The role of imaging in evaluating patients with idiopathic inflammatory myopathies

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Abstract:

Objective: To describe imaging modalities for diagnosing and monitoring of patients with idiopathic inflammatory myopathies.

Methods: A detailed literature search summarizing recent data documenting the contribution of different imaging techniques to current management of idiopathic inflammatory myopathies was performed.

Results: An overview of methods most frequently used for evaluation of inflammatory myopathies and the description of their role in the diagnostic and monitoring process is presented.

Conclusion: MRI is currently the most useful method capable of demonstrating both inflammatory and post-inflammatory changes in the muscles and surrounding soft tissue. Several studies have documented potential usefulness of other imaging techniques, such as ultrasonography, positron emission tomography, scintigraphy, and dual-energy X-ray absorptiometry.

Keywords: imaging, idiopathic inflammatory myopathy, MRI, ultrasonography
Introduction

MRI of skeletal muscles has been widely used to assess several types of myopathies, including inherited and acquired muscle diseases. In inherited myopathies, specific patterns of muscle involvement are well described on MRI. Thus, these unique patterns of muscle involvement are helpful in terms of identifying the possible genotypes relevant to individual muscle diseases.

MRI in the acquired myopathies, such as the idiopathic inflammatory myopathies (IIMs), can be helpful in phenotyping disease (information regarding the anatomical localisation i.e. affected muscles), defining the extent of muscle involvement, the level of disease activity (water signal changes), and the chronicity of the disease (fatty replacement and muscle atrophy). Muscle MRI therefore is appropriate diagnostic and monitoring tool that can reflect both inflammation and damage of the affected muscles.

MRI also has potential as an outcome measure for research studies, including drug treatment trials. Other MRI and non-MRI imaging techniques potentially useful in the assessment of the IIMs will also be discussed in this review, including real-time MRI, MR spectroscopy, diffusion weighted imaging, MR elastography, ultrasonography, positron emission tomography, scintigraphy and dual-energy X-ray absorptiometry.

Magnetic resonance imaging of skeletal muscles

MRI has become a fundamental imaging tool for assessment of muscle involvement in the IIMs (1), although it is relatively costly and not always readily available. MRI allows detailed imaging of large muscle volume at once. It helps in diagnosis by depicting important pathological alterations: muscle oedema/inflammation, fasciitis, subcutaneous inflammation, muscle atrophy and fatty replacement. It can assist in choosing the optimal site for muscle biopsy (2), reducing the rate of false-negative biopsies (3). In patients with established diagnosis MRI can help to determine whether clinical muscle weakness is based on chronic muscle damage or relapse of active disease (4).

Muscle abnormalities are mostly assessed on T1-weighted sequences and on T2-weighted sequences sensitive for free water, such as short tau inversion recovery (STIR) or T2 fat suppressed sequences. Healthy muscle generates an intermediate signal intensity on T1-weighted sequences; slightly higher than water, but lower than bone marrow and a much lower signal intensity than both fat and water on T2-weighted sequences (5). Muscle inflammation is manifested by hyperintense signal on T2-weighted sequences due to increased water content triggered by oedema in the affected area, or by muscle contrast enhancement on a T1-weighted sequence, such as T1 fat suppressed sequence post-gadolinium. Fluid sensitive techniques such as fat suppressed or STIR sequences are therefore typically used for evaluation of muscle inflammation (6). The same phenomenon caused by fasciitis results in
hyperintense sign in the perifascial compartment. **Muscle atrophy** and **fatty replacement** can be assessed easily on T1 weighted sequences.

There is no universally accepted and validated scoring system for evaluation of muscle MRI findings (7). Various semi-quantitative scoring systems and quantitative methods for assessing different MRI signal parameters have been proposed. However large variability of design and differences in patient populations make comparisons difficult. None of the previous studies has provided convincing evidence of added clinical value of performing a whole-body MRI (WB-MRI) rather than MRI of thigh muscles, which seems to provide a sufficient extent for diagnostics and biopsy guidance. A study by Filli (8) documented similar diagnostic accuracy of restricted WB-MRI with the omission of the trunk compared to extended WB-MRI; however some case reports (9) showed the positive contribution of WB-MRI e.g. in detecting complications like osteonecrosis (10).

