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Inclusion body myositis. Clinical aspects

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Chapter 5

Magnetic Resonance Imaging of skeletal muscles in sporadic inclusion body myositis

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Abstract

To analyze whether magnetic resonance (MR) imaging of upper and lower extremity muscles in a large patient group with sporadic inclusion body myositis (IBM) is of additional value in the diagnostic work-up of sporadic IBM, 32 sporadic IBM patients were included in this study. MR parameters were evaluated in 68 muscles of upper and lower extremity including muscle atrophy, fatty infiltration and inflammation. These findings were correlated to disease duration, weakness and serum creatine kinase (sCK) levels. Fatty infiltration was far more common than inflammation. Muscles most frequently infiltrated with fat were the flexor digitorum profundus (FDP), anterior muscles of the upper leg and all muscles of the lower leg, preferentially the medial part of the gastrocnemius. The rectus femoris was relatively spared compared to other quadriceps muscles as well as the adductors of the upper leg.

Inflammation was common in general, but individually sparse, present in 78% of the patients with a median of 2 inflamed muscles per patient. A statistically significant correlation was found between the amount of fatty infiltration and disease severity, disease duration and sCK.

We provide a detailed description of the MR imaging in sporadic IBM and show a distinct pattern of muscle involvement. Relatively severe affliction of the medial compartment of the gastrocnemius, combined with relative sparing of the rectus femoris or involvement of the FDP can be indicative of sporadic IBM. MR imaging can contribute to the diagnosis in selected patients with clear clinical suspicion, but lacking the mandatory set of muscle biopsy features.

Introduction

Sporadic inclusion body myositis (IBM) belongs to the idiopathic inflammatory myopathies and is characterized by painless multifocal muscle weakness and wasting manifesting after the age of 40 years. Diagnosis is based upon the clinical features and characteristic muscle biopsy findings. Symptoms usually follow the onset of weakness in the quadriceps, finger flexor or pharyngeal muscles. The spread of muscle weakness is erratic and asymmetric, but in general ventral muscle groups are more affected than dorsal muscle groups in the extremities, and girdle muscle groups are least affected.[1] The characteristic features in the muscle biopsy are mononuclear inflammation with T-cell invasion of non-necrotic muscle fibers, and rimmed vacuoles. In a subgroup of patients, histology does not show these characteristic biopsy features initially, leading to a delayed or wrong diagnosis.[2, 3]

Magnetic Resonance (MR) imaging has become a useful modality in the evaluation of inflammatory myopathies.[4] MR imaging provides detailed anatomic information and edema-like signal intensity changes give information on the activity of the disease, an advantage compared with other imaging modalities. Five previous studies describe MR imaging in patients with sporadic IBM. However, in contrast to our study, those studies comprise much smaller patient groups and were restricted with regard to the number of muscles studied.[5-9] It has been stated that MR imaging could distinguish polymyositis (PM) from sporadic IBM by the presence of isolated muscle inflammation in the absence of fatty infiltration or atrophy, as opposed to the findings in sporadic IBM.[6] Another study focused on the forearm muscles, and showed explicit fatty changes in the flexor digitorum profundus muscle, sometimes preceding clinically detectable weakness in this muscle.[9]

To give an elaborate view on the severity and distribution of abnormalities in MR imaging, we investigated a large and well-defined group of sporadic IBM patients. We investigated whether MR imaging could be of additional value to the clinical features during the diagnostic process.

Patients and Methods

Patients

The study comprised 32 patients diagnosed with sporadic IBM. All patients fulfilled the ENMC criteria[10] for definite (n=31) or probable (n=1) sporadic IBM. Patients were randomly selected from the Leiden University Medical Center (LUMC) registry of sporadic

IBM patients. The study was approved by the Ethics committee of the LUMC and all patients gave informed consent.

History taking included functional grading scales (Barthel index, scale 0-20, Rivermead mobility index, scale 0-15 and Brooke's grading system, scale 3-23 [with 23 being the worst score]). Physical examination comprised manual muscle strength testing (MMT) of 34 muscle groups using the six-point British Medical Research Council (MRC) scale.

Serum creatine kinase activity (sCK) was measured (normal value ≤ 170 U/L in women and ≤ 200 U/L in men).

