suggested that the natural history can be altered,[6–9] but existing methods for monitoring disease status (including biopsy and physical examination) are invasive and/or time-consuming. In addition, the heterogeneity of muscle involvement causes biopsy to be prone to sampling error, whereas physical examination results may be distorted by functional compensations for muscle weakness. Such limitations underscore the need for improved techniques to quantify and stage disease, particularly as subjects are stratified for future clinical trials.

Whole-body MRI has begun to show promise in screening, diagnosis, and sensitive tracking of a variety of neuromuscular diseases.[10–13] Unfortunately, fatty infiltration of muscle, which is the dominant musculoskeletal abnormality in Pompe disease, can be technically challenging to quantify accurately on MR. As a result, nearly all MR studies in neuromuscular diseases have historically been qualitative, including the only existing whole-body MR description of LOPD patients,[14] which employed the standard 4-point Mercuri classification.[15] More recently, technical innovations in MRI have produced clinically useful quantitation of fat in the liver, skeletal muscle, and other organ systems. Comparison of these quantitative methods to traditional qualitative MRI in patients with Duchenne muscular dystrophy (DMD) has shown increased precision and reliability of the quantitative techniques.[16] However, to date, quantitative studies of fatty muscle infiltration in most

Abbreviations: DMD, Duchenne muscular dystrophy; ERT, enzyme replacement therapy; GAA, acid α-glucosidase; GSD, glycogen storage disease; IOPI, Iowa Oral Performance Instrument; MRC, Medical Research Council; LOPD, late-onset Pompe disease; PDFF, proton-density fat fraction; SSFSE, single-shot fast spin echo; ULN, upper limit of normal

Key words: glycogen storage disease; metabolic disease; MRI; Pompe disease; quantitative MRI

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neuromuscular diseases have only focused on selected muscles.[17–20] No quantitative MRI study of Pompe disease has yet been published.

To address this clinical opportunity, we obtained quantitative whole-body MRI in 7 patients with LOPD and compared their muscle involvement to a cohort of normal controls. The MRI data were correlated with data from the physical examination of muscle function.

METHODS

Eleven control subjects were recruited over a 1-year period under an institutional review board (IRB)–approved protocol. All subjects underwent the whole-body MR protocol described below.

Seven patients with confirmed Pompe disease were encountered via the GSD program at our institutional metabolic clinic during routine clinical care. These patients were enrolled in the study under a larger IRB-approved natural history protocol for GSD II. The diagnosis of Pompe disease had been previously confirmed with gene mutation analysis and/or enzymatic assay in all patients. Patients who required ventilatory support or did not anticipate being able to lie flat for the duration of the scan were excluded.

Whole-body MRI was performed on a 3-T MRI system (Magnetom TimTrio; Siemens Healthcare, Erlangen, Germany). Imaging was performed using a proton-density fat-fraction technique previously validated in the liver and using methods widely accepted in the MRI literature, including T1 insensitivity, T2* correction, and correction for the spectral complexity of fat.[21] Identical protocols were obtained for both the control and patient cohorts. All subjects were imaged in the supine position with their arms at their sides or over the abdomen.

Imaging of the neck was performed in the coronal and sagittal planes. Then, breath-hold axial imaging was performed from above the shoulders to the ankles in 4 or 5 stations. Multi-station single-shot fast spin echo (SSFSE) images were also performed for co-localization utilizing the high spatial resolution and image contrast of those pulse sequences. Data were processed in real-time on the MRI scanner to provide quantitative proton-density fat-fraction (PDFF) images of the entire volume. The PDFF images were transferred to a stand-alone workstation for measurement (OsiriX; Pixmeo Sarl, Geneva, Switzerland). Tongue PDFF was measured as the mean PDFF of the entire cross-section of the tongue on multiple sagittal slices, including the fibrofatty septum at the base. In the remaining muscle groups (see full listing of groups in Table 1), volumetric measurements were performed on axial images, and the mean PDFF in each group was recorded. Muscle groupings were determined to correspond with the muscle groups typically tested on physical examination, including those that were quantified adequately in the field of view.

Table 1. MRI values of muscle fat fractions for normal controls.