**Semi-quantitative scoring systems** assign a severity of involvement to numerically defined analogue scales based on visual assessment. This technique is relatively easy to implement, but it is somewhat subjective, as is the case with any scoring by physicians, and results likely are influenced by experience of the evaluator. Different assessment systems using analogue scales with varying level of complexity have been developed. In some studies, muscle oedema was evaluated in individual muscles (11-12), whereas others reported scoring of whole muscle compartments (13). For example, a recent Norwegian study has proposed a sophisticated system assessing the extent of muscle oedema and its intensity, fatty replacement and fascial oedema, with a maximum total score of 78 points (13). Another extensive analysis of a large cohort of patients from John Hopkins University presented results expressing the percentage of muscles affected by each pathological feature, which allowed a clear comparison between different myositis subgroups (14).

**Quantitative evaluation systems** aim to assess muscle changes more precisely. They use continuous scales based on MRI findings that reflect muscle composition / haemodynamic imaging. The evaluation is based on computer analysis of pixel intensity values and therefore produces a statistically well-defined outcome. These quantitative methods showed a good correlation with semi-quantitative evaluation systems in several studies (15-16).

These methods are dependent on specific software tools and their reproducibility on different MRI scanners has not been studied extensively. Fat fraction (which quantifies tissue fat content on a 0-100% fat-fraction scale), transverse relaxation time (T2), and magnetisation transfer ratio (MTR) (T2 and MTR being sensitive to changes in muscle water distribution and lipid content), are the most frequently used quantitative muscle imaging methods.
In a recent prospective MRI quantitative study, Morrow et al. (17) showed that, in patients with sporadic inclusion body myositis (IBM), whole calf and thigh muscle fat fraction (measured using MRI Dixon fat water imaging) increased significantly after 1 year and was correlated with the lower limb components of the IBM functional rating score (IBMFRS). This study demonstrated validity and responsiveness of MRI outcome measures (particularly fat fraction) in IBM, suggesting that MRI biomarkers might prove valuable in experimental trials, with the potential to decrease sample size if used as the primary endpoint, namely in early phase clinical trials, although not for routine care at this time (17).

**Specific MRI patterns**

Widespread use of MRI and growing knowledge of clinical manifestations of IIMs in the context of their immunological characteristics has raised interest in defining specific MRI patterns associated with individual phenotypes (Tab. 1). Some studies demonstrated that polymyositis (PM) involves the thigh muscles in the proximal area either in global, or predominantly the posterior muscle group (18). The muscle oedema seems to be diffuse due to immune reaction in the myofibers. The oedema in dermatomyositis (DM) involves predominantly anterior muscle groups and is more focal and patchy, similar to juvenile dermatomyositis (JDM) (19). This has been attributed to the underlying pathophysiology in DM, which is characterised by perivascular and perifascicular inflammation and possible ischaemic damage (20).

In sporadic inclusion body myositis, similar to the clinical presentation, within the forearm there is preferential fatty infiltration within the flexor digitorum profundus (20-23) whilst in the thigh, quadriceps femoris is preferentially affected (18, 22-24) with some authors reporting relative preservation within quadriceps of rectus femoris (22, 23), the sartorius generally involved and gracilis variably involved (25). The distal portion of the quadriceps tends to be more affected than the proximal portion, particularly the vastus medialis and vastus intermedius (with a “melted appearance”) and the distal-proximal gradient being better appreciated in coronal sections (25). Within the lower leg, the medial head of gastrocnemius typically shows maximal intramuscular fat accumulation (22-25), a feature not recognized clinically as ankle plantar flexion weakness, as soleus and the lateral gastrocnemius show lesser involvement. Muscle inflammation is commonly seen, but in a smaller number of muscles than affected by fat accumulation (20-22, 25).

In a recent cross-sectional study of patients with immune-mediated necrotising myopathies (IMNM), Pinal-Fernandez et al. (14) showed that had significantly more widespread muscle oedema, atrophy and fatty replacement compared with those with PM and DM, using semi-quantitative scoring systems.
Anti-Signal Recognition Particle (SRP) patients were more severely affected than those with anti-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). IBM patients had more muscle atrophy and fatty replacement that PM, DM and anti-HMGCR patients (but similar to anti-SRP patients) and fascial oedema was more prominent in DM (in line with previous studies). Data discussing individual MRI patterns in context of antibodies are summarized in Table 1; however these results need to be verified in large patient cohorts.

