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255th ENMC workshop: Muscle imaging in idiopathic inflammatory myopathies. 15th January, 16th January and 22nd January 2021 – virtual meeting and hybrid meeting on 9th and 19th September 2022 in Hoofddorp, The Netherlands

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ABSTRACT

The 255th ENMC workshop on Muscle Imaging in Idiopathic Inflammatory myopathies (IIM) aimed at defining recommendations concerning the applicability of muscle imaging in IIM. The workshop comprised of clinicians, researchers and people living with myositis. We aimed to achieve consensus on the following topics: a standardized protocol for the evaluation of muscle images in various types of IIMs; the exact parameters, anatomical localizations and magnetic resonance imaging (MRI) techniques; ultrasound as assessment tool in IIM; assessment methods; the pattern of muscle involvement in IIM subtypes; the application of MRI as biomarker in follow-up studies and clinical trials, and the place of MRI in the evaluation of swallowing difficulty and cardiac manifestations. The following recommendations were formulated: In patients with suspected IIM, muscle imaging is highly recommended to be part of the initial diagnostic workup and baseline assessment. MRI is the preferred imaging modality due to its sensitivity to both oedema and fat accumulation. Ultrasound may be used for suspected IBM. Repeat imaging should be considered if patients do not respond to treatment, if there is ongoing diagnostic uncertainty or there is clinical or laboratory evidence of disease relapse. Quantitative MRI is established as a sensitive biomarker in IBM and could be included as a primary or secondary outcome measure in early phase clinical trials, or as a secondary outcome measure in late phase clinical trials. Finally, a research agenda was drawn up.

1. Introduction

The organisers of this 255th ENMC workshop welcomed 19 participants from 10 countries worldwide (Belgium, the Czech Republic, Denmark, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden, the United Kingdom, and the United States of America) online for the first part of the workshop on Muscle imaging in idiopathic inflammatory myopathies, a virtual meeting on January 15, 16 and 22, 2021.

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of diseases that can affect the skeletal muscles, skin, lungs, joints, and heart. IIM are currently classified as dermatomyositis (DM), nonspecific/overlap myositis (NSM/OM), immune-mediated necrotising myopathy (IMNM), anti-synthetase-associated myositis (ASyS), and inclusion body myositis (IBM) [1–3]. Polymyositis is a disputed entity and may constitute cases of ASyS, IMNM and OM [4]. These entities have similarities but may also differ considerably in clinical symptomatology, autoantibody presence,

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response to therapy and outcome. Diagnosis is established based on clinical manifestations and ancillary investigations, i.e. serum creatine kinase (CK) activity, assessment of myositis-specific (MSAs) or -associated autoantibodies (MAAs), electromyography (EMG) by some, muscle imaging and morphological analysis of a skeletal muscle biopsy. Muscle imaging can be applied in numerous ways. First, magnetic resonance imaging (MRI) may demonstrate disease activity, i.e. muscle oedema, and disease damage, i.e. replacement of muscle by fatty tissue, muscle atrophy or both. Second, MRI-guided muscle biopsy targeting signs of inflammation increases the diagnostic yield, especially its specificity [5]. Third, MRI patterns of involvement may be helpful in establishing a diagnosis of IIM. Fourth, MRI may be considered a biomarker to monitor the course of the disease in response to therapeutic interventions or during clinical trials [6]. There are also other imaging modalities such as ultrasound (US), positron emission tomography -computer tomography (PET-CT), single-photon emission computer tomography (SPECT), etc. which may be used for diagnostic and monitoring (e.g. ultrasound) purposes in IIMs.

Dysphagia frequently occurs in all IIMs subtypes, but there is no consensus on the most appropriate imaging modality. Finally, cardiac MRI (CMR) might be considered as a potentially viable diagnostic tool to evaluate the possibility of silent myocardial inflammation in IIM patients with normal routine noninvasive evaluation [7].

To date, muscle imaging has not yet found a firm place in the diagnostic armentarium for various reasons. First and foremost, there is a lack of a universally accepted and validated imaging protocol and scoring system for evaluation of muscle MRI findings [8]. Large variability of design and differences in patient populations in previous studies make comparisons difficult [8,9].

Here we propose to reach consensus on the applicability of muscle imaging for diagnosis and as a biomarker for disease activity and muscle damage. The workshop participants also discussed the applicability of muscle imaging in the evaluation of swallowing impairment and cardiac complications of IIM. To this end, the following goals were addressed:

- Consensus about a standardized protocol for the evaluation of skeletal muscle images in various types of IIMs.
- Consensus about the exact parameters, anatomical localizations and MRI/MRS techniques.
- Consensus about assessment methods in the different IIM subtypes.
- Consensus about the pattern of muscle involvement in IIM subtypes (IMNM, IBM, DM).
- Consensus about the application of MRI as a biomarker for disease activity and disease damage in follow-up studies and clinical trials.
- Consensus of the place of MRI in the evaluation of swallowing difficulty and cardiac manifestations.

2. Setting the scene - Overview on classification, MRI/MRS protocols and scoring methods

2.1. Overview on various classification systems

Marianne de Visser openened the workshop with an overview on various classification systems: European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria for adult and juvenile IIMs and their major subgroups [10] and a classification system for IIMs based on clinical manifestations and MSAs [11]. Both have their strengths and limitations. The strengths of the former study included a large cohort (n = 976) of patients and comparators from various centres across the world and a large validation cohort (n = 592). The limitations were the following: polymyositis (PM) was included whereas this is probably a very rare disease, and very likely mimics other myositis subtypes such as IBM, IMNM or OM/NSM [4,12–14], a limited number of IMNM and no ASyS patients were included, and only a limited number of MSAs was tested. Strengths of the latter publication were the multicentre design and the use of unsupervised analysis. However, there were also some limitations: four clusters of disease entities were distinguished, not including nonspecific/overlap myositis, and the validation study was limited to 50 individuals.