MR imaging

MR imaging examinations were performed at 1.5T (Gyroscan NT15; Philips Medical System, Best, The Netherlands) by the following standard protocol. Each series was obtained with a body coil with the patient supine. The following sequences were used: (a) axial T1-weighted spin-echo series with 600/20 (repetition time msec/echo time msec), section thickness of 6.0 mm, field of view 250 mm, rectangular field of view of 59%, NSA=2 and an acquisition matrix of 205 x 256. (b) axial STIR series with 1400/15 (repetition time msec/echo time msec), section thickness of 6.0 mm, field of view 250 mm, rectangular field of view of 59%, NSA=4 and an acquisition matrix of 202 x 256. Imaging was performed of the right shoulder, upper and lower right arm, the pelvis, and both upper and lower legs. Two musculoskeletal radiologists, with respectively 4 and 14 years of clinical experience, without knowledge of the clinical findings, but aware of the diagnosis sporadic IBM, evaluated all MR examinations in consensus. Muscles were scored for muscle atrophy, fatty infiltration and edema-like changes. Muscle atrophy was defined as evident loss of muscle volume, scored as present or absent. T1-weighted MR images were used to estimate the degree of fatty infiltration. Abnormal signal intensity was consequently classified as mildly abnormal if only fatty streaks of increased signal intensity could be observed (<30% of fat compared to muscle), moderately abnormal if 30-60% of the muscle showed increased signal intensity and severely abnormal if at least 60% of the muscle showed an increased signal intensity.[11]

On STIR images any level of high signal intensity of the muscles was considered an abnormal finding: edema-like changes. In this population this is considered inflammation as previously used.[4, 6, 8, 12, 13] This was scored as present or absent. Asymmetry could be scored in the lower extremities only, as both sides were visualized.

The examined muscles were:

i) shoulder region: deltoid, infraspinatus, supraspinatus, subscapularis; ii) *upper arm*: biceps, triceps; iii) *forearm*: flexor carpi ulnaris, flexor carpi radialis, flexor

digitorum profundus (FDP) and superficialis (FDS), brachioradialis, extensor carpi ulnaris and radialis, extensor digitorum communis, supinator, pronator teres; iv) *pelvis*: gluteus minimus, gluteus medius, gluteus maximus, iliopsoas, obturatorius internus and externus, pectineus; *v) upper leg:* quadriceps femoris (rectus femoris, vastus lateralis, medialis and intermedius), semimembranosus, semitendinosus, biceps femoris, sartorius, gracilis, adductor brevis, longus and magnus; vi) *lower leg*: gastrocnemius (lateral and medial part), soleus, tibialis posterior, tibialis anterior, peroneus longus, and extensor digitorum longus. In total, 68 separate muscles were evaluated.

Statistics

Descriptive measures are presented as mean ± standard deviation, unless otherwise stated. Correlation between MR imaging and different clinical parameters were calculated using the Spearman rank test. The Mann-Whitney U-test was performed to compare total strength of patients with and without a fatty infiltrated FDP. A *p*-value of < 0.05 was considered to be significant.

Results

History, clinical examination and serum creatine kinase (sCK)

Mean age of the 32 included patients (19 men) was 68 ± 9 years, with a mean disease duration of 12 ± 5 years. Mean time to diagnosis was 8 ± 5 years. Median Barthel index score (range) was 19 (6-20), Rivermead mobility index score 12 (0-15) and for Brooke's grading system 6 (3-16).

With MMT, the most frequent affected muscles were the ventrally located muscles in the arm, the upper and the lower leg. The most frequent and severely (MRC-scale 0-3) affected muscles were the FDP (n=15, 47%) and quadriceps (n=11, 34%). Relatively spared muscles were the infraspinatus and adductors of the upper leg, which had normal strength in 19 (59%) and 21 (66%) patients respectively.

sCK was elevated in 28 patients (88%). Median sCK was 739 (121-3360) for men and 265 (44-802) for women.

MR imaging

General findings:

In two patients, the quality of MR imaging of the forearm was not sufficient to be evaluated due to motion artifacts. In all patients MR images showed abnormalities.

All patients had fatty infiltrated muscles. The median number of muscles infiltrated by fat per patient was 40 (range 5-68, interquartile range 29)

With regard to the extent of involvement, the leg muscles were more frequently and severely affected as compared to the arm muscles. The lower legs were more frequently and severely affected than the upper legs. The shoulder and pelvic girdle muscles and adductors of the upper leg were relatively spared (Table 1).

Table 1. Mean frequency of fatty infiltrated muscles and of those with severe fatty infiltration in different extremities

Body region	Fatty infiltration, %	Severe fatty infiltration, %
Shoulder	36	12
Arm	44	15
Upper	42	15
Lower	44	15
Pelvis	33	15
Leg	81	42
Upper	76	38
Anterior part	84	50
Posterior part	58	26
Lower	87	44

Inflamed muscles were present in 78% of the patients. The median number of inflamed muscles was 2 (range 0-20, interquartile range 4). The most frequent inflamed muscles were the deltoid muscle (16%), the extensor carpi ulnaris (20%), the medial (22%) and lateral part of the gastrocnemius (16%) and the soleus muscle (16%). Isolated muscle inflammation (i.e. without fatty infiltration) was observed in 13 of all observed muscles. This phenomenon was mostly seen in muscles which were relatively spared from fatty infiltration, such as the thigh adductors (n = 5) and in the extensor carpi ulnaris (n = 2) (Figure 6C and 6D).