**Real-time MRI**

Real-time (RT) MRI is safe, well-tolerated and equally capable as video-fluoroscopy and flexible endoscopy in the assessment of dysphagia in patients with IBM (Tab.2). RT-MRI allows assessment of tissue morphology without x-ray exposure and more reliable timing analysis, which provided more precise information about quantitative function when compared to video-fluoroscopy and flexible endoscopic evaluations of swallowing. It also correlated well with the Swallowing-Related Quality of Life Questionnaire (26). Therefore, RT-MRI has potential for longitudinal evaluation of swallowing (frequently affected in IBM and other muscle diseases) in clinical practice and research studies. Although not yet widely available, RT-MRI also has potential not only in the assessment of swallowing and speaking but also in dynamic joint assessment and evaluation of cardiac function.

**MR spectroscopy**

Magnetic resonance spectroscopy captures muscle metabolic pathways by measuring pH and monitoring phosphate metabolites such as adenosine triphosphate (ATP), phosphocreatine (PCr) and inorganic phosphate (Pi) (27). By evaluation of these parameters before, during and after exercise, information about oxidative phosphorylation in mitochondria and its defects can be obtained. Small studies examining patients with PM showed impaired post-exercise results with prolonged recovery time. In DM and JDM patients, abnormal outcomes of phosphorylation at rest and during exercise is seen, which has been attributed to the microangiopathic abnormalities in muscles affected by DM (28). There also are some limited data suggesting that mitochondrial oxidative capacity is not impaired in IBM (29).
**Diffusion weighted imaging**

Diffusion weighted imaging (DWI) is a special method providing information about fluid motion in tissues. Since inflammatory muscle diseases involve water content in muscles, DWI can be helpful in assessment of muscle oedema. Apparent diffusion coefficient (ADC) is a parameter derived from this random water motion within the muscles, which is further used for determination of diffusion in muscles and random perfusion dephasing in the capillary bed (pseudodiffusion). By studying these characteristics, oedematous muscles of patients with DM and PM showed increased diffusive properties and increased capillary perfusion, but reduced perfusion volume compared to healthy individuals (30).

**Magnetic resonance elastography**

MR elastography (MRE) investigates tissue elasticity, based on the propagation of shear waves in soft tissue. After a shear wave is induced in a tissue, a motion sensitizing gradient synchronized with the shear wave is applied. From this process, a phase shift is measured using a phase-contrast MRI. The displacement at each voxel is then calculated from this phase shift and the move of shear wave through the tissue can be imaged.

A small study of PM, DM and JDM patients found a statistically significant reduction in MR measurements compared with matched healthy controls when muscle was in a relaxed state. The authors postulated that the reduction in muscle stiffness may generate problems with force transmission within muscle and contributes to the lack of endurance in these patients (31). Interpretation of MRE in muscle disorders is challenging, but the finding of reduced stiffness in IIM patients warrants further investigation in a large cohort of patients.

**Ultrasonography**

Ultrasonography is a method for assessing muscle involvement in the IIMs, on the basis of good accessibility of muscles for dynamic examination, ease of use, lack of contraindications and absence of exposure to ionizing radiation (32). Improvements in the technical parameters of the method has led to better resolution of the soft tissue structures and facilitated the possibility to display more accurate pictures of muscle morphology and the capacity to detect other important parameters such as blood perfusion in the skeletal muscles.

Complete evaluation of muscles requires transverse and longitudinal slices (33). Broad-band linear-phased 7-15 MHz transducers are normally used to see the widest possible amount of muscle tissue.
Normal muscle appears hypoechoic, surrounded by fibroadipose septa (perimysium), which is seen as hyperechoic lines separating the muscle bundles. Fascia and tendons are hyperechoic structures organized parallel to muscle fibres (34).