Recently, two ENMC workshop reports on classification criteria in IMNM and adult DM, respectively, were published [15,16].

In 2017, a retrospective study showed that the presence of finger flexor and quadriceps weakness and of histopathological features (endomysial inflammation, and either invasion of nonnecrotic muscle fibers or rimmed vacuoles were associated with 90% sensitivity and 96% specificity for IBM [17]. A recent review on the use of anti-NT5C1A antibodies as a diagnostic marker showed a moderate sensitivity and a high specificity [18]. As regards ASyS there are no formal classification criteria. A recent publication [19] showed that the presence of specific anti-synthetase autoantibodies may determine presenting clinical manifestations. Anti-Jo1 was predominantly associated with the characteristic triad of arthritis, myositis and interstitial lung disease (ILD). In addition the following disease entities were discussed: OM/NSM which is ill-defined, and associated with connective tissue disorder (MCTD - mixed connective tissue disease, Sjögren syndrome, rheumatoid arthritis, scleroderma) in 20–40% and associated with myositis-associated antibodies in 40–70% [12,13,20], DM sine dermatitis, associated with nuclear matrix protein 2 (NPX-2) [21] and juvenile DM and its association with MSAs [22].

2.2. Overview on MRI/MRS protocols, processing tools and biomarkers

Next **Pierre Carlier**, also on behalf of **Harmen Reyngoudt**, provided an overview on imaging protocols, processing tools and biomarkers for the investigation of IIM.

MRI and magnetic resonance spectroscopy (MRS) acquisition sequences, sequence parameters and processing tools used in IIM are not fundamentally different from those used in muscle diseases in general.

For purely diagnostic purposes, routine qualitative T1 and T2 sequences are still standard. The existence, extent and severity of chronic degenerative changes are evaluated with T1-weighted spin echo sequences. These changes appear as hyperintensities generated by the muscle fatty replacement. Oedema, reflecting inflammatory changes, is detected as hyperintensity in images generated with T2-weighted sequences. These sequences must include a fat saturation module in order to suppress the lipid signal, which also appear bright on T2-weighted images and would be confounding. Fat suppression is most often obtained with a non-selective or a fat selective inversion module, known as Short Tau Inversion Recovery (STIR) or Spectral Attenuated Inversion Recovery (SPAIR). The hyperintensities revealed by the STIR/SPAIR T2-weighted sequences identify hypervascularisation, perifascial oedema, intra and/or extra myocytic oedema. A simple but critical quality control of the fat saturation must

be systematically performed by verifying the fat suppression in subcutaneous tissue and bone marrow. The STIR/SPAIR T2-weighted sequences are of particular importance in IIM, revealing sometimes very severe 'inflammatory changes' contrasting with the absence of 'degenerative changes' at the early stages of the disease.

With the qualitative T1- and fat-saturated T2-weighted sequences, the lesions' severity and extent receive a score per individual muscle. Different scales have been proposed (see below, Jiří Vencovský's summary). All are based on a visual inspection and are therefore subjective and reader-dependent.

Very often, imaging is limited to the lower limbs, or even to the thighs because of the frequent proximal involvement in IIMs. Whole-body (WB-)MRI can help in several instances, by revealing fatty replacement patterns relatively specific in IBM and IMNM. It can also help in the differential diagnosis of dystrophies such as dysferlinopathy or anoctaminopathy, sometimes initially considered and treated as IIM.

Imaging may have an important role to play in the monitoring of disease progression and in the evaluation of response to therapy of IIMs. For these applications, quantitative evaluation and generation of parametric maps are mandatory. The human eye cannot pick up the relatively subtle differences in contrast that occur over a short observation period. Also, the contrast of qualitative sequences can vary with small changes in the acquisition parameters and hamper comparisons. In quantitative imaging, the fatty replacement in muscle is determined with water-fat imaging sequences, which separate and measure the water and fat components. The Dixon sequences, named after the inventor, use the differences in resonance frequencies between the water and lipid resonances to generate water images and fat images. The two are easily combined to create fat fraction maps, which strictly speaking represent the fraction of the detected MRI signal arising from the lipids. The intramuscular fat fraction can be considered biomarker of the 'chronic degenerative changes' and is increasingly being used as an outcome measure in clinical studies. In longitudinal studies, the fat fraction increase is a measure of the disease progression. The muscle fatty replacement rate, which normalizes the fat fraction increase to the remaining muscle, is less frequently calculated, but gives a more exact estimate of the disease severity.

The Dixon sequences have evolved into a large family with many different options for both the acquisition and the processing. Great care must be taken when comparing fat fractions determined with different Dixon variants or even with simply different acquisition parameters. In multicentre studies, calibration phantoms or even volunteers travelling from site to site are important to ensure comparability of data acquired on different platforms, particularly when confrontation with other outcome measures is planned. Recommended Dixon options are: 3-point sequence, 3D gradient echo acquisition, proton density weighting, millimetric in-plane resolution, offline reconstruction using a fixed multipeak lipid model when available. Another option is the multi echo gradient acquisition proposed as an option by the main vendors. The multi echo time (TE) imposes longer acquisition times but the multipeak reconstruction is included in the optional package.

Water T2 maps quantify muscle oedema, whatever its origin is: extracellular, intracellular, related to inflammation, necrosis, dystrophy, etc. It is the quantitative equivalent of the STIR/SPAIR T2-weighted hyperintensities. While non-specific, the increase in water T2 reflects the intensity of the underlying mechanisms. This is why it is interpreted as a biomarker of disease activity. Muscle water T2 can be as high as 50 ms (+15 ms compared to normal condition) in untreated IIM, values that are very seldom seen in other conditions. Water T2 maps allow for non-invasive monitoring of the inflamed muscle response to treatment. To the contrary, global T2 maps, obtained by fitting a single exponential to the signal decay, combine water and fat contributions. When muscles are moderately to severely fatty replaced, muscle global T2 values are driven by the long T2 of fat, reflect the muscle fat fraction and largely duplicate the Dixon sequences. Readers should always identify the kind of T2 maps and values that are presented in publications; their meaning are very different [23].