Muscle group	Mean PDFF (%)	Upper limits ofnormal PDFF (%)	2× ULN PDFF (%)
SH-AB	6.1	9.1	12.1
SH-ER	4.5	6.2	7.9
SH-FL	3.8	5.8	7.8
SH-EX	5.8	8.8	11.8
EB-EX	4.8	6.6	8.4
EB-FL	5.1	7.9	10.7
NK-FL	5.5	7.8	10.1
NK-EX	3.3	4.9	6.5
TNGE	3.6	5.5	7.4
SP-EX	5.3	8.6	11.9
TK-FL	4.6	6.6	8.6
HP-FL	4.9	7.0	9.1
HP-EX	7.7	12.7	15.7
HP-AB	5.8	10.2	14.6
HP-LR	5.5	8.0	10.5
HP-AD	4.7	7.2	9.7
KN-EX	5.4	9.3	13.2
KN-FL	5.8	9.5	13.2
AK-DF	5.0	7.8	10.6
AK-EV	6.0	8.5	11.0
AK-IN	5.1	7.7	10.3
AK-PF	6.7	12.6	18.5

SH-AB, shoulder abductors; SH-ER, shoulder external rotators; SH-FL, shoulder flexors/internal rotators; SH-EX, shoulder extensors/horizontal abductors; EB-EX, elbow extensors; EB-FL, elbow flexors; NK-FL, neck flexors/rotators; NK-EX, neck extensors; TNGE, intrinsic tongue muscles; SP-EX, spine extensors; TK-FL, truck flexors/rotators; HP-FL, hip flexors; HP-AB, hip abductors; HP-LR, hip lateral rotators; HP-AD, hip adductors; KN-EX, knee extensors; KN-FL, knee flexors; AK-DF, ankle dorsiflexors; AK-EV, ankle eversion; AK-IN, ankle inversion; AK-PF, ankle plantar flexion; ULN, upper limit of normal (for controls).

For physical examination, manual muscle testing was completed in accordance with standard procedures, and data are reported using the modified Medical Research Council (MRC) scale ranging from 0 to 5.[22–24] Tongue strength was measured with an intraoral tongue bulb coupled with a differential pressure transducer [Iowa Oral Performance Instrument (IOPI); IOPI Medical, Carnation, Washington]. The tongue bulb was placed medially on the anterior tongue, and patients were instructed to push it against the hard palate with maximal effort. Mean peak pressure value over 3 trials was obtained in kilopascals (kPa) and compared with normative values (IOPI 2.2 manual, 2011). If strength was found to be abnormal, severity was estimated as mild, moderate, or severe.

For the normal controls, mean and standard deviation of PDFF was calculated for each muscle group across the cohort and used to construct 95% confidence intervals (CIs). The upper limits of the 95% CIs for measurements in the normal

Table 2. Patients' characteristics and MRI quantitative muscle group values (PDFF %) for axial and upper extremity musculature.

Patient	1	2	3	4	5	6	7
Age	59	48	61	65	48	38	13
Age at diagnosis	54	43	44	63	48	36	5
Disease duration (y)	5	5	17	2	0.5	2	8
Gender	W	M	W	M	W	M	M
BMI (kg/m^2)	20.13	22.61	23.22	32.83	24.91	30.85	20.73
GAA mutation	c.2481+102_2646 +31del c.−32-13T>G	c.1143delC c.−32-13T>G	N/A	c.1143delC c.−32-13T>G	c.1548G>A c.−32-13T>G	c.−32-13T>G	c.−32-13T>G c.1437+2T>C
Ambulatory device	Cane	None	None	None	None	Cane;wheel-chair	None
Right SH-AB	10.1*	8.5	16.7†	12.5†	8.9	8.7	6.7
Left SH-AB	9.4*	7.5	11.5*	8.7	8.6	10.1*	7.3
Right SH-ER	7.0*	7.5*	10.3†	37.2†	4.7	5.1	7.6*
Left SH-ER	6.4*	7.5*	7.7*	30.0†	4.3	5.6	6.8*
Right SH-FL	68.6†	77.3†	70.0†	71.3†	18.5†	8.7†	5.0
Left SH-FL	74.1†	76.0†	67.3†	56.2†	22.4†	11.0†	5.2
Right SH-EX	15.5†	11.1*	10.9*	47.1†	11.4*	7.3	5.3
Left SH-EX	15.5†	8.6	7.9	20.7†	9.0*	7.4	5.6
Right EB-EX	6.0	5.2	8.2*	8.7†	4.8	4.5	5.6
Left EB-EX	5.7	7.5*	5.6	7.5*	5.0	5.0	5.0
Right EB-FL	11.4†	9.3*	13.8†	N/A	5.2	7.5	6.5
Left EB-FL	8.4*	6.6	6.9	10.4*	4.2	9.1*	4.8
Right NK-FL	9.0*	6.4	9.8*	6.7	5.6	4.1	7.2
Left NK-FL	9.2*	7.3	11.9†	6.6	4.7	5.8	6.8
Right NK-EX	8.8†	6.0*	10.5†	7.9†	8.3†	7.7†	4.0
Left NK-EX	7.2†	5.7*	10.8†	7.5†	7.1†	8.6†	5.2*
TNGE	63.6†	82.9†	51.8†	29.2†	58.7†	27.2†	8.8†
Right SP-EX	73.8†	68.7†	69.8†	50.0†	59.1†	62.7†	5.6
Left SP-EX	74.0†	66.5†	69.3†	42.3†	51.8†	65.7†	5.3
TK-FL	28.2†	86.9†	55.7†	81.8†	17.5†	32.8†	5.7