Most diagnostic and clinically important pathological changes involving muscle inflammation and atrophy can be detected on ultrasound, in addition to calcifications and fasciitis. Results of previous studies (35) indicate muscle inflammation as an increase of echogenicity. Hyperechoic inflammatory muscle fibres are surrounded by fibroadipose septa, which are filled by inflammatory exudates causing their hypoechoic appearance (36). Muscle volume tends to enlarge due to increased intra- and extracellular water content and cell infiltration. These alterations in echogenicity and size of muscles are generally non-specific in diagnosis, because they may be a consequence of a posttraumatic or infectious processes (37). However, they can indicate activity in patients with an already established diagnosis. In IBM, higher echo intensity of the flexor digitorum profundus muscle than in the flexor carpi ulnaris muscle has been suggested as diagnostically useful in a small population of patients (38).

**Muscle atrophy** is characterised by diminished volume with hyperechoic appearance due to fat substitution of muscle fibres. Great inter-individual variability is seen in muscle volume, based on age, gender, level of training etc., and the assessment of muscle volume might therefore be very subjective. Muscle atrophy occurs as a consequence of denervation or neuromuscular disease, in addition to inflammation.

**Calcifications** are relatively rarely seen in patients with adult forms of IIMs, but they are frequently an accompanying clinical picture of juvenile dermatomyositis (39). They present as hyperechoic structures with posterior acoustic shadowing. Calcifications are located most frequently in the skin, but can be detected in perifascial compartments or directly intramuscular; central calcification within abnormal intramuscular soft tissue might raise the suspicion of neoplasm (40). **Fasciitis** can be documented as thickening of fibrous septa that envelops the muscle bundles, not rarely inhomogeneous (41).

**Traditional grayscale ultrasonography** was extended by new techniques such as Doppler sonography, contrast enhanced ultrasound and sonoelastography. These methods have not yet been fully implemented in standard diagnostic algorithms, but they provide further information about the pathological conditions in muscles.

**Doppler sonography** helps in the detection of large vessel flow, but its use is limited to the evaluation of regional tissue perfusion. The Power Doppler technique increases the sensitivity for detecting low flow in the microvasculature and therefore is more appropriate for assessment of soft tissue hyperaemia (42). According to a prior study of Meng et al. (43) as well as recent data published by Sousa Neves et al. (36), both conventional grayscale and power Doppler ultrasonography findings are
correlated with clinical status of subjects, distinguishing between those affected by the disease and healthy controls.

Contrast enhanced ultrasound (CEUS) is a modern technique to evaluate tissue perfusion. Contrast agents used in CEUS are small microbubbles of a diameter from 2 to 6 μm, which are administered intravenously. This investigation method exploits a principle of resonant frequency, when radial oscillation of the microbubbles becomes amplified, which allows to distinguish microbubble signal from tissue clutter (44). Microbubbles, filling the small vessels, can be visualised and quantified. A study in patients suspected of having myositis demonstrated a significantly higher muscle perfusion in the group with histologically proved myositis (45).

Sonoelastography provides a different form of tissue assessment, describing the mechanical properties of muscles. It portrays the strain relations that change with applied stress or pressure. A longitudinal strain occurs when the muscle is compressed or stretched; shear strain responds to angular forces, such as twisting (46). There are currently two main elastography methods, on the basis of the mechanism of strain formation: strain elastography and shear wave elastography. In strain elastography, a force is generated by repetitive manual pressure and the displacement (strain) is then determined by return velocities in time. Shear wave elastography applies a vibration to tissues through a focussed ultrasound pulse, which generates the transducer itself. In principle, the stiffer the tissue is, the less compliant it is to shear forces (47). A study performing elastography in patients with myositis documented decreased elasticity of inflamed muscles, probably due to fibrosis and atrophy changes (48).

**Positron Emission Tomography**

Positron Emission Tomography combined with Computed Tomography (PET-CT) provides information about localization of abnormal metabolic activity within the body. Metabolically active cells at sites of neoplasm, infection or inflammation show increased uptake of a fluorine-labelled glucose analogue (FDG). This phenomenon can be used to detect inflammation in active muscle disease (49), but data from previous studies suggest that increased FDG muscle uptake may be due to a broad spectrum of different causes leading to increased metabolic activity and is not specific for myositis (50). In addition, a higher uptake can be observed even in normal muscles after physical exercise, therefore patients have to rest for a certain time in order to minimize non-specific FDG uptake. There is a well-known association between IIMs and malignancy. PET/CT can be used as a reliable screening tool (51).