Atrophy was present in 94% of the patients. The median number of atrophic muscles was 22 (range 0-68, interquartile range 28). The most frequent atrophic muscles were the FDP (60%), the vastus muscles (69%) and the medial head of the gastrocnemius (81%). No hypertrophy was found.

Asymmetry of abnormalities (fatty infiltration as well as inflammation) was present in 14 patients (44%) in the lower extremities. Asymmetry of fatty infiltration was mostly seen in the adductor magnus and the tibialis anterior muscle (13% in both),

whereas asymmetry of inflammation was mostly seen in the tibialis posterior and soleus muscle (9% in both).

MR imaging findings per body region:

Shoulder (Figure 1-3):

Involvement through fatty infiltration of shoulder muscles as a group was less frequent and severe than in other upper extremity muscles groups (Table 1). Fatty infiltration in the shoulder region was most frequently observed in the subscapular muscle (n=18, 56%). Inflammation was most frequent in the deltoid muscle; five (16%) patients had inflammatory changes in the deltoid muscle compared with one (3%) patient in each of the other shoulder muscles.

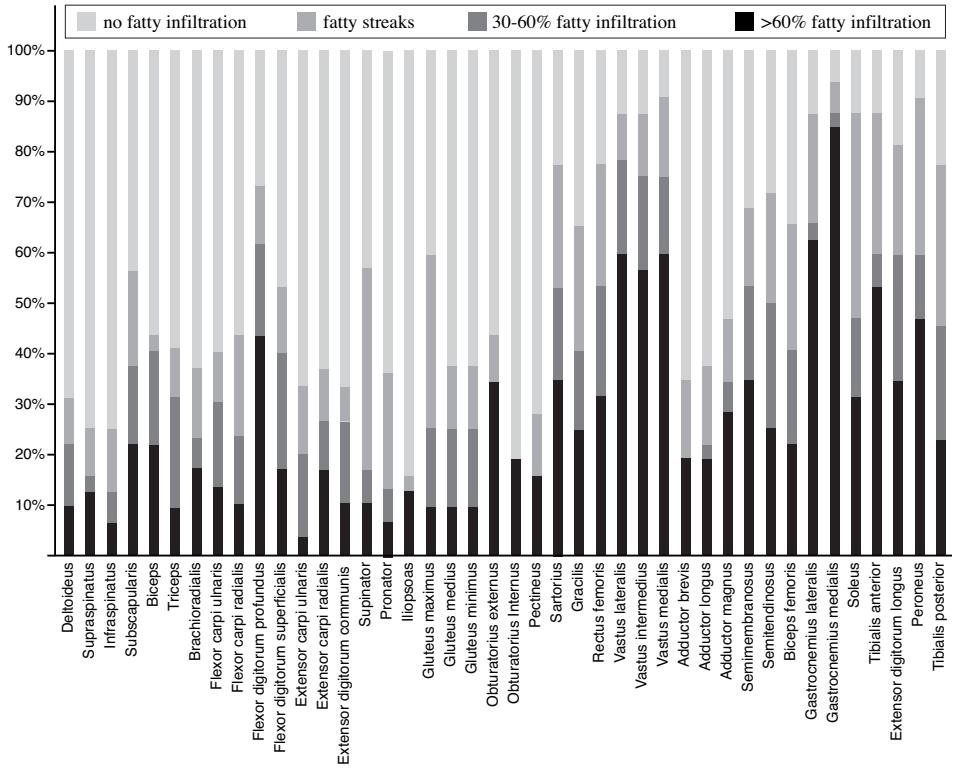

Figure 1. Severity and frequency of fatty infiltration of muscle groups for the total group of patients.