The evaluation of muscle trophicity is another benefit of a quantitative imaging approach, resulting in the assessment of parameters such as cross-sectional area and contractile cross-sectional area (which is defined as lean muscle cross-sectional area corresponding to the muscle volume fraction containing the contractile apparatus). Most imaging sequences can be used to that end but the out-of-phase images of the Dixon raw acquisitions are very often preferred. No additional acquisition is indeed required if the fat fraction is to be determined, which is systematically the case in quantitative imaging protocols. The muscle contours are better visualized than with any other sequence, which helps the muscle segmentation task whether it is performed manually or automatically. Until very recently, only the manual drawing was giving reliable results in the hands of experienced operators. It was a long and tedious process, limiting the clinical applicability of quantitative imaging. The automatic muscle segmentation software were performing poorly. The introduction of artificial intelligence based segmentation algorithms has revolutionized the field and excellent and very promising results have been reported by several groups [24].

Technically speaking, the sequence required for water T2 determination is standard. It is the multi spin echo sequence and can be implemented almost everywhere. However, the extraction of the water component from the global signal decay requires specific software, not provided by MRI scanner vendors. Several freeware options are available for the processing of water T2 maps. Another possibility is to measure the water T2 in selected muscle areas using single voxel proton MRS. It is considered as the gold standard method but it is not an imaging method and gives one localized measurement per acquisition.

Sequences that would provide simultaneously the water-fat composition and the water T2 measurement would be a significant progress. They would shorten the examination time and would help to accommodate more patients in tight scanner schedules. Such sequences exist with, first, the multi spin echo sequence. The process to determine the water T2 separates the lipids and water components of the MRI signal and fat fraction maps can be generated at the same time. Second, the main manufacturers are now also proposing a fast (turbo) spin echo sequence that includes a Dixon module. These sequences are heavily T2-weighted. Hence, when they are processed, they generate both T2-weighted water images, very similar to a STIR/SPAIR T2-weighted scan, and T2-weighted fat fraction maps. These sequences are increasingly being used, largely because the processing software is included in the option. This is really an advantage in clinical routine. However, one should keep in mind that water T2 is not quantified and the fat fraction maps overestimate the fat component because of the T2-weighting of the sequence.

The use of different imaging protocols for diagnostic purpose and for disease monitoring can be counterproductive. It hampers a rigorous evaluation of disease progression in a patient who initially underwent just qualitative diagnostic imaging. Quantitative Dixon imaging is now largely available and the qualitative information, in particular the identification of patterns of fatty replacement, can be easily derived from fat fraction maps. For these reasons, a

recommendation to systematically use Dixon sequences for muscle diagnosis was issued at a recent ENMC meeting on muscle imaging [25].

Gadolinium contrast agent injection coupled to T1-weighted imaging sequences has been regularly used in the context of IIM in the past but is less popular nowadays. Enhancement patterns distinguish the inflammation related hypervascularization predominantly at acute stages from more chronic muscle damage and fibrosis. Additionally, necrotic areas are detected.

There have been safety issues related to gadolinium contrast agent stability and gadolinium retention and toxicity in tissues. Also, while minimally invasive, the need of an intravenous injection can be seen as a drawback, but it is more the significant lengthening of the examination that is problematic. To record all the information that the gadolinium contrast agent can reveal, the dynamics of the muscle signal enhancement must indeed be recorded during at least 15 min. Despite this time penalty, gadolinium contrast injection can reveal useful information on disease pathology and pathophysiology.

Other types of MRI/MRS sequences are available to investigate IIMs. Muscle functional imaging measures diffusion, perfusion, oxygenation, etc. Proton and phosphorus MRS identifies and quantifies a number of metabolites involved in the lipid and energy metabolism. While they can provide new insights into pathogenic mechanisms and also responses to intervention, they have been applied in a few clinical research studies so far.

The actual choice of the imaging protocol for IIM patients will be guided by the study objective. It will be different for a diagnostic reassessment or for the evaluation of therapeutic response. It will also be guided by practical and technical considerations, such as the MRI scanner availability, the sequences and options present in the scanner, the expertise of the imaging team and the access to dedicated processing tools.

2.3. Overview on MRI scoring methods

Jiří Vencovský, also on behalf of **Kateřina Kubínová**, gave an overview on MRI scoring methods in order to evaluate the degree of muscle disease activity, muscle damage, disease progression over time and effect of treatment [8]. None of the scoring systems developed so far has been universally accepted. Semiquantitative scorings include numerically defined grades that span from simple (yes/no) to complex grading. A significant variability in muscle areas selected for assessment exists, ranging from all the muscles available on the image taken together (global muscle segment) to a choice of individual muscles. Several muscles are frequently classified together as one muscle group, e.g. the thighs composed of the quadriceps, hamstrings, and adductors. Scores include extent of oedema or its intensity or both. One study assessed distribution of oedema in muscle (diffuse, patchy, peripheral) and patterns of signal (honeycomb, foggy, strong high signal intensity) [26]. In most of the studies the scoring has been performed by two experienced experts and the agreement between the two is considered as final result. Several different semiquantitative methods have been used for assessment of oedema and replacement of muscle by fat, ranging from simple assessment (present/absent) [27] to more sophisticated approaches scoring oedema and replacement of muscle by fat on a five-point scale [28]. Extent and intensity of oedema and replacement of muscle by fat can also be evaluated with a 4-grade and 3-grade scale, respectively [29].