SH-AB, shoulder abductors; SH-ER, shoulder external rotators; SH-FL, shoulder flexors/internal rotators; SH-EX, shoulder extensors/horizontal abductors; EB-EX, elbow extensors; EB-FL, elbow flexors; NK-FL, neck flexors/rotators; NK-EX, neck extensors; TNGE, intrinsic tongue muscles; SP-EX, spine extensors; TK-FL, truck flexors/rotators; HP-FL, hip flexors; HP-AB, hip abductors; HP-LR, hip lateral rotators; HP-AD, hip adductors; KN-EX, knee extensors; KN-FL, knee flexors; AK-DF, ankle dorsiflexors; AK-EV, ankle eversion; AK-IN, ankle inversion; AK-PF, ankle plantar flexion; N/A, not applicable, data not obtained.

**Greater than ULN.*

†Greater than 2× ULN.

control group were considered the upper limit of normal (ULN). The PDFF values for the LOPD patient cohort were compared with the ULN values established by the normal control cohort as well as with physical examination measures. Color-coded maps were generated to facilitate display and visual analysis of PDFF and physical examination measures using a method described previously.[25] All statistical data were analyzed using Excel (Microsoft Corp., Redmond, Washington; 2008).

RESULTS

A total of 11 volunteers (6 men and 5 women; mean age ± standard deviation: 35 ± 9 years) were imaged. Mean PDFF and ULN values for the normal controls are reported in Table 1. The mean PDFF for individual muscle groups ranged from 3.3% (neck extensors) to 7.7% (hip extensors). The ULN values ranged from 4.9% (neck extensors) to 12.7% (hip extensors).

Seven patients (4 men and 3 women) with LOPD were imaged using the MR protocol. Patient age was 41 ± 18 (mean ± standard deviation) years, and mean body mass index was 25 ± 5 kg/m^2. Whole-body MRI was completed successfully with a scan time of 45–90 minutes in all patients, depending on individual breath-holding capacities and time needed for positioning. Images obtained were sufficient for calculation of quantitative fat fraction in nearly all muscle groups. Peripheral muscle groups in the upper extremities were measured inconsistently due to inadequate field-of-view limitations in some cases.

The calculated fat fraction for each muscle group across the patient cohort is shown in Tables 2 and 3, along with the relevant clinical characteristics of each patient. Representative fat-fraction images showing abnormal fat infiltration in hip extensors (Fig. 1a), intrinsic tongue muscle (Fig. 1b), spine extensors (Fig. 1c), and knee flexors (Fig. 1d) are provided, as is a composite whole-body T1-weighted fat-only MR image for the same patient (Fig. 1e). Muscle groups meeting abnormal (greater than ULN) or very abnormal (PDFF value more than twice the

Table 3. MRI quantitative muscle group values (PDFF %) for patients' lower extremity musculature.

Patient	1	2	3	4	5	6	7
Age	59	48	61	65	48	38	13
Right HP-FL	87.0†	82.2†	76.5†	65.4†	31.9†	25.0†	6.3
Left HP-FL	81.4†	78.3†	82.2†	80.7†	37.9†	45.8†	5.4
Right HP-EX	74.3†	15.3*	61.6†	24.7†	10.8	51.5†	5.7
Left HP-EX	76.3†	14.7*	67.3†	30.7†	11.6	54.8†	6.0
Right HP-AB	80.1†	82.5†	78.0†	52.7†	6.2	53.9†	8.1
Left HP-AB	84.5†	85.5†	75.6†	86.2†	22.8†	43.2†	8.2
Right HP-LR	79.2†	81.4†	56.8†	28.2†	7.6	7.2	6.7
Left HP-LR	74.1†	78.5†	48.0†	58.2†	6.5	8.5*	7.9
Right HP-AD	72.8†	60.1†	72.6†	75.0†	33.6†	31.9†	5.3
Left HP-AD	57.8†	69.0†	52.8†	70.3†	27.1†	34.3†	5.6
Right KN-EX	34.6†	8.9	39.2†	10.4*	10.9*	21.3†	3.7
Left KN-EX	32.1†	8.8	35.2†	13.8†	9.5*	20.3†	3.3
Right KN-FL	79.3†	9.1	68.1†	29.7†	25.2†	31.7†	5.0
Left KN-FL	82.5†	10.2*	72.4†	18.7†	16.8†	31.3†	5.5
Right AK-DF	6.6	4.7	9.8*	9.4*	5.0	7.8	7.0
Left AK-DF	11.9†	6.0	12.9†	9.3*	5.5	9.2*	6.0
Right AK-EV	8.3	8.3	10.8*	6.2	4.7	8.7*	5.5
Left AK-EV	7.8	6.8	10.8*	6.1	4.8	9.8*	6.5
Right AK-IN	4.3	4.7	11.9†	10.4†	6.2	9.5*	5.5
Left AK-IN	7.7	7.4	12.0†	9.8*	5.0	11.8†	4.8
Right AK-PF	11.5	9.7	9.5	8.3	4.7	12.0	6.3
Left AK-PF	9.7	11.3	8.8	8.9	4.9	15.4†	7.5