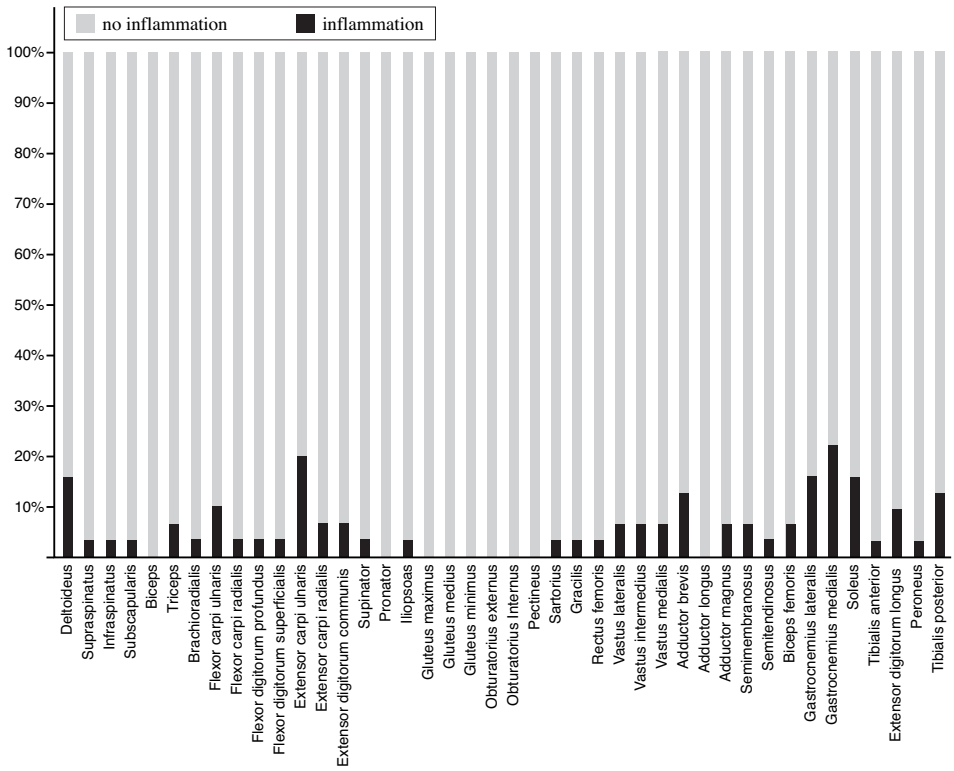

Figure 2. Frequency of inflammation of muscle groups for the total group of patients.

Upper arm (Figure 1-4):

Fatty infiltration was equally present in the biceps and triceps. No inflammation was seen in the biceps. Only two patients had inflammatory changes of the triceps.

Forearm (Figure 1-4, 5A, 5B, 6B,6C and 6D):

The most frequently and severely affected muscle of the upper extremity by fatty infiltration was the FDP. Twenty-two (73%) patients had an FDP infiltrated with fat, in 13 patients (43%) affliction was considered as severe. Atrophy was also most frequently observed in the FDP (n=18, 60%). In 8 patients (27%), the FDP was unaffected.

As a rule, if the FDP did not show fatty infiltration, then it was absent in all forearm muscles. The only exception was a patient with some fatty streaks in the supinator muscle. Preference for fatty infiltration was also seen in the FDS and the supinator muscle, but they were clearly less severely affected than the FDP.

Patients with an unaffected FDP on MR imaging had a mean disease duration of 13 years (± 5), demonstrating that the FDP can remain unaffected for a long time.

Inflammatory changes were most frequently seen in the extensor carpi ulnaris (n=6, 20%).

Pelvis (Figure 1-3):

The muscles around the pelvis were less frequently and severely affected by fatty infiltration than other muscle groups of the lower extremity (Table 1). The gluteus maximus was the most frequently affected muscle by fatty infiltration (n=19, 59%) of the gluteal musculature, although not severely (9%) and without asymmetry. None of the gluteal muscles had inflammatory changes.

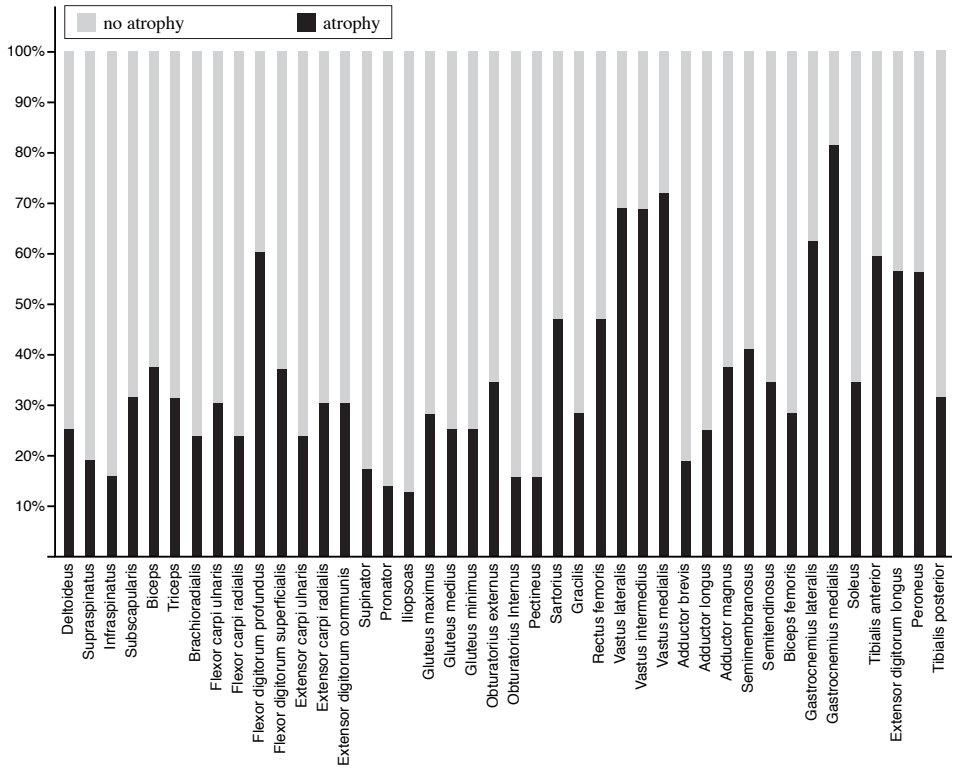

Figure 3. Frequency of atrophy of muscle groups for the total group of patients.

Upper leg (Figure 1-4, 5C and 5D):

The anterior muscle group of the upper leg was frequently affected by fatty infiltration. The rectus femoris was relatively spared compared to other quadriceps muscles, but normal in only 7 patients (22%). Complete sparing of the quadriceps muscles was seen in only two cases. In these patients, all other anterior and posterior thigh muscles

were spared as well, but both patients had abnormalities in the lower legs. No patient had exclusive involvement of quadriceps.

The posterior muscle group of the upper leg was far less frequently and less severely affected by fatty infiltration as compared to the anterior compartment (Table 1). The hamstring muscles more often had a preference for fatty infiltration as compared to the relatively spared adductor muscles.