Semiquantitative scorings often correlate with traditional parameters of disease activity, albeit cases with no significant agreement for improvement between any of the MRI metrics and the IMACS Definition of Improvement were seen [30]. This may suggest that MRI contributes added information to the traditional multidimensional assessment of outcomes in patients with IIM. Most recently, quantitative measurement of muscle inflammation and fat fraction have been introduced. Some studies show significant correlations with semiquantitative measurements; however, some show higher sensitivity of quantitative MRI [31]. In patients who had been classified as unaffected using semiquantitative scoring, quantitative T2 measurements were still higher than those obtained in age- and gender-matched healthy controls [32]. In IBM, MRI showed a proximal-to-distal gradient replacement of muscle by fat. The magnitude of the whole muscle fat fraction in the thighs correlated negatively with clinical functional score and muscle strength. A Z-score was calculated as mean pixel intensity (MPI) obtained from healthy controls and this was deducted from MPI of patients and divided by standard deviation from the controls. This approach enables calculation of continuous Z-score or division into categories – normal, moderate or severe muscle replacement by fat. In another study, different segmentation approaches were used to draw regions of interest (ROIs) in individual muscles, muscle groups, and the global muscle segment [33]. Global muscle segment fat fraction has shown very good sensitivity to change in the lower legs and thighs in several neuromuscular diseases including IIMs. The global muscle segment approach has several advantages – it is faster and simpler than drawing ROIs, and in the later stages of muscle fat replacement, it may be the only option because boundaries of individual muscles may not be recognizable. Finally, any efforts to provide recommendations for a standard scoring system need to take into account previous experience and aim for a simple, reproducible and comparable method.

3. Pattern recognition

A general overview of the patterns in different forms of myositis using qualitative MRI (T1-weighted, T2-weighted) is shown in Table 1.

3.1. Anti-SRP and anti-HMGCR immunemediated necrotizing myopathy

On January 16, 2021, **Andrew Mammen** and **Jemima Albayda** presented the patterns of involvement and the differences between anti-signal recognition particle (SRP) and anti-3–hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) immunemediated necrotizing myopathy. There were only three MRI studies that compared IMNM with other types of myositis. The largest was a cohort that looked at 666 subjects and had a standard protocol looking at bilateral thighs and used a 0–3 scale for oedema, muscle replacement by fat, atrophy and fascial oedema [27]. Another study had 76 subjects and imaged mostly the whole lower limb with a

Table 1
MRI patterns in myositis subtypes.

Specific MRI patterns	Oedema	Atrophy, fatty replacement	Fascial oedema	Other signs
Antisynthetase syndrome	- Predominantly anterior compartment of the thighs [29]	- Predominantly posterior compartment of the thighs [29]	- Frequent [34] - Equal in all thigh compartments [29]	
Overlap myositis	- Predominantly in the gluteal and thigh muscles [35]	- Not known	- Not known	
IMNM	- proximal thigh muscles affected - vastus lateralis with relative sparing of the vastus intermedius [36]; thigh adductors – esp. adductor brevis [27,37] involvement of paraspinal muscles and m. rectus abdominis [36] **- Anti-SRP**: vastus lateralis most affected with relative sparing of vastus intermedius, rectus femoris, biceps femoris, adductor magnus [15] - **Anti-HMGCR**: more symmetrical involvement than anti-SRP [27]); predominantly anterior thigh compartments [38] and medial comp. esp. adductors [39]; lower leg - medial gastrocnemius, arm - triceps and deltoid	- Mostly in the lateral hip rotators, glutei, medial and posterior thigh compartment, esp. obturator externus [27,37] + lumbar extensors and m. subscapularis [40] - **Anti-SRP**: predominantly affected: adductor magnus, gluteus maximus, biceps femoris long head, semimembranosus and semitendinosus; the least affected m. quadriceps femoris [15] -**anti-HMGCR**: posterior and medial thigh compartments [38]	- Infrequent	
DM	- Symmetrical - Focal and patchy oedema - Frequent involvement of quadriceps femoris [37], gluteal muscles [35]	- Symmetrical involvement of the pelvic and shoulder girdle muscles [41] - Milder than in polymyositis [42] - Honeycomb pattern (reticular appearance) [26]	- More asymmetrical - More prevalent in the anterior (esp. rectus femoris), medial compartment and surrounding m. semimembranosus [27,43]	- Subcutaneous soft tissue oedema [41]
JDM	- Symmetrical - Adductors, quadriceps and gluteus more involved [44] and axial muscles – neck, paraspinal and abdominal muscles [45]	- Atrophy of quadriceps, especially vastus medialis [46] - Pattern similar to oedema	- Frequent [44,47] - On WB-MRI fascial oedema limited to the limbs [45]	- Subcutaneous involvement: calcinosis and panniculitis [47,48]
IBM	- Asymmetric involvement and distal predominance - Anterior thigh compartment involvement [27], esp. distal quadriceps muscle [49,50] and sartorius; lower leg: gastrocnemius medialis [49]	- Predominantly forearm (esp. flexor digitorum profundus) and anterior compartment of the thigh - Involvement of m. quadriceps with relative sparing of rectus femoris [51–53] associated with atrophy resulting in a “melted appearance” - Lower leg: esp. medial gastrocnemius [40,49,51]	- No oedema	- “Undulating fascia sign” – fascia drawing a line between atrophic vastus intermedius and vastus lateralis [50]
PM*	- Symmetrical - Diffuse, homogeneous oedema - Both anterior and posterior muscle groups of thighs, esp. vastus lateralis [42,50]	- More prevalent in anterior thigh compartment [42]	- Fascial oedema of rectus femoris uncommon [27]	

ASyS – 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, PM – polymyositis; WB-MRI – whole-body magnetic resonance imaging; IBM – inclusion body myositis; IIM – idiopathic inflammatory myopathy.
PM* The existence of polymyositis is disputed. Many patients diagnosed in the past as polymyositis would nowadays receive a different diagnosis (e.g. ASyS, IMNM, overlap syndrome, non-specific myositis, or IBM).