SH-AB, shoulder abductors; SH-ER, shoulder external rotators; SH-FL, shoulder flexors/internal rotators; SH-EX, shoulder extensors/horizontal abductors; EB-EX, elbow extensors; EB-FL, elbow flexors; NK-FL, neck flexors/rotators; NK-EX, neck extensors; TNGE, intrinsic tongue muscles; SP-EX, spine extensors; TK-FL, truck flexors/rotators; HP-FL, hip flexors; HP-AB, hip abductors; HP-LR, hip lateral rotators; HP-AD, hip adductors; KN-EX, knee extensors; KN-FL, knee flexors; AK-DF, ankle dorsiflexors; AK-EV, ankle eversion; AK-IN, ankle inversion; AK-PF, ankle plantar flexion; N/A, not applicable, data not obtained.

**Greater than ULN.*

†Greater than 2× ULN.

95% confidence interval) thresholds were tabulated for each patient and are displayed in Figure 2a.

Tongue involvement was observed in all patients and was diffuse and very abnormal in 6 of 7 Pompe subjects. Muscles involved in all hip movements, trunk flexion and rotation, spine extension, knee flexion and extension, and shoulder rotation were consistently abnormal. Involvement of peripheral musculature responsible for ankle, elbow, wrist, and neck movement was less frequent and less severe.

Five of 7 Pompe patients had at least partial data from the physical examination of muscle function by manual muscle testing or measurement of maximal lingual pressure. The MRI results for the muscle groups with physical examination testing are displayed in Figure 2b. Results from manual muscle testing were classified as normal (score = 5), likely abnormal (score 4 or 4^-), or clearly abnormal (score $<4^-$) for each patient (Fig. 2c). The most severely and frequently involved groups were those for hip movement, trunk flexion, and spine extension, although some muscle groups (e.g., trunk flexion, spine extension) were only tested in a subset of patients.

Comparison of the MRI and physical examination data shows the sensitivity of MRI for detection of abnormalities in multiple muscle groups. These included musculature responsible for ankle eversion and dorsiflexion, knee flexion and extension, tongue movement, neck extension, elbow flexion and extension, and most of the isolated movements of the shoulder (Fig. 2b). Data from physical examination were, however, also abnormal in some muscle groups with normal or near-normal MRI measures in 4 patients, including the hip extensors, neck flexors, and neck rotators (Fig. 2c).

Representative visual muscle maps summarizing data for 1 patient are shown in Figure 3a. A comparison map showing MRI data for a normal control (along with theoretical normal physical exam data, for display purposes only) is shown in Figure 3b.

DISCUSSION

This study has demonstrated the clinical implementation of quantitative whole-body MRI for assessment of muscle involvement in LOPD. All 7 LOPD patients imaged had abnormal fatty infiltration of axial and, to a lesser extent, peripheral musculature that was demonstrated reliably by our MRI protocol. The cohort of healthy controls provided a robust data set for establishment of normal control values for fatty muscle involvement on MRI. Furthermore, comparison with physical