Increased Pittsburgh Compound B (a PET biomarker that detects amyloid β) uptake levels in the gastrocnemius muscle have been described in seven IBM patients (compared with six non-IBM
patients) (52). Larger studies with this PET biomarker are needed to confirm these results and to clarify the potential utility of Pittsburgh Compound B in clinical practice and in the research setting, namely in terms of its differential diagnostic value which is yet to be established.

**Scintigraphy**

Scintigraphy with technetium-99m – labelled diphosphonate is mostly used to detect pathological changes in bone metabolism, but it can also capture the inflammatory process at extra-skeletal sites. This fact has been repeatedly described in case reports (53-54). However, the most common indication for performing scintigraphy remains in the diagnostics of malignant processes. Recent published study suggested that technetium-99m pyrophosphate quantitative 3D scintigraphy might be a helpful complementary tool for diagnostic of IIM due to increased uptake of this tracer in inflamed muscles (55).

**Dual-energy X-ray absorptiometry (DXA)**

Dual-energy X-ray absorptiometry (DXA) can be used to measure human body composition. Total lean body mass (LBM) and appendicular LBM measured by dual-energy X-ray absorptiometry (DXA) have been used as outcome measures in the IIMs, namely in IBM clinical trials (56-57).

**Conclusion**

In conclusion, imaging techniques, particularly MRI, have become fundamental tools in the assessment, diagnosis and monitoring of patients with rheumatic muscle diseases. MRI provides a lasting detailed topographical picture of regional variations and it can quantify IIMs pathological processes, including disturbance of intramuscular water distribution and intramuscular fat accumulation, and therefore differentiate between chronic inflammation and chronic damage. Various MRI techniques as applied to muscle have the potential to revolutionize management of the IIMs in the same way that MRI has transformed the management of diseases of the central nervous system.

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Conflict of interest: There are no conflicts of interest.
### Table 1: MRI patterns in myositis subtypes

<table>
<thead>
<tr>
<th>Specific MRI patterns</th>
<th>Oedema</th>
<th>Atrophy, fatty replacement</th>
<th>Fascial oedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>- Symmetrical</td>
<td>- More prevalent in anterior compartment (58)</td>
<td>- Fascial oedema of rectus femoris uncommon (14)</td>
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<tr>
<td></td>
<td>- Diffuse, homogeneous oedema</td>
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<td></td>
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<td></td>
<td>- Both anterior and posterior muscle groups (18) (58)</td>
<td></td>
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</tr>
<tr>
<td>ASS</td>
<td>- Predominantly anterior compartment (13)</td>
<td>- Predominantly posterior compartment (13)</td>
<td>- Equal in all compartments (13)</td>
</tr>
<tr>
<td>Overlap myositis</td>
<td>- Predilection in the gluteal and thigh muscles (59)</td>
<td>- Not known</td>
<td>- Not known</td>
</tr>
<tr>
<td>IMNM</td>
<td>- Mostly in the lateral rotators, glutei, medial and posterior compartment; frequent oedema of adductor brevis (14)</td>
<td>- Frequent atrophy of obturator externus (14)</td>
<td>- Infrequent (14)</td>
</tr>
<tr>
<td></td>
<td>- Anti-SRP: most affected vastus lateralis with relative sparing of vastus intermedius, rectus femoris, biceps femoris, adductor magnus (60)</td>
<td>- Anti-SRP: predominant affection of adductor magnus, gluteus maximus, biceps femoris long head, semimembranosus and semitendinosus; the least affected m. quadriceps femoris (60)</td>
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<tr>
<td></td>
<td>- Anti-HMGCR: more symmetrical involvement than anti-SRP (14)</td>
<td></td>
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<tr>
<td>DM</td>
<td>- Symmetrical</td>
<td>- Milder than PM (58)</td>
<td></td>
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<tr>
<td></td>
<td>- Focal and patchy oedema</td>
<td></td>
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<td></td>
<td>- Frequent involvement of quadriceps femoris (6)</td>
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<tr>
<td>JDM</td>
<td>- Symmetrical</td>
<td>- Atrophy of quadriceps, especially vastus medialis (61)</td>
<td>- On WB-MRI fascial oedema limited to the limbs (19)</td>
</tr>
<tr>
<td></td>
<td>- No differences between proximal and distal muscles (19)</td>
<td></td>
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</tr>
<tr>
<td>IBM</td>
<td>- Distal predominance</td>
<td>- Predominantly forearm and anterior compartment of the thigh</td>
<td>- No oedema, but “undulating fascia” sign – fascia drawing a line between atrophic vastus intermedius and vastus lateralis (18)</td>
</tr>
<tr>
<td></td>
<td>- Anterior group involvement (14), esp. quadriceps muscle (18) and sartorius (25)</td>
<td>- Relative sparing of rectus femoris compared to other quadriceps muscles (22, 23)</td>
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<tr>
<td></td>
<td></td>
<td>- Medial gastrocnemius more affected in the lower leg (22-25)</td>
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</table>