0–3 scale for 0edema and muscle replacement by fat [37]. A third study compared qualitative scores of WB-MRI data between IMNM (n = 42) and IBM (n = 60) [40]. The remaining studies were case series of anti-HMGCR- [38,39] and anti-SRP-positive patients [28,54].

IMNM had a higher proportion of oedema, atrophy and muscle fat replacement as compared to dermatomyositis (DM) or polymyositis (PM) [27]. Atrophy and muscle replacement by fat were noted preferentially in the lateral rotators and gluteal groups, medial and posterior compartments. When looking at individual muscle groups and MRI features that most uniquely associated with IMNM, this study found that adductor brevis oedema and obturator externus atrophy were more common in IMNM. Muscle fat replacement was also noted to occur early in the disease course. Similar findings were seen in another study [37]. In those patients that had available serial imaging, they found that total atrophy and fat replacement scores reduced over time in a number of patients that had available serial imaging, suggesting some reversibility to these processes. Using WB-MRI, the most severely affected muscle groups in IMNM were located in the pelvifemoral muscle groups, as well as the lumbar and shoulder regions. There was more severe involvement of the gluteus maximus and the adductor magnus in seropositive IMNM [40]. In a study with mostly statin naïve anti-HMGCR-positive myositis, oedema was found to be diffuse and more likely to affect the anterior compartments [38]. Muscle fat replacement was moderate or severe in most, and seen more predominantly in the posterior and medial compartments. In younger statin naïve HMGCR, the severity of muscle fat replacement and atrophy resembled a limb girdle muscular dystrophy. In contrast, a small study of HMGCR myositis patients who were statin exposed showed that the most affected muscle groups by oedema were the adductors in the thighs, the medial gastrocnemius for the leg, and triceps and deltoid for the arm [39]. Post-treatment MRIs showed complete resolution of oedema but largely unchanged scores for muscle replacement by fat. For SRP myositis, an MRI study found that the most severely affected muscles in the thighs for oedema were the rectus, vastus lateralis and adductors, with relative sparing of the vastus intermedius [28]. For muscle fat replacement, the most severely affected muscles were the adductors and hamstrings. Three patterns have also been described in another qualitative study for SRP: 1) nearly normal MRI, 2) focal muscle fat replacement and diffuse oedema in quadriceps and biceps femoris, and 3) severe muscle fat replacement and atrophy in the posterior compartment and myofascial orientation of oedema and inflammation on axial STIR image [54]. In terms of actual comparisons between SRP and HMGCR, the study by Pinal-Fernandez et al. [27] showed that there was a trend to increased severity of findings with SRP. As for the diagnostic potential of MRI for distinguishing IMNM from other types of myositis, even when using an optimal combination of MRI features, only a 55% positive predictive value was found. Correlating MRI features with clinical parameters, oedema did not perform well. There was no correlation between oedema, disease duration, CK activities or MyoACT scores [28], or with bedside disease activity measures [37]. In contrast, muscle fat replacement correlated better with disease duration [28] and a negative correlation was seen between combined scores for muscle fat replacement and oedema and muscle strength. Disease duration was found to be the most important predictor of muscle damage. For treatment response, no correlation was found between oedema and therapeutic response. However, more severe fat replacement was consistent with poor immunosuppressive agent responses, and there was a significant negative correlation between muscle fat replacement and therapeutic effect [38,28].

In conclusion, MRI demonstrated oedema and replacement of the muscle by fat both in SRP and HMGCR. Fat replacement is pronounced, more so in SRP as compared to HMGCR and it can be found at an early stage. There is no distinctive pattern for IMNM and there was a negative correlation between treatment response and muscle replacement by fat.

3.2. Juvenile dermatomyositis

In the same session, **Lisa Rider** shared the results of muscle MRI and US studies in juvenile DM (JDM). MRI has demonstrated increased spin-echo T2-weighted signal intensity and increased global T2-weighted relaxation times (with T2 values highly biased by the fat tissue) in the thigh and hip girdle muscles of JDM patients with active disease, compared to non-inflammatory myopathy control subjects or a smaller group of JDM patients with inactive disease [44,46]. Signal intensity was found to be highest and more frequently abnormal in the adductors > quadriceps > gluteus >> hamstring muscle groups, with hamstrings similar in signal intensity to control subjects [44,45]. Fifty percent of JDM patients with chronic active disease were found to have increased STIR T2-weighted signal intensity in muscle [47]. Fat-corrected T2 maps (with T2 values highly biased by the fat tissue) of thighs, as a quantitative methodology, also correlate with STIR thigh muscle oedema [30].

Muscle MRI is an important test to assist in the diagnosis of JDM. In the Childhood Arthritis and Rheumatology Research Alliance (CARRA) North American registry, 90% of more than 300 patients obtained an MRI, which was consistent with the diagnosis in 90%. In contrast electromyography (EMG) was performed in only 32% of patients and consistent with diagnosis in 50%, and muscle biopsy was obtained in 50% and consistent with diagnosis in 76% of patients [55]. In the UK JDM Cohort and Biomarker Registry, 68% of patients had a MRI documented at diagnosis, and in 76% the study was abnormal and consistent with a diagnosis of an inflammatory myopathy [56]. Since the workshop was held, a publication [57] found a radiomics and machine learning algorithm using fat suppressed T2 MRI, particularly when combined with clinical and laboratory findings, was sensitive in discriminating JDM from mimicking conditions at diagnosis.