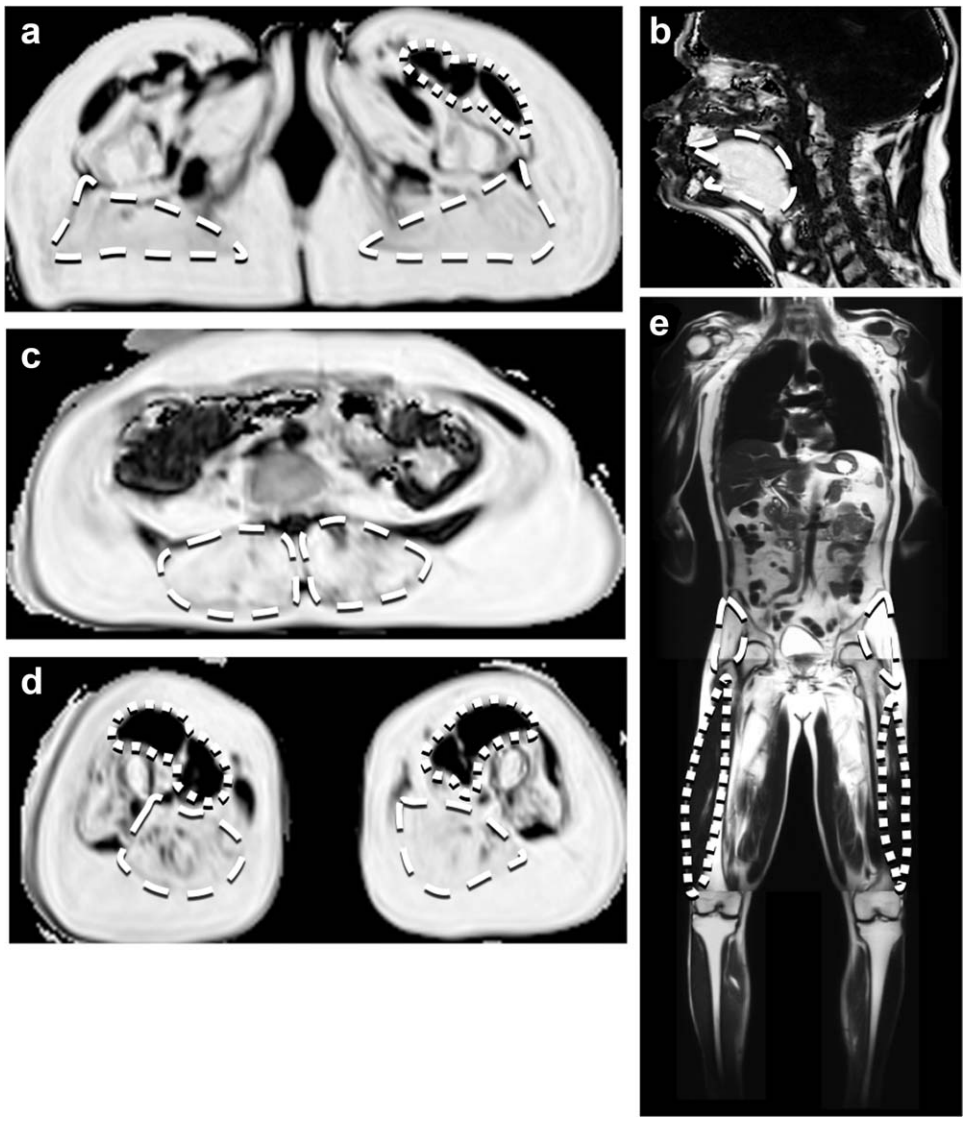

FIGURE 1. Representative MRI PDFF images and whole-body composite image. Axial image of the lower pelvis of patient 1 **(a)** shows near-complete fatty replacement of bilateral gluteus maximus muscles (rectangular white dashed outline), with only trace normal muscle seen at the lateral femoral insertion and thin residual fascia. Additional generated fat-fraction map images from this patient show severe, fatty replacement of the tongue **(b)**, lumbar spine extensors **(c)**, and knee flexors **(d)**. A composite coronal half-Fourier acquisition single-shot turbo spin-echo (HASTE) image **(e)** of patient 2 aids in muscle group localization and volumetric selection for quantitative analysis, whereas the axial images generally prove superior for the quantitative analysis. For reference, quadriceps muscles normal fat-fraction values and gray-black low MRI signal is outlined in white square dashes on **(a)**, **(d)**, and **(e)**.

examination data in this cohort demonstrated greater sensitivity of MRI for detection of muscle involvement, although these assessment methods appeared largely complementary.

The whole-body quantitative MR protocol was tolerated successfully by all imaged Pompe patients, including those who required protocol modification to shorten breath-hold sequences. The overall in-room scan time averaged approximately 60 minutes. This examination time is clinically feasible, as it is similar to the time needed to perform a physical examination of muscle function to the level of detail used in our clinical environment. In addition, this period also matches the time required for some of the abdominal and neurological MR examinations performed at our institution.