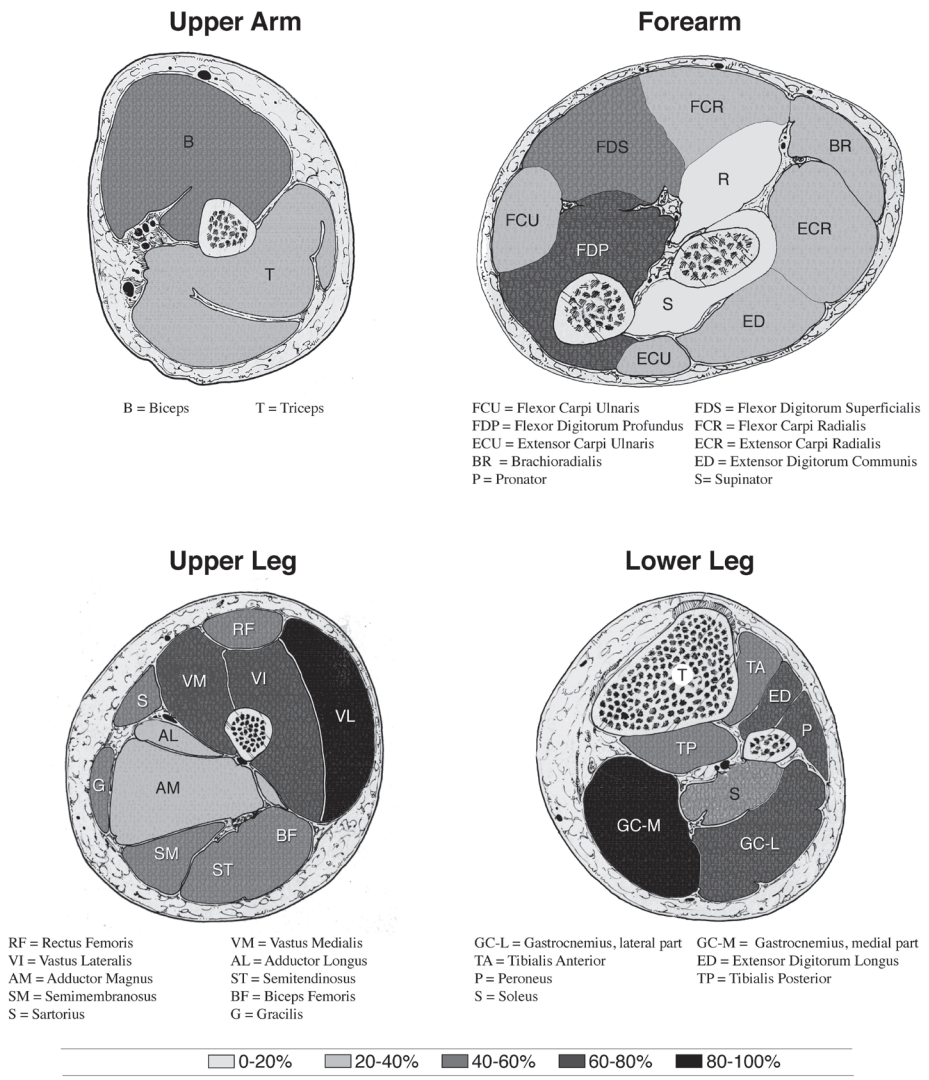

Figure 4. Frequency of muscles in the different extremities being infiltrated with fat by > 30%.

Inflammation was rare, the most frequently inflamed muscle was the adductor brevis (n = 4, 13%).

Atrophy was common in all muscles of the anterior compartment of the upper leg with exception of the gracilis muscle. This muscle was regarded atrophic in only 28% of the patient group.

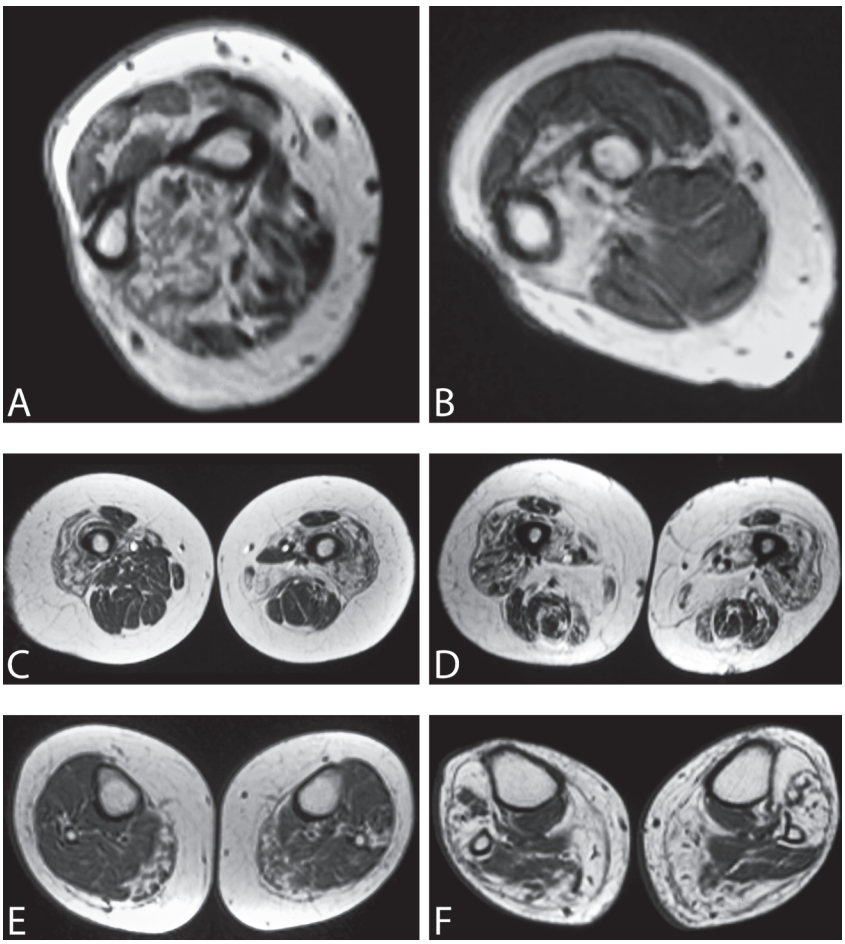

Figure 5. T1-weighted images with different levels of fatty infiltration in the forearm and legs
Right forearm showing moderate (A) and severe (B) fatty infiltration of the FDP.
Upper legs (C and D) showing severe fatty infiltration of the vastus muscles, with relative sparing of the rectus femoris muscle and hamstrings.
Lower legs showing moderate (E) and severe (F) fatty infiltration of the gastrocnemius muscles, especially the medial part. Image F shows relative sparing of the extensor digitorum longus, tibialis posterior and soleus muscles.

Lower leg (Figure 1-4, 5E, 5F and 6A):

All muscles of the lower leg were commonly affected by fatty infiltration, the medial part of the gastrocnemius muscle appearing as the most severely affected one.

Inflammatory changes in the lower extremity were also more common in the lower leg, again with a preference for the medial part of the gastrocnemius, showing inflammation in 7 patients (22%). Atrophy was common in all lower leg muscle groups with the exception of the soleus and the tibialis posterior muscles; these muscles were atrophic in respectively 11 (34%) and 10 (31%) patients only.

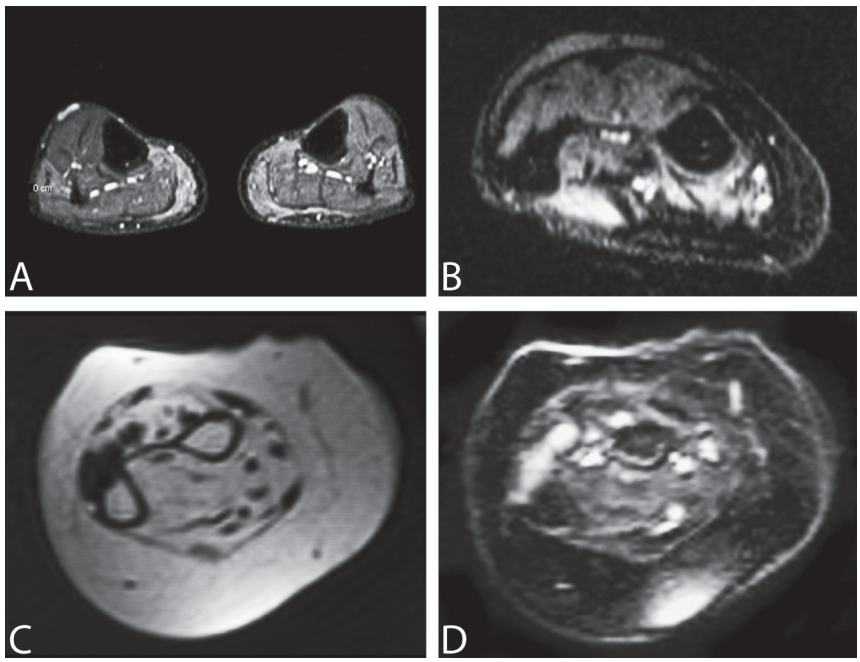

Figure 6. Images of inflammation (STIR) of the forearm and legs
Lower legs (A) showing inflammation in the medial part of the gastrocnemius muscle.
Right forearm (B) showing inflammation in the extensor carpi ulnaris muscle (ECU).
Right forearm forearm (C, T1-weighted) showing extensive fatty infiltration of all muscles, with sparing of the ECU. A STIR image (D) of the same patient shows exclusive inflammation of the ECU.

Correlation between MR imaging and other findings

There was a statistically significant correlation between disease duration and number of muscles infiltrated by fat (r= 0.6, p= 0.001). However, the pattern of muscles invaded with fat in patients with short and long disease duration was similar. No correlation was found between disease duration and the number of inflamed muscles (r= 0.4, p= 0.8), implying that short disease duration was not a prerequisite for inflammation. In

fact, the three patients with the highest frequency of inflamed muscles (> 11) had a disease duration of 10, 11 and 16 years. No correlation was found between age and MR imaging abnormalities. The seriousness of functional incapacity, as measured by the grading scales, was associated with the number of muscles infiltrated with fat. (Barthel r= -0.646, p< 0.005, Rivermead r= -0.743, p< 0.005, Brooke r= 0.628, p< 0.005). Functional grading scales did not correlate with the number of inflamed muscles.

Weakness was associated with more fatty infiltration as the sum score of all muscles, tested with MMT, had a negative correlation with the number of muscles infiltrated by fat (r= -0.8, p< 0.005). The number of inflamed muscles showed no correlation with the MMT sum score (r= -0.2, p= 0.4).

Patients with an FDP infiltrated with fat, scored significantly worse on MMT sum score (median = 245, n = 22) than patients with a normal FDP on imaging (median = 286, n = 8) (p = 0.002).

FDP muscles of normal strength with MMT, present in 5 patients, were normal on MR imaging, except for one case with some fatty streaks.

sCK levels showed a moderate, although negative correlation with the number of fatty infiltrated muscles on MR imaging (r= -0.417, p= 0.017), but did not correlate with the number of inflamed muscles (r = 0.252, p= 0.16).

Discussion

MR imaging is an easy and excellent technique to visualize muscle pathology in sporadic IBM, as demonstrated by the results of this large cohort of patients. All sporadic IBM patients showed abnormalities on MR imaging of their muscles. Fatty infiltration was the most common abnormality in all patients. It was observed, in decreasing order of frequency, in the lower legs, then the upper legs, followed by the forearm, pelvis, upper arm, and the shoulder girdle. However, within these body parts large differences were seen. In the upper legs the adductors were most frequently spared, the hamstrings intermediately affected, and the quadriceps most affected. In the forearm, there proved to be preferential affliction of the FDP muscle, sometimes as single muscle involvement.

Overall, in MR imaging, ventrally located muscles were more frequently and severely affected than dorsally located muscles, and abductors and adductors of the pelvic and shoulder girdle were the most spared, confirming the clinical findings.[1]

MR imaging also provides information on muscles that cannot be tested clinically. For example, in the lower leg the plantar flexors of the foot, the gastrocnemius and

soleus muscles, are clinically relatively spared; however, MR imaging points out that especially the medial head of the gastrocnemius is abnormal, with relative sparing of the soleus muscle. In the upper leg, the rectus femoris is relatively spared compared to the other quadriceps muscles.

Involvement of the FDP appeared not to be obligatory for the disease. Although Sekul et al[9] found a very high incidence of fatty infiltration in the FDP in 20/21 sporadic IBM patients with an average disease duration of 6.5 years, we found unaffected FDP muscles in a quarter of sporadic IBM patients. In one patient, MR abnormalities in the FDP preceded clinical detectable weakness, which has been described earlier.[9]

Edema-like changes are not specific for inflammatory myopathies, but can also be seen in other neuromuscular disorders (NMDs), *e.g.* in muscular dystrophy.[11]. As in muscular dystrophy, sporadic IBM patients also showed that muscles affected by edema-like changes showed less fatty infiltration. As edema-like changes were not associated with disease duration, in contrast to fatty infiltration, these findings hint towards inflammation preceding fatty infiltration.

The pattern of fatty infiltration is the most informative when one wants to discriminate between different NMDs. The sporadic IBM pattern described here is distinct from other myopathies that are to be considered in an elderly patient with insidious onset of muscle weakness, including dystrophinopathies, polymyositis (PM) and dermatomyositis (DM).

In dystrophinopathies (Becker muscular dystrophy and limb-girdle muscle dystrophies), the quadriceps muscles are also commonly invaded with fat. The biceps femoris, the semimembranosus and the adductors of the upper leg are also preferably affected in these disorders, in contrast to sporadic IBM.[14] In PM, fatty infiltration is far less pronounced than in sporadic IBM. Another difference is the pronounced localization of fat in the anterior muscle groups of the upper and the lower leg in sporadic IBM contrary to PM.[6]

In DM, inflammation is more pronounced than fatty infiltration and edema is found along the fascia and subcutaneous fat.[15] PM and DM have more symmetrical abnormalities in contrast to sporadic IBM. The marked abnormalities of the FDP as observed in sporadic IBM have never been described in another myopathy.

In clinical practice, selective MR imaging is preferred above imaging of 6 different body regions, mainly because imaging is time consuming. To differentiate between the myopathies mentioned above we suspect imaging of the upper legs and forearm to be the most informative. The sporadic IBM pattern of the upper leg (relative sparing of the rectus femoris, hamstrings and adductor muscles) and the extend of fatty infiltration (87%), as well as the asymmetry, mostly seen in the adductor magnus, can effectively differentiate sporadic IBM from other myopathies.

Although there is a high frequency of FDP abnormalities in sporadic IBM on imaging, subclinical involvement appeared rare. Imaging of the forearm can be used to confirm weakness of the FDP, especially when the presence of weakness is subtle or uncertain.

The absence of a control group limits the interpretation of the study. Discrimination from other myopathies was therefore not based on direct comparison, rather on knowledge from published articles describing MR findings in other myopathies. The awareness of the diagnosis may also raise concern about bias by the radiologists .

Although the patients in this study had a relatively long mean disease duration, subgroups of patients with a shorter and longer disease duration had a similar pattern of fatty infiltration.

In summary, although muscle involvement on MR imaging in individual sporadic IBM patients is diverse, it shows a pattern in sporadic IBM, different from other myopathies. The diagnosis of sporadic IBM is often made after a mean disease duration of 7 years due to a combination of patient and doctor's delay.[16] Not uncommonly the diagnosis is difficult to establish because of a not yet typical clinical picture or repeated muscle biopsies not showing the mandatory features. MR imaging of the skeletal muscles can, especially in these cases, contribute to a diagnosis of sporadic IBM.

Key messages

1. Fatty infiltration is the most common MR abnormality in sporadic IBM and correlates with weakness
2. The pattern of distribution of fatty infiltration in sporadic IBM muscle is thought to be specific for the disease
3. MR imaging can contribute in diagnosing sporadic IBM

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