Fascial or perimuscular oedema on thigh MRI is also frequently increased in the thighs more than buttocks, and correlates with muscle oedema. Fascial oedema is uniformly present in newly-diagnosed patients and in 50% of patients with chronically active disease, and is more often present in patients with higher muscle oedema scores [44,47,58]. This myofascial oedema pattern has not been observed in patients with juvenile polymyositis or non-inflammatory myopathies. Increased subcutaneous oedema on STIR T2-weighted thighs has also been observed in MRIs of 30–100% of chronically-active patients with JDM, compared to 25% of patients with juvenile polymyositis, and in 56% of newly diagnosed JDM patients. Subcutaneous oedema is more frequently present in the buttocks than the thighs, and may be independent of muscle oedema, correlating moderately with skin oedema on MRI [44,47,58]. The subcutaneous oedema signal may be a homogeneously increased signal, or it may appear as increased signal intensity interspersed with linear areas of low signal intensity, appearing as reticulation in the subcutaneous fat [44,47].

A study of WB-MRI using a semi-quantitative scoring system has revealed the pattern of muscle involvement in 34 of 41 JDM patients within one year of diagnosis [45]. Proximal muscles most frequently had increased oedema signal (present in 60–70% of patients) compared to distal muscles (63% of patients had oedema in distal legs and 46% in forearms), and the lower extremities were more frequently involved than the upper extremities (70% vs. 40–60%). Axial muscles were frequently involved, including neck, paraspinal and abdominal muscles in 44–61% of JDM patients. In

66% of JDM patients, the STIR T2-weighted signal abnormality was found to be focal and patchy, whereas 17% of patients had diffuse hyperintense, homogeneous STIR T2-weighted signal present in the muscles. Fascial and subcutaneous oedema were present as well, as reported in other studies. Muscle atrophy and fatty replacement of muscle (based on T1-weighted MRI) have been detected in 43% and 29% of JDM patients, respectively, a mean of 16.8 years after diagnosis [59]. The pattern of muscle atrophy is similar to the STIR oedema, with the adductors most frequently affected, followed by quadriceps more than gluteus, and least often affected are the hamstrings. JDM patients also have a lower thigh muscle diameter to total thigh circumference as another potential indicator of thigh muscle atrophy [60], and increased Dixon-based fat fraction that correlates with T1 damage scores of thigh muscles [30]. Other radiographic patterns of involvement on MRI that may be seen in JDM patients include detection of calcinosis in the subcutaneous fat or muscle [47]. Partial and total lipodystrophy also have a pattern of fat loss demonstrable on thigh T1-weighted MRI, with loss of subcutaneous fat anteriorly, laterally, and posteriorly and an increase in the medial relative to lateral fat, with sparing of the medial fat loss in the thigh. In total lipodystrophy, there is also loss of subcutaneous abdominal fat, and an increase in the intra-abdominal fat [61].

Studies of muscle US in a small number of JDM patients have demonstrated increased echogenicity of the tibialis anterior muscle more than biceps brachii or forearm flexors in patients at diagnosis compared to healthy control subjects. There is also a decrease in the muscle thickness, as a measure of muscle atrophy, in proximal muscles, such as biceps brachii and quadriceps, in active JDM patients at diagnosis compared to healthy control subjects. These findings are notably improved when patients enter clinical remission [62,63].

In conclusion, MRI is a helpful aide to support diagnosis in children with myositis and may spare more invasive studies. Muscle oedema, fascial or perimuscular oedema on thigh MRI is frequently present, also in a proportion of patients with chronic disease. Oedema is most frequently seen in proximal muscle, thighs more than arms, but also in distal and axial muscles. Replacement of muscle by fat has a pattern similar to that of oedema. Ultrasound studies have been performed on small JDM cohorts.

3.3. Inclusion body myositis

Next, **Giorgio Tasca** presented the results of a study on the assessment of the accuracy of an MRI pattern identified in the lower limbs of patients with IBM [49]. The pattern showed a “melted” appearance of the distal part of the anterior thigh muscles, accompanied by the hyperintense signal on STIR sequences in the same region, supported by the involvement of gastrocnemius medialis in the leg and relative sparing of the pelvis. The observers were blinded to all other patient data, and this yielded high values of diagnostic accuracy to detect definite IBM: 95% sensitivity in case of recognition of the typical pattern (with 100% specificity) and 97% for both typical and consistent patterns (with 97% specificity). The control group was composed of other inflammatory and hereditary myopathies with clinical or pathological overlap with IBM. After the publication, Tasca and colleages refined the criteria aiming to make them more objective and easily scorable:

3.3.1. Main criteria

1) T1-weighted based muscle fat replacement of both quadriceps muscles in the distal portion (above the knee), particularly involving the vastus intermedius and medialis, or atrophy with a “melted” appearance; 2) Hyperintensities on STIR sequences of the distal quadriceps; 3) The anterior compartment of the thigh more involved than the posterior one in the distal part.

3.3.2. Supporting criteria

1) Sartorius involvement; 2) Gastrocnemius medialis is the most involved muscle in the leg. However, the leg can also be normal; 3) Pelvic muscles are relatively spared compared to the thigh muscles.

Three main and 2 supporting criteria are needed for the diagnosis of IBM. These new criteria proved to be very sensitive in the previously tested cohort and in a new retrospective cohort (unpublished).

In conclusion, lower limb MRI is useful in the diagnostic investigation of IBM.

3.4. Distinction between myositis and other myopathies

Anneke van der Kooi stressed that the diagnosis of myositis can be challenging, and that MRI can be very helpful in addition to a detailed history and examination. She pointed out that fatty degeneration, as observed in SRP- and HMGCR-related myositis can also be found in hereditary myopathies. For different subtypes of hereditary myopathies characteristic patterns of imaging abnormalities have been recognized using machine learning [64], although the reliability of distinction between the different subtypes is debated [65]. In contrast to myositis, most genetic disorders present with a more slowly progressive weakness. A detailed clinical history is therefore of utmost importance to identify the first symptoms and the duration of the disease.

During the 247th ENMC workshop on MRI as a diagnostic tool for rare genetic myopathies standardisation of protocols, development of a muscle MRI imaging databank and intention to increase education and training of key MRI imaging features was discussed [25]. Oedema is the hallmark of acute myositis, but can be seen in numerous neuromuscular disorders, such as rhabdomyolysis, muscle injury, toxic myopathies, diabetic muscle infarction, and a whole spectrum of neurogenic disorders (motor neuron disorders, radiculopathies, plexus involvement), infectious (pyo)myositis, sarcoidosis and active stages of disease progression, the latter in combination with more pronounced muscle fat replacement. The most difficult to distinguish from myositis because they present with symmetric (sub)acute limb girdle weakness are rhabdomyolysis, toxic myopathies and motor predominant chronic inflammatory demyelinating polyneuropathy.

In conclusion, MRI can be very helpful in addition to a detailed history and physical examination to distinguish between myositis and other neuromuscular disorders. Being aware of myositis mimics during MRI interpretation is important: replacement of muscle by fat can be caused by hereditary myopathies and oedema can be seen in a range of diseases in which corticosteroid treatment is not indicated.

4. Muscle imaging as biomarker

4.1. Quantative MRI in inclusion body myositis

Jasper Morrow provided data which assessed the validity, reliability and responsiveness of quantitative muscle MRI in IBM in a natural history study [66]. Finding good outcome measures can be challenging in diseases such as IBM, which cause gradually progressive disability. The three-point Dixon fat-water separation technique was used to quantify chronic fatty atrophy in lower limb muscles which demonstrated significantly increased fat fraction compared with controls and strong correlation with myometric strength and the IBM functional rating scale. Over one year follow-up, significant increases in fat fraction were seen at

thigh and lower leg level with high responsiveness. There was also longitudinal correlation between loss of muscle strength in quadriceps and progression of fatty atrophy on MRI. Intramuscular increase in fat fraction is unlikely to be reversible, however MRI can assess acute muscle changes, often described as oedema, likely reflecting changes in muscle water distribution. In IBM this has been measured by water T2-quantification which was shown to be elevated even in patients without significant muscle fat fraction, and correspond to changes seen on the qualitative STIR T2-weighted sequence. Furthermore, muscles with STIR hyperintensity at baseline show greater progression of muscle fat fraction over the subsequent 12 month period.

In conclusion, quantitative MRI has thus been demonstrated to provide both longitudinally responsive and potentially reversible biomarkers in IBM. Similar techniques could be applied to other IIMs.

Pierre Carlier and **Olivier Benveniste** reported on results of the phase 2b Rapamycin trial in IBM [67]. RAPAMI was a prospective, randomised, controlled, double blind, single centre, proof-of-concept trial. The primary endpoint was relative changes in maximal voluntary quadriceps isometric strength between baseline and 12 months after treatment initiation. Secondary endpoints included changes in strength of other muscle groups (grip, elbow flexion and extension, knee flexion), 6-minute walk distance (6MWD), forced vital capacity (FVC), IBM weakness composite index (IBMWCI), IBM functional rating scale (IBMFRS), Health Assessment Questionnaire (HAQ), analyses of CD8 T cell subpopulations by mass cytometry, and the lower limb muscle fat fraction by quantitative MRI. A total of 44 patients were treated with oral sirolimus ($n = 22$) or placebo ($n = 22$) for 12 months. There was no difference in the primary outcome of relative percentage change from baseline to 12 months of the maximal voluntary isometric knee extension strength. For secondary outcomes, the differences between the groups were not significant except for thigh fat fraction, HAQ, FVC and 6MWD which showed less decline in the sirolimus arm. These encouraging results led to an ongoing phase III trial (NCT04789070).

In conclusion, quantitative MRI is a promising measure in clinical trials on IBM.

4.2. Dual-energy X-ray absorptiometry

Pedro Machado discussed the usefulness of dual-energy X-ray absorptiometry (DEXA) for measurement of fat-free mass percentage. Although this method is more often used to evaluate bone mineral density, it can also be used to estimate total body mass, lean soft tissue mass, bone mineral content, and fat mass. Both regional and whole-body DEXA can be performed [68]. Validation against other measures of muscle mass and demonstration of sensitivity to change/responsiveness has been performed in several neuromuscular diseases [69–73]. DEXA has several advantages, namely having a lower cost and being a quick, widely available and relatively easy to perform procedure, with low level of radiation exposure. However, it may skew the calculation of fat mass because of its method of indirectly calculating fat mass by subtracting lean soft tissue mass and mineral content, which are the elements that DEXA actually measures. Moreover, as opposed to MRI/CT, DEXA is not able to account for anterior and posterior compartments despite its regional compartmentalization capability given that it is a 2-dimensional imaging modality.

Despite no improvement in measures of strength/physical performance, a dose-dependent increase in lean body mass was noted both in the randomized clinical trial (RCT) of bimagrumab in IBM and in the RCT of albuterol in facioscapulohumeral dystrophy (FSHD).

In conclusion, DEXA is a safe, non-invasive, cost-effective, time-efficient measure potentially useful as outcome measure in muscle disease. However, the 2-dimensional nature reduces the potential compared to MRI/CT.

5. Other imaging modalities

5.1. Cardiac MRI, blood oxygenation level dependent (BOLD) MRI, MRS, magnetic resonance elastography

On Friday 22, 2021 **Nicolò Pipitone** demonstrated that in addition to its established role, MRI has also some novel applications. Cardiac MRI (CMR) can demonstrate myocarditis if two of the following signs are present: myocardial oedema (T2) with signal intensity greater than 2 between myocardium and skeletal muscle; capillary leak on early gadolinium-enhanced MRI (signal intensity greater than 4 between myocardium and skeletal muscle); and fibrosis (on late gadolinium-enhanced MRI [74]. However, the role of CMR in clinical practice is as yet not fully established; in particular, there is some evidence that it may be too sensitive by revealing subclinical myocarditis that does not warrant treatment [75].