Imaging of the control group showed variability in the "normal" amount of fat in non-diseased muscle groups and substantial differences between the healthy volunteers and LOPD group. For example, mean shoulder abductor PDFF for healthy volunteers was 6.1% and ULN was 9.1%, whereas the mean PDFF in the LOPD group was 11.0%. In addition, the PDFF of tongue muscles was reliably low and relatively narrowly distributed, averaging 3.6% in the normal controls, whereas normal hip extensor musculature had more than

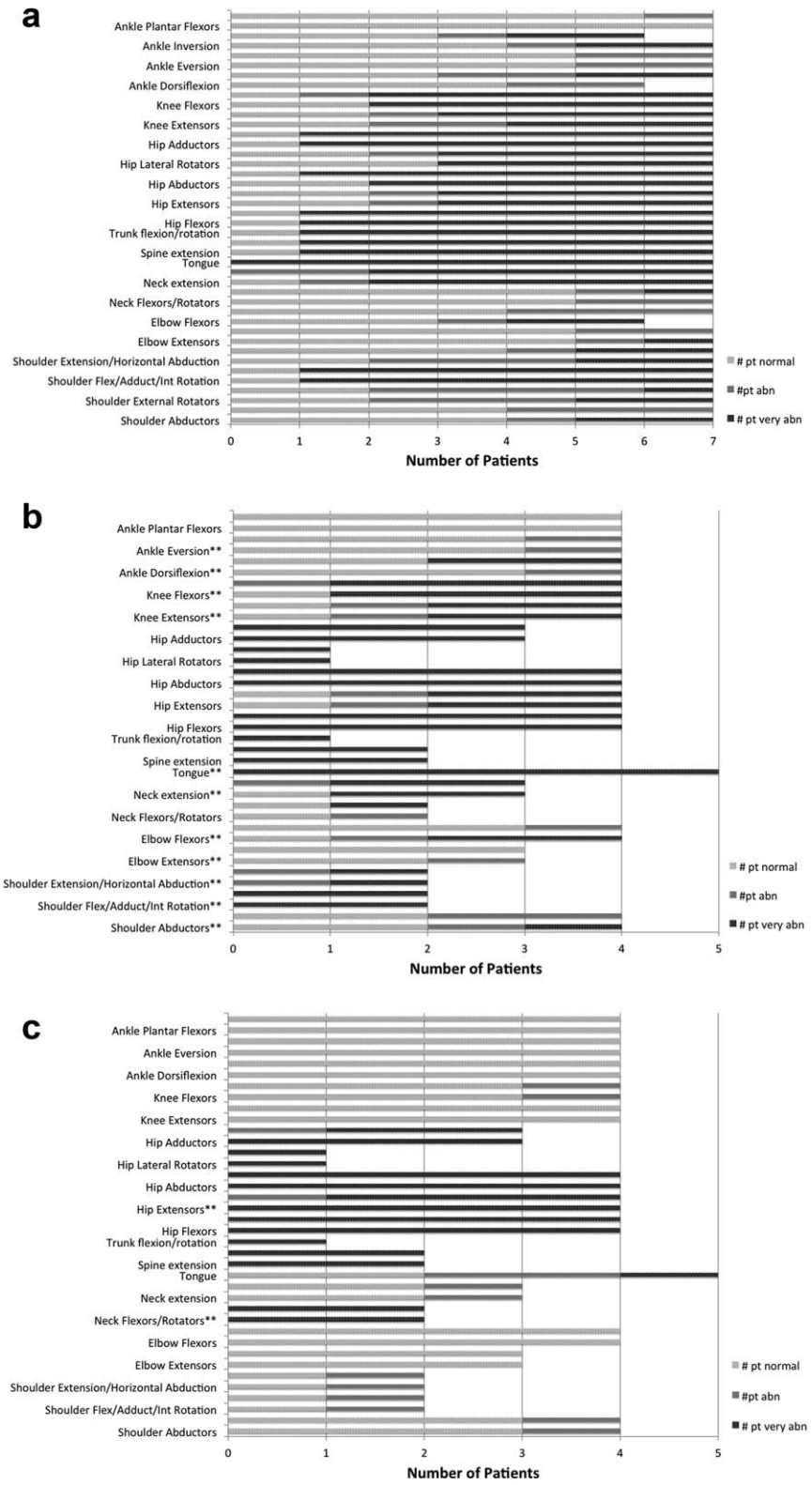

FIGURE 2. Pompe patients with normal, abnormal, and very abnormal muscle groups at MRI and physical examination. Muscle groups as quantitated on MR are displayed **(a)** as are the subset of muscle groups with physical examination correlation **(b)**. Muscle groups as quantitated on physical examination with MR correlation are also provided **(c)**. **More sensitive modality for muscle group assessment. Right-sided muscles are represented in the upper bar and left-sided muscles in the lower bar for each muscle group.

twice the mean level of intrinsic fat as well as greater overall variability (Table 1). These results suggest an intrinsic limitation of subjective systems like the Mercuri classification for whole-body muscle group analysis, as they are not individualized by muscle group; PDFF levels individualized to

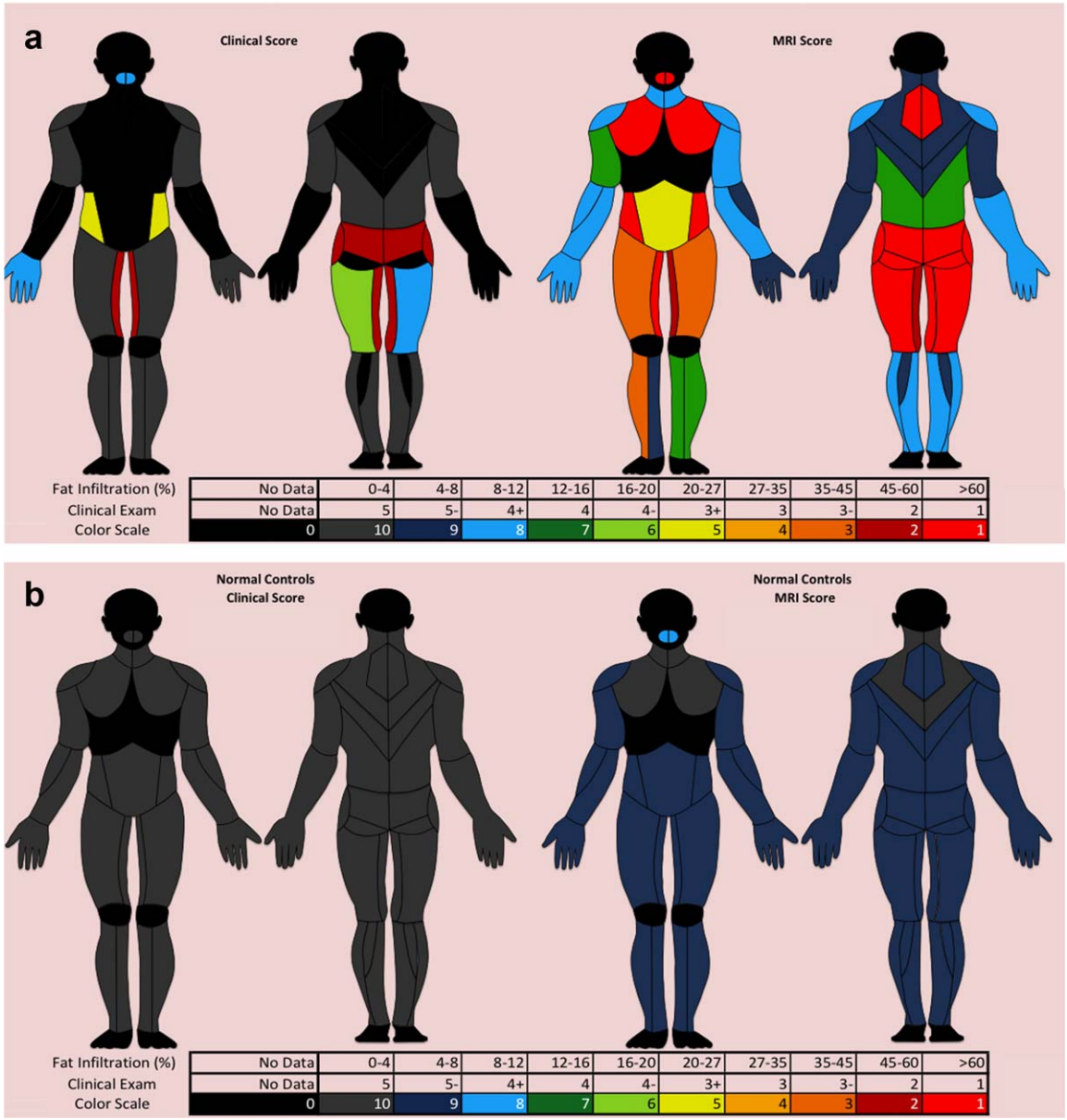

FIGURE 3. Muscle map MRI and physical examination correlation. Muscle group diagrams with corresponding data values are shown for physical examination on left and MRI on right of a Pompe patient **(a)** with heterogeneous severe muscle involvement (yellow through red colors). Data from a control patient **(b)** with normal values (gray through blue) are also displayed.

particular muscle groups are much simpler to determine using the quantitative methods demonstrated here.

Marked heterogeneity of fatty replacement within muscle groups themselves revealed another advantage of our approach. For example, in the rotator cuff, the subscapularis muscles were involved consistently and had high PDFF values (generally 50–80%), whereas the supraspinatus and infraspinatus were affected less severely. Although muscles responsible for complex movements such as those seen in the shoulder can be carefully isolated during physical examination, these techniques are very time-consuming, are often exhausting for patients when large numbers of muscles are tested individually, and may not offer additional functional value clinically. In contrast, this level of detail is easily achieved by imaging without requiring additional time for more detailed testing.

Nonetheless, there were a few muscle groups for which physical examination appeared to show slightly greater sensitivity than MRI (hip extensors: 1 patient with mild unilateral examination weakness and normal PDFF, and another patient with clearly abnormal examination weakness with only mildly abnormal PDFF; neck extensors: 2 patients clearly abnormal at examination, but with only

mildly abnormal PDFF). These discrepancies suggest that imaging and muscle testing may have complementary roles in detecting early-stage disease, and that PDFF MRI alone may not always accurately reflect clinically significant muscle pathology.

These results show a similar distribution of fatty muscle infiltration as described in the qualitative whole-body muscle MR study by Carlier *et al.* in 2011.[14] As Wokke *et al.* showed in patients with DMD, quantitative MR fat-fraction methods are more accurate than visual assessment, which tends to overestimate fatty infiltration and produce higher variability.[16] Although we did not directly compare qualitative with quantitative MR techniques, the relatively narrow normal range of fat within muscle groups in control patients (<10% in 22 of 25 groups) was often scored as normal (level 1) under the Mercuri classification analyzed by Wokke and colleagues. Thus, as we initially suspected based on the normal control data, qualitative MR assessment of many muscle groups may underestimate early or mild disease.

The clinical management of patients with LOPD has evolved rapidly over the past 2 decades. Diagnosis can now be made rapidly with blood-based assays and gene sequencing, treatment involves targeted enzyme replacement, and physical examination techniques are increasingly using quantitative measurement approaches. MRI techniques have developed at a similarly brisk pace, with whole-body imaging now possible in reasonable time frames and with excellent quality. Through the use of quantitative whole-body MRI, our study may help to further the accuracy and reproducibility of muscle imaging of Pompe disease. Similar to the recent intense interest in quantitative liver MRI for evaluation of hepatic steatosis, quantitative whole-body muscle MRI may represent an important frontier in the evaluation of many neuromuscular diseases. Indeed, as the importance of early treatment in Pompe patients with subtle clinical or subclinical disease is being recognized increasingly from newborn screening data,[6] we infer that quantitative MRI may be an important addition to the LOPD management algorithm. We now routinely provide an integrated approach for Pompe patients at our institution that allows for whole-body quantitative MRI assessment, correlation with physical examination, and simplified display of results for the clinical environment (Fig. 3).

This pilot study has several intrinsic limitations. Our sample size of 7 Pompe patients is small, and our controls were not precisely age-matched, although mean age in the patient and control groups was similar (41 vs. 35 years). The MR method had signal and resolution limitations in the most peripheral musculature. In LOPD, axial muscle group involvement predominates, and this particular technique may need to be modified for diseases that have subtle manifestations in primarily peripheral musculature. In addition, the overall time required for accurate muscle group quantification was high, requiring 60 minutes of analysis by an experienced radiologist, with another 30 minutes required for data conversion into the visual mapping tool. These time requirements may be reduced in the future through the use of automated measurement tools for volumetric muscle analysis. MRI also has intrinsic limitations for patients with claustrophobia and non-MRI compatible devices, as well as those with severe pulmonary or respiratory muscle disease. Finally, the physical examination data obtained for some of the LOPD patients was limited to selected muscle groups. We have begun to expand the scope of future physical therapy and speech-language therapy examinations of Pompe patients at our institution, in part guided by initial MRI data.

In conclusion, quantitative whole-body MRI for assessment of fatty muscle degeneration in LOPD is feasible. MRI was more sensitive than physical examination for the detection of abnormality in multiple muscle groups involved frequently in Pompe disease, but physical examination also provided important complementary and functional data. As recently described in studies of other neuromuscular diseases,[17,18,20] future work using quantitative whole-body MRI should focus on longitudinal tracking of disease over time. Such imaging-based biomarkers allow detection of subclinical changes in disease status and could serve as objective, quantitative measures of disease progression, stabilization, and response to therapy.

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