PM – polymyositis; ASS – anti-synthetase syndrome; IMNM – Immune-mediated necrotising myopathy; anti-SRP – anti-signal recognition particle; DM – dermatomyositis, anti-HMGCR - anti-hydroxy-3-methylglutaryl-coenzyme A reductase; JDM – juvenile dermatomyositis, WB-MRI – whole-body magnetic resonance imaging; IBM – inclusion body myositis;
Table 2: Novel imaging modalities and their results in patients with IIM

<table>
<thead>
<tr>
<th>Imaging method</th>
<th>Field of interest</th>
<th>IIM patient specifics</th>
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<tbody>
<tr>
<td><strong>Magnetic resonance imaging</strong></td>
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<tr>
<td>real-time MRI</td>
<td>dysphagia</td>
<td>prolonged pharyngeal transit time in IBM patients (26)</td>
</tr>
<tr>
<td>MR Spectroscopy</td>
<td>mitochondrial metabolism at rest and exercise</td>
<td>prolonged recovery time in DM and JDM patients (28), normal regeneration in IBM patients (29)</td>
</tr>
<tr>
<td>DWI</td>
<td>soft tissue oedema</td>
<td>increased capillary perfusion in muscles in PM and DM patients (30)</td>
</tr>
<tr>
<td>MR Elastography</td>
<td>soft tissue elasticity</td>
<td>reduced stiffness in the relaxed state in PM, DM, and JDM patients</td>
</tr>
<tr>
<td><strong>Ultrasonography</strong></td>
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<tr>
<td>Power Doppler</td>
<td>soft tissue hyperaemia</td>
<td>higher vascularity scores indicating muscle inflammation in IIM patients (43)</td>
</tr>
<tr>
<td>Contrast enhanced US</td>
<td>soft tissue perfusion</td>
<td>high muscle perfusion correlating with disease activity (44)</td>
</tr>
<tr>
<td>Sonoelastography</td>
<td>soft tissue elasticity</td>
<td>decreased elasticity of atrophic muscles, increased elasticity in muscles with fatty infiltration (48)</td>
</tr>
<tr>
<td><strong>PET/CT</strong></td>
<td>abnormal uptake of radionuclide in inflamed muscles</td>
<td>detection of amyloid β in the gastrocnemius muscle in IBM patients (52)</td>
</tr>
<tr>
<td><strong>Scintigraphy</strong></td>
<td>abnormal metabolic activity in bones / extra-skeletal sites</td>
<td>detection of deep muscular fasciitis and calcifications in ASS patient (53)</td>
</tr>
<tr>
<td>Dual-energy X-ray absorptiometry</td>
<td>body composition</td>
<td>reduced lean body mass in patients with IBM (57)</td>
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</table>
Figures:

Fig. 1 (Axial STIR seq.): PM – symmetrical involvement of both anterior and posterior compartments

Fig. 2 (Axial STIR seq.): IMNM – symmetrical involvement of adductors

Fig. 3 (Axial STIR seq.): DM – anti Mi2+; patchy symmetrical involvement of quadriceps femoris, subcutaneous soft tissue oedema corresponding with skin involvement
Fig. 4 (Axial T1-weighted seq.): IBM – atrophy and fatty replacement predominantly involving anterior muscle group

Fig. 5 (Axial STIR seq.): IBM – undulating fascia sign

STIR seq. – short tau inversion recovery sequence; PM – polymyositis, IMNM - immune-mediated necrotising myopathy; DM – dermatomyositis; IBM – inclusion-body myositis
References:


