Received: 24 March 2019 | Revised: 7 January 2020 | Accepted: 11 January 2020

DOI: 10.1002/mus.26813

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Quantitative muscle MRI study of patients with sporadic inclusion body myositis

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Funding information
APHM; Centre National de la Recherche Scientifique; FILNEMUS

Abstract

Background: Fat infiltration in individual muscles of sporadic inclusion body myositis (sIBM) patients has rarely been assessed.

Methods: Sixteen sIBM patients were assessed using MRI of the thighs and lower legs (LL). The severity of fat infiltration, proximal-to-distal and side asymmetries, and the correlations with clinical and functional parameters were investigated.

Results: All the patients had fat-infiltrated muscles, and thighs were more severely affected than LL. A proximal-to-distal gradient of fat infiltration was mainly observed for adductors, quadriceps, sartorius, and medial gastrocnemius muscles. A strong negative correlation was observed between the whole muscle fat fraction in the thighs and LL and the Inclusion Body Myositis Functional Rating Scale and Medical Research Council scores for the lower limbs.

Conclusions: Fat infiltration in individual muscles of sIBM patients is heterogeneous in terms of proximal-to-distal gradient and severity was correlated with clinical scores. These results should be considered for both natural history investigation and clinical trials.

KEYWORDS
fat infiltration, IBM, MRI, quantitative

1 | INTRODUCTION

Sporadic inclusion body myositis (sIBM) is the most frequent acquired myopathy presenting over the age of 50 years.[1-3] The disease course is slowly progressive and muscle weakness is highly selective and frequently asymmetric. Quadriceps and flexor digitorum profundus are often involved.[4,5] sIBM diagnosis has evolved with time. While the presence of canonical pathological features was initially emphasized, the importance and specificity of clinical criteria has been more recently put forth.[3,6] Although no treatment has been proven as effective, multiple clinical trials are ongoing (clinicaltrials.gov,

Abbreviations: AC, anterior leg compartment: tibialis anterior, extensor halluces longus, and extensor digitorum longus; ADD, adductor brevis, longus, and magnus; ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; BF, biceps femoris; BMI, body mass index; DP, deep posterior leg compartment: tibialis posterior flexor hallucis longus and flexor digitorum longus; ENMC, European Neuromuscular Center; GR, gracilis; IBMFRS, Inclusion Body Myositis Functional Rating Scale; LC, lateral leg compartment: fibularis brevis / longus; LG, lateral gastrocnemius; MG, medial gastrocnemius; MPI, mean pixel intensity; MRC, Medical Research Council; $MRCS_{LL}$, Medical Research Council score of the lower limbs; RF, rectus femoris; SA, sartorius; sCK, serum creatine kinase; sIBM, sporadic inclusion body myositis; SM/ST, semimembranosus and semitendinosus; SO, soleus; T_1W, T1-weighted; VAS, vasti muscles (vastus lateralis, medialis, and intermedius).

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NCT02753530, NCT0404909, NCT03440034), and appropriate outcome measures have been acknowledged as being important for assessment of treatment efficiency. The quadriceps muscle strength and the 6-min walk test have been frequently used as primary endpoints in previous trials but are recognized as being dependent on patient motivation and effort.[7,8]

The Inclusion Body Myositis Functional Rating Scale (IBMFRS) is a disease-specific rating scale that has been commonly used to assess patients' capabilities and independence.[9] This specific scale is a modified version of the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS).[10] It has been demonstrated that the IBMFRS provides a sensitive assessment of disease-related changes in function.[11] Based on a visual analysis of muscle MR images, a selective pattern of muscle involvement has been reported in sIBM, with the vastus lateralis, medial gastrocnemius, and flexor digitorum profundus being the most-affected muscles.[5,12] A previous qualitative MRI study has found a typical pattern to be highly specific (100%) but poorly sensitive (59%).[13] It has been suggested that quantitative MRI can be more sensitive than clinical scores for detecting disease progression in muscular dystrophies.[14-17] Such an approach has been used once in sIBM patients.[18] MRI and a supervised segmentation approach[19] were combined in the present study. We intended to quantitatively characterize fat infiltration in a large set of individual muscles from both legs and thighs in terms of distribution of fat infiltration, asymmetry and proximal-to-distal gradient. We also aimed to assess correlations with clinical and functional scores.

2 | METHODS

Patients followed in the Reference Center for Neuromuscular Diseases in Marseille were enrolled between 2013 and 2017 after providing written informed consent. The inclusion criterion was a definite or probable sIBM diagnosis according to the European Neuromuscular Center (ENMC) criteria (2011).[20] Exclusion criteria were: history of hereditary IBM, history of other neuromuscular diseases, nonambulatory patients, patients unable to give an informed consent. Baseline demographics (age, body mass index [BMI], disease duration, gender, serum creatine kinase (sCK) were collected. The local ethics committee (Comité de Protection des Personnes Sud Méditerranée I) approved the study.

2.1 | Clinical assessment

Muscle strength was assessed using a modified Medical Research Council (MRC) scale (from 0: no movement to 5: normal movement). Quadriceps and hamstring muscles were evaluated bilaterally and the corresponding MRC score ranged from 0 to 10 on each side. Plantar flexion, dorsiflexion and ankle eversion were also evaluated bilaterally and the corresponding MRC score ranged from 0 to 15 on each side. The MRC score of the lower limbs ($MRCS_{LL}$) was computed as the sum of each individual score for both thighs and both lower limbs (LL) and ranged from 0 to 50. All subjects were assessed by a single rater. The IBMFRS was used to assess the functional severity.[9]

2.2 | Muscle MRI

Muscle MR images were acquired at 1.5 T (Avanto, Siemens, Erlangen, Germany). Both thighs and both LL were imaged using flexible coils positioned on the top and a spine coil located on the bottom. We scanned a 20.9 to 26.9 cm region for each LL and each thigh, centered on the mid-fibula and mid-femur, respectively. T1-weighted (T_1W) images in the axial plane (from 35 to 50 slices according to the patient's height) were recorded with the following parameters: 400 mm field of view, 160*320 acquisition matrix, 4-mm slice thickness, and 2-mm gap. The repetition time-echo time values (ms) were 578–11, the flip angle was 90° and the refocusing flip angle was 120°. Image uniformity correction (prescan normalization) was used to reduce signal inhomogeneity due to the receiver coils.

2.3 | Image postprocessing

2.3.1 | Supervised segmentation of individual muscles

A total of 26 muscle groups for both thighs and LL were semi-automatically segmented on the T_1W images as previously described.[19] At the thigh level: vasti (VAS) (vastus lateralis, medialis, and intermedius), rectus femoris (RF), semimembranosus and semitendinosus (SM/ST), biceps femoris (BF), sartorius (SA), gracilis (GR), adductors (ADD) (adductor brevis, longus and magnus). At the lower leg level: anterior compartment (AC) (tibialis anterior, extensor hallucis longus, extensor digitorum longus), lateral compartment (LC) (fibularis brevis / longus), deep posterior compartment (DP) (tibialis posterior flexor hallucis longus, flexor digitorum longus), medial gastrocnemius (MG), lateral gastrocnemius (LG), and soleus (SO).

Muscles were manually segmented using FSLview[21] in five slices and the corresponding masks were propagated in the z-direction for the whole set of slices.[19] As previously described,[19] slice selection was based on three independent criteria: (i) a muscle is appearing, (ii) a muscle is disappearing, (iii) a muscle shape is changing significantly. These criteria ensured that the semi-automated process generated an accurate segmentation. Results were double checked by two experts (B.A. and E.S.C.).

2.3.2 | MRI indices

A N4 bias correction algorithm was used as previously reported[22] for each dataset and a normalization with respect to the bone signal intensity was performed as previously described.[23] For each mask, fat infiltration was assessed from the mean pixel intensity (MPI_{total}) of the normalized histogram.[23] MPI_{total} illustrating the pixel intensity distribution was computed as the sum of each pixel signal intensity divided by the corresponding number of pixels (supplementary figure). An increased MPI_{total} value indicates a raised fat infiltration and/or a reduced muscle volume. $MPI_{control}$ has been previously quantified as

30 ± 3 (SD).[23] $MPI_{proximal}$ and MPI_{distal} were the MPI values averaged for the five most proximal and distal slices, respectively. MPI_{left} and MPI_{right} were the averaged MPI values quantified for the left and right sides, respectively.

2.3.3 | Severity of fat infiltration

We calculated the Z score for each MPI value as: Z = (MPI – $MPI_{control}$) / SD $MPI_{control}$ with MPI control = 30 ± 3 (SD). For a normally distributed population, 99.9% of the values should be within an interval ranging from mean – 3 SD to mean + 3 SD. On the basis of the Z score, we classified a muscle as normal (N) if the Z score <=3, as moderately infiltrated (M) if the Z score was >3 and <5, and as severely infiltrated (S) if the Z score was ≥5. Then, for each muscle we computed the frequency of each occurrence N, S, and M on each side (left and right) and in each segment (distal, proximal). In addition, the right–left asymmetry was defined as a difference, at least equal to 1, between the Z scores, and was determined for each segment (distal and proximal). The corresponding occurrences were also calculated. The proximal-to-distal gradient was determined by the N, M, and S scale.

2.3.4 | Correlations

Correlations between MPI values of whole thigh and LL muscles and clinical scores (IBMFRS and MRC), duration of disease, sCK level, and age were analyzed.

2.4 | Statistical analyses

Statistical analyses of the data were performed using SPSS-25.0 (IBM, Bois-Colombes, France). To assess the proximal-to-distal gradient, the corresponding MPI values were compared for each muscle using paired t tests and a *P* value < .05 was considered as significant. Spearman's rank tests analyses were performed to assess the correlations between clinical scores and MRI parameters. A *P* value lower than .05 was considered as significant.

3 | RESULTS

3.1 | Clinical characteristics of patients

Sixteen patients (8 women) were included: 13 patients had definite IBM and 3 had probable IBM. Eight patients had dysphagia. None was nonambulatory. Mean age, BMI, and disease duration was 70.1 ± 8.5 years, 23.8 ± 4.3 kg/m^2, and 12 ± 3 years, respectively. Mean MRCSLL and IBMFRS scores were 34.8 ± 11.3 and 30.3 ± 7.3, respectively.

3.2 | MRI findings

3.2.1 | MPI values

The MPI value averaged in patients over the whole set of thigh muscles was 55.6 ± 10.3 and 45.3 ± 10 in LL muscles with no significant difference between the left and the right sides. MPI values calculated for the

TABLE 1 Individual muscle mean pixel intensity (MPI) values for the proximal and distal segments

Muscle	Proximal	Distal	Whole	*P*-Value
Vas	49.0 ± 11.2	59.7 ± 12.2	54.3 ± 10.3	.014
RF	48.7 ± 12.3	60.5 ± 11.4	54.6 ± 10.0	.009
SA	58.2 ± 9.6	68.4 ± 11.7	63.3 ± 9.2	.011
SM/ST	50.2 ± 12.8	55.5 ± 14.0	52.8 ± 12.3	.266
BF	55.1 ± 11.2	56.7 ± 11.8	55.9 ± 10.6	.697
GR	57.5 ± 10.9	65.6 ± 12.8	61.6 ± 10.6	.064
ADD	46.5 ± 10.5	61.7 ± 12.1	54.1 ± 10.0	.001
AC	39.4 ± 6.9	41.9 ± 8.6	40.7 ± 7.1	.366
SO	42.6 ± 12.7	46.1 ± 13.8	44.3 ± 12.7	.463
DP	36.8 ± 6.9	37.9 ± 10.0	37.4 ± 8.1	.713
LG	54.8 ± 18.5	55.9 ± 13.8	55.3 ± 14.4	.858
MG	48.1 ± 18.0	64.9 ± 16.6	56.5 ± 14.2	.010
LC	44.0 ± 10.2	44.0 ± 12.1	44.0 ± 10.4	.992

Abbreviations: VAS, vasti muscles (vastus lateralis, medialis, and intermedius); RF, rectus femoris, SM/ST, semimembranosus and semitendinosus; BF, biceps femoris; SA, sartorius; GR, gracilis; ADD, adductor brevis, longus, and magnus; AC, anterior leg compartment (tibialis anterior, extensor hallucis longus, extensor digitorum longus); LC, lateral leg compartment (fibularis brevis / longus); DP, deep posterior leg compartment (tibialis posterior, flexor hallucis longus, flexor digitorum longus); MG, medial gastrocnemius; LG, lateral gastrocnemius; SO, soleus.

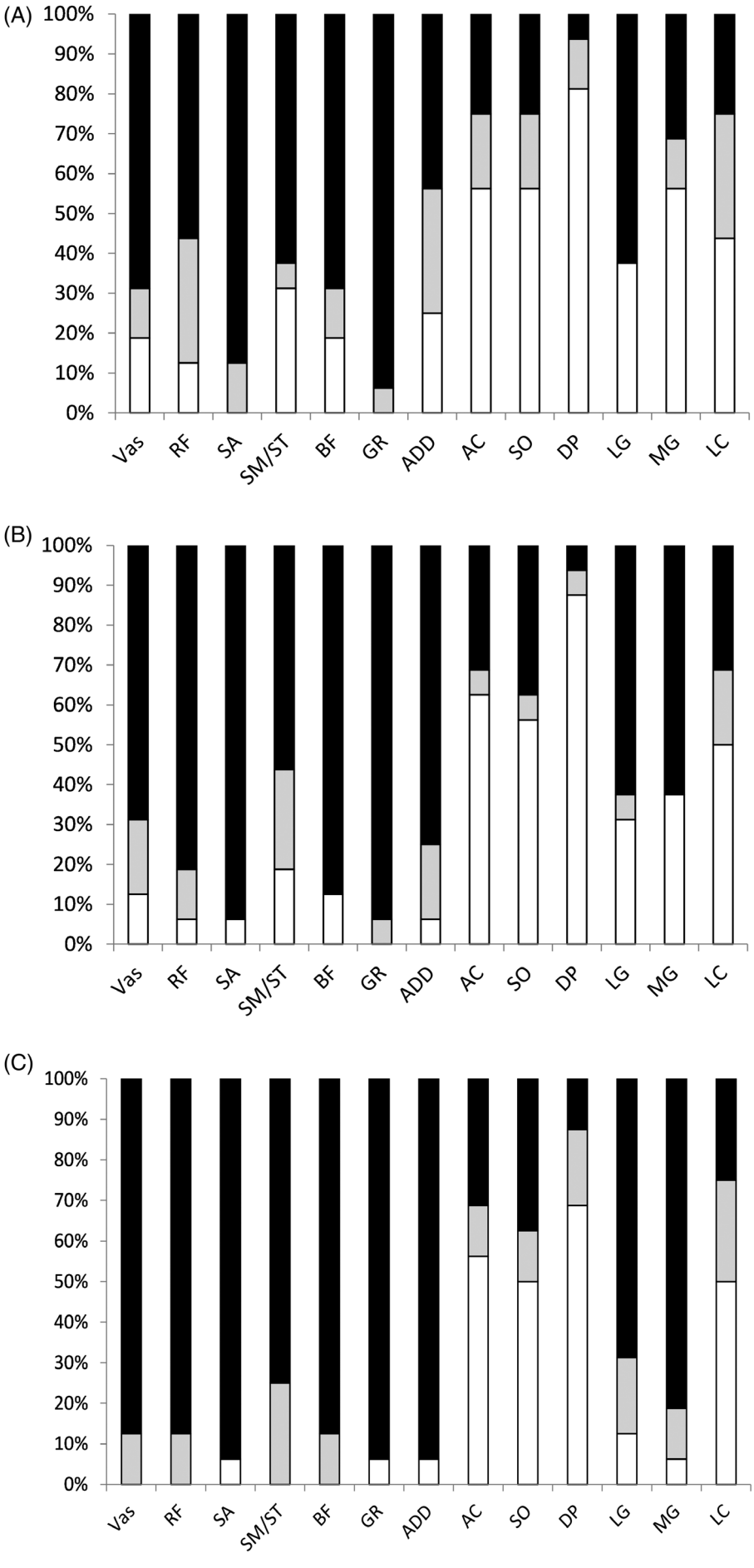

FIGURE 1 Frequency of the fat infiltration status (black, severe; gray, moderate; white, normal) for each muscle. A, Proximal. B, Medial, C, Distal. VAS, Vasti muscles (vastus lateralis, medialis and intermedius); RF, rectus femoris; SM/ST, semimembranosus and semitendinosus; BF, biceps femoris; SA, sartorius; GR, gracilis; ADD, adductor brevis, longus and magnus; AC, anterior leg compartment (tibialis anterior, extensor hallucis longus, extensor digitorum longus); LC, lateral leg compartment (fibularis brevis / longus); DP, deep posterior leg compartment (tibialis posterior, flexor hallucis longus, flexor digitorum longus); MG, medial gastrocnemius; LG, lateral gastrocnemius; SO, soleus

entire volume of each muscle group are listed in Table 1. The largest MPI values illustrating the largest fat infiltration and muscle atrophy were observed in SA (63.6 ± 9.7) and GR (61 ± 10.6) for the thigh. In LL, MG (56.2 ± 15.4) and LG (56.3 ± 16.1) were the most infiltrated muscles. As illustrated in Figure 1 and Table 1, MPI values were significantly different in the proximal and distal segments (P = .007).

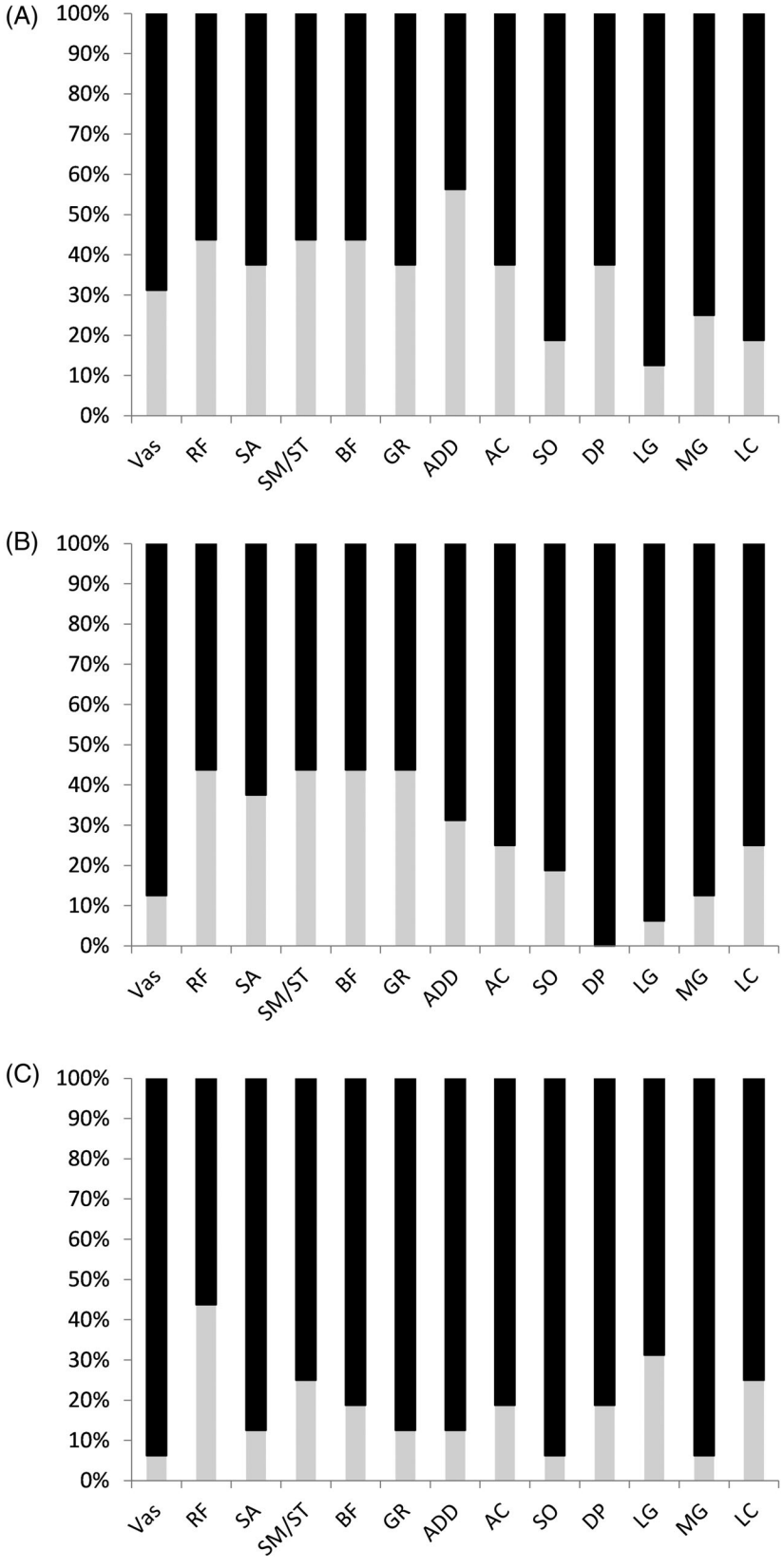

FIGURE 2 Frequency of the right–left asymmetry for each muscle (black, no asymmetry; gray, asymmetry). A, Proximal. B, Medial. C, Distal. VAS, Vasti muscles (vastus lateralis, medialis, and intermedius); RF, rectus femoris; SM/ST, semimembranosus and semitendinosus; BF, biceps femoris; SA, sartorius; GR, gracilis; ADD, adductor brevis, longus and magnus; AC, anterior leg compartment (tibialis anterior, extensor hallucis longus, extensor digitorum longus); LC, lateral leg compartment (fibularis brevis / longus); DP, deep posterior leg compartment (tibialis posterior, flexor hallucis longus, flexor digitorum longus); MG, medial gastrocnemius; LG, lateral gastrocnemius; SO, soleus

3.2.2 | Severity of fat infiltration

Figure 1 illustrates the frequencies of the fat infiltration status (severe, moderate or normal) for each muscle in the medial, proximal and distal segments. In the medial segment, the highest frequency of severe involvement of the thigh was identified for GR (93.8%), SA (93.8%), RF 81.3%), and VAS (68.8%). In LL, it was LG (62.5%) and MG (62.5%) muscles. In contrast, DP was the muscle compartment most frequently normal in terms of fat infiltration regardless of the muscle segment, followed by MG (56.3%) and AC (62.5%) in the proximal and distal segments, respectively.

3.2.3 | Proximal-to-distal gradients of fat infiltration

MPI values of each muscle group in the proximal and distal segments are reported in Table 1. In the thigh proximal and distal segments, the most infiltrated muscles were SA and GR (Table 1). These muscles were significantly most infiltrated in the distal segments. In the distal segment of the thigh, all muscles were severely infiltrated, with the fat infiltration in the VAS, RF, and BF found to be severe or moderate in 100% of subjects (Figure 1). In the proximal LL, LG (62.5%) was the muscle most frequently found to be severely infiltrated whereas in the distal LL both LG (68.8%) and MG (81.3%) were severely infiltrated in a majority of patients.

Regarding the severity of fat infiltration quantified in the proximal and distal segments, a proximal-to-distal gradient was clearly observed with a significantly larger infiltration in the distal segment for ADD, MG, GR, VAS, RF, and SA muscles (Table 1). This proximal-to-distal gradient was further supported by the frequencies of the severely infiltrated status illustrated in Figure 1. As an example, ADD was severely infiltrated in 43% of the patients in the proximal segment, whereas 81% of patients displayed a severe fat infiltration in the distal segment.

3.2.4 | Asymmetry of fat infiltration

Comparing the frequency of severely infiltrated status on the right and left sides, no clear asymmetry was identified in the distal segments of thigh and LL as illustrated in Figure 2. In the thigh proximal segment, a frequency of asymmetry >40% was observed in several thigh muscles: ADD (56.5%), BF (43.75%), SM/ST (43.75%), and RF (43.75%). For the other muscles and regardless of the segment, no asymmetry was observed for 56.25 to 100% of patients (Figure 2).

3.2.5 | Correlation between clinical data and MRI indices

The relationships between the total MPI value of the LL and the IBMFRS score and the MRCSLL are illustrated in Figure 3. A negative correlation was observed between IBMFRS, MRCSLL score and the total MPI values in the whole LL muscles. Considering individual muscles, the IBMFRS was significantly correlated with the MPI values of AC (r = –0.51; *P* = .04), ADD (r = –0.58; *P* = .03), DP (r = –0.67; *P* = .009), LG (r = –0.73; *P* = .003), MG (r = –0.70; *P* = .002), LC (r = –0.81; *P* = .002), and VAS (r = –0.59; *P* = .01). Similar significant correlations were observed for the MPI values of ADD (r = –0.59; *P* = .008), DP (r = –0.63; *P* = .01), LG (r = –0.76; *P* = .001), MG (r = –0.70; *P* = .001), LC (r = –0.84; *P* = .01), VAS (r = –0.58; *P* = .01), and the MRCSLL score. Neither disease duration, nor sCK were related to MPI values and IBMFRS.

4 | DISCUSSION

In the present study, we showed that, in sIBM patients, thighs and LL muscles were fat-infiltrated, in agreement with previous studies.[13,18,24] As an extension of this observation, we reported that thigh

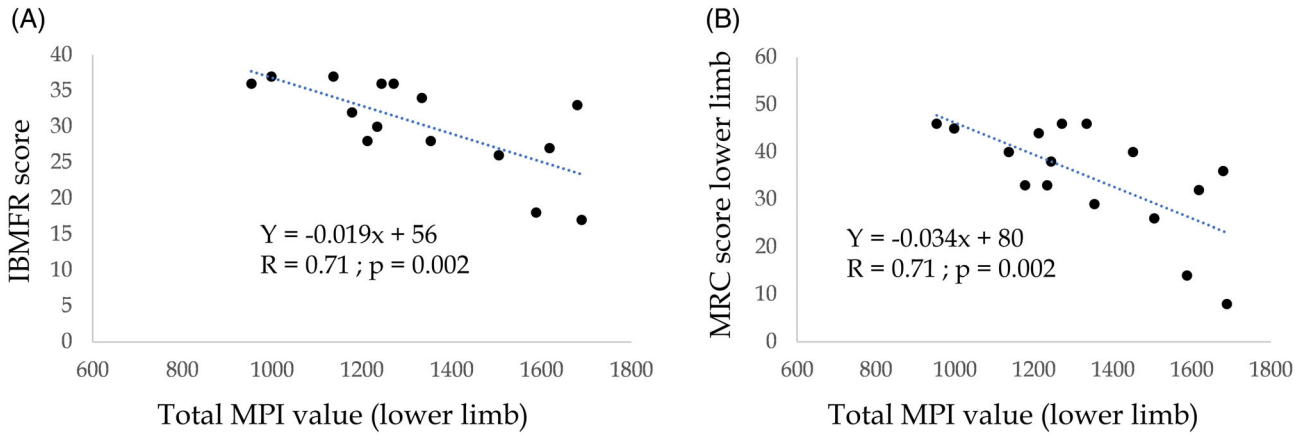

FIGURE 3 Correlation between the Inclusion Body Myositis Functional Rating Scale (IBMFRS) score (A), the Medical Research Council score of the lower limbs ($MRCS_{LL}$) (B) and the total mean pixel intensity (MPI) value in the LL

muscles were more infiltrated than LL muscles and that fat infiltration in thighs was prominent in the distal segment and more frequently asymmetric in the proximal segment. Previous MRI observations in sIBM patients have been mainly based on visual analyses,[12,13,24,25] whereas quantitative measurements have been reported in one study that considered only a single MRI slice.[18]

In previous studies, contradictory results have been reported in terms of muscle involvement. FDP, VL, and MG were reported as the most infiltrated muscles while MG was reported as consistently involved.[5,12] In contrast, another study did not support the preferential involvement of thigh muscles.[26] In the present study, SA was the most infiltrated muscle in the thighs. This is of interest given that the involvement of SA together with VAS has been considered a useful diagnostic clue in adult-onset myopathies.[13,24] We were able to distinguish fat infiltration in distal and proximal segments of thighs and LL. GR, SA, and LG were the most infiltrated muscles proximally while prominent distal fat infiltration occurred in GR, SA, VAS, RF, and BF and MG. GR was a severely infiltrated muscle both distally and proximally with a higher frequency in the distal (93.75%) than the proximal (81.25%) segment.

Our results did not support those from a previous study indicating that GR was a variably involved muscle in sIBM.[13] This apparent discrepancy might be accounted for by the fact that the prior study was based on visual analysis. It has previously been reported that RF is less severely infiltrated than VAS.[5,12,24] In agreement with the visual analysis of Tasca et al.,[13] we did not find a difference in fat infiltration between RF and VAS. Similar to previous reports,[12,13] the pattern of muscle involvement did not differ between patients with short and long disease durations except for the GR muscle for which fat infiltration increased with disease duration.

In a previous qualitative MRI study, the authors identified a pattern of LL muscle involvement in sIBM based on published studies and personal experience.[13] They reported a large fat infiltration of both thighs and LL, with a predominant distal distribution and atrophy, particularly involving the quadriceps muscle. This peculiar feature of fat infiltration in sIBM was confirmed by our findings. Based on a quantitative analysis of whole thigh and LL, our analysis clearly showed that the frequency of severe infiltration was always larger in the distal segments regardless the region of the leg (thigh, lower leg) or the side (left, right).

This observation was made possible using MPI measurements in each MR slice. This proximal-to-distal gradient of fat infiltration was mainly observed for ADD, GR, VAS, RF, and SA in the thigh and MG in the LL. One might speculate that this feature is part of the natural history of the disease with the distal segment being affected earlier than the proximal one. Of interest, ADD was severely infiltrated in 87.5% of the patients in the distal segment. Previous results indicated that hamstring muscles were more infiltrated than the relatively spared adductor muscles but without considering the gradient.[12] Our results suggest that the analysis of the proximal-to-distal pattern of muscle involvement may be of high interest in sIBM. This feature will need to be considered in future clinical trials using muscle MRI.

In sIBM, the spread of muscle weakness is often erratic and asymmetric.[18] A previous study[12] reported asymmetry of fat infiltration in 44% of patients in LL. Based on a quantitative analysis, we observed asymmetry in the proximal segment of thighs, mainly in adductors. Such an asymmetry regarding both fat infiltration and inflammation has also been previously reported in other studies.[12,24,26]

The highly negative correlations observed between IBMFRS and MRI metrics, such as the whole muscle fat fraction in thighs and LL, are similar to those previously reported.[18] The correlation between IBMFRS and fat infiltration was stronger in the distal than the proximal segment. This would have to be considered in longitudinal prospective studies. Previous studies using visual scoring have reported a significant correlation between the number of fat-infiltrated muscles and the MRC score.[12,24] Dion et al. did not find any correlations between fat infiltration and muscle strength,[26] whereas, based on a quantitative analysis, a significant correlation between the averaged thigh fat fraction and MRC score was reported.[18] We found that neither disease duration, nor sCK were related to MPI values or IBMFRS whereas previous studies have reported correlations between fat infiltration and disease duration either on the basis of visual inspection[12,24] or from quantitative results.[18] This apparent discrepancy might result from the small sample size in the present study.

A few limitations must be acknowledged in the present study. Control MPI values were recorded in a young control group. Although one can expect an increased fat infiltration with respect to age,[27] the very conservative calculation of the thresholds should not compromise the results. MPI values were computed from T1W images whereas Dixon techniques could have been more appropriate for a proper quantification of fat fraction as they are expected to handle biasing factors such as B0 field in homogeneity, T2 relaxation, phase and spectral complexity of fat. As previously reported[23] T1W imaging is also not susceptible to the same confounders because it depends only on the T1 difference between fat and muscle and can also tolerate some B1 inhomogeneity. Considering that our analysis was performed similarly for each subject, one can consider that the potential bias was the same in each case and did not compromise the results as we previously reported a high reproducibility of the MPI metric.[23]

5 | CONCLUSIONS

Overall, using quantitative MRI analysis combined with a supervised segmentation strategy, we have been able to characterize the quantitative pattern of fat infiltration in sIBM patients in a large number of muscles with regard to severity, asymmetry and proximal-to-distal gradient. If confirmed in a larger group of subjects, such an approach might be considered for both natural history investigations and clinical trials in sIBM patients.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to declare.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Ansari B, Salort-Campana E, Ogier A, et al. Quantitative muscle MRI study of patients with sporadic inclusion body myositis. *Muscle Nerve*. 2020;1–8. https://doi.org/10.1002/mus.26813