In active myositis, there is increased diffusion of water molecules within affected muscles, leading to a greater apparent diffusion coefficient (ADC). Therefore, diffusion-weighted MRI which measures random motion of water protons within muscle could potentially be useful to demonstrate disease activity in myositis. However, it is unclear whether diffusion-weighted MRI is superior to oedema- weighted MRI sequences: in fact, in a study MRI STIR T2-weighted sequences were more sensitive than diffusion-weighted sequences for the diagnosis of myositis.

The BOLD MRI signal depends on the oxygen saturation and on the blood flow, and correlates with other techniques for flow measurements, such as plethysmography and laser Doppler flowmetry. Therefore, it may be helpful in diagnosing myositis, however, at the present there is no data on this potential application [76].

MRS has been used to evaluate metabolic changes in various disorders including myopathies. The rationale for the use of MRS in myositis is that the inorganic phosphate (Pi) to phosphocreatine (PCr) ratio is elevated in patients with myopathies due to lower levels of PCr in the patients' muscles and correlates with disease severity. Therefore, MRS may have a role in the early diagnosis of patients with myositis, because bioenergetic defects precede other changes and may persist after resolution of inflammation [77]. On the other hand, the role of MRS remains to established, not least since MRS and conventional MRI are often discordant [78].

Magnetic resonance elastography (MRE) is a technology that combines MRI imaging with low-frequency vibrations to create a visual map (elastogram) that shows stiffness of body tissues. Typically, MRE is used to detect stiffening of the liver e.g. in liver fibrosis. MRE can be used to evaluate muscle stiffness in myositis, where muscle stiffness is decreased in the relaxed state compared to healthy controls. The decreased stiffness is probably due to the destruction of structures of the extracellular matrix like collagen within the affected muscles [79]. It may thus be hypothesized that MRE could be an index of muscle damage in myositis [80].

In conclusion, various MRI and MRS techniques are potentially useful to assess the muscles of patients with myositis, but there is as yet a great unmet need to define their precise role in myositis.

5.2. FDG-PET for cancer screening in myositis

Next, **Georges Demonceau** showed that fluorodeoxyglucose (FDG)-PET, preferably combined with CT or MRI, quantified the glycolytic metabolic shift in the inflamed muscle, thus enabling

robust monitoring of the disease activity [81]. It can also diagnose a wide range of pathologies associated with IIM: myocarditis, interstitial lung disease, arthritis, dermatitis, calcinosis, Sjögren's syndrome and benign and malignant tumors. tumour detection should be performed not only at the time of diagnosis, but also up to 3 years after diagnosis. With a systematic screening, the tumors are more likely to be detected at an early stage, while being of small size and with few or no metastasis [82–84]. In this role, FDG-PET, which is remarkably sensitive in this application, has an essential role to play, even at the cost of false positives, which are relatively easily correctable

Demonceau shared data on the role of nuclear medicine in IIM which has a long history of detection of IIM by conventional nuclear medicine tracers, particularly markers of bone metabolism. Their indications are nevertheless in decline, in favour of 2 types of PET tracers.

IBM is associated with the accumulation of proteins in excess, amyloid and tau protein. Although IBM preferentially affects the forearm flexors and the quadriceps, all muscles appear to be affected, facilitating quantification. Because of its high sensitivity, the largely available tracer, F18-florpetapir, is promising for the detection of this protein accumulation [85], but a multicenter study is needed to validate the indication of F18-florpetapir.

5.3. Ultrasound as a diagnostic tool and as a biomarker for follow-up

Next, **Camiel Verhamme** discussed the usefulness of skeletal muscle US in diagnosis and as a biomarker for follow-up of IIMs [86–88]. Several parameters can be assessed, such as echo intensity (EI), thickness, and distribution of changes which can be focal or homogeneous. EI assessment is qualitative, semi-quantitative or quantitative. Qualitative analysis visually rates EI as normal or abnormal. These visual changes also include a 'shine-through' appearance or 'see-through echogenicity increase' as described for muscle oedema, which is an overall echogenicity change without attenuation of the underlying bone echo. This may be missed by the semi-quantitative analysis, and/or focal changes in echotexture. Semi-quantitative analysis rates EI using the 4-point Heckmatt grading scale. Quantitative analysis measures the mean EI of standardized predefined muscle ROIs which are compared to muscle-specific reference values from a healthy control population, so that Z-scores can be calculated.

Few, and relatively small, studies exist in adult IIM, excluding IBM. In the acute phase an increase in semiquantitive EI was shown [89,90] which is presumed to be related to inflammation with accompanying oedema. In the chronic phase more pronounced increase in echogenicity may appear supposed to reflect fat replacement and fibrosis, which cannot be distinguished on US. Changes may be (partially) reversible with treatment [89]. Likewise, only few, and relatively small, studies exist on US in juvenile DM (Habers et al., 2015). [91]. Quantitative EI was only slightly increased at baseline, was further increased at three months, but afterwards decreased over time during treatment [63,91]. In a cross-sectional study in patients at varying stages of treatment, quantitative EI was increased [91].

Fascial thickening and increased Doppler signal in fascia indicating fasciitis have been detected [62,92]. Skin and subcutaneous inflammation and calcinosis are detetectable, but systematic studies are lacking. In IBM, US may be helpful to show patterns of (asymmetric) muscle involvement with selective involvement of flexor digitorum profundus, gastrocnemius, quadriceps. Affected muscles may show markedly increased echogenicity, a moth-eaten appearance and decreased muscle thickness, which is more pronounced with longer duration of disease [87,93,94].

Several other techniques have been developed based on US, such as vascularity and blood flow with Doppler and contrast enhanced ultrasonography [95], tissue stiffness - elastography – shear wave [96,97], advanced texture analysis [98,89], amongst others with machine learning [99]. Although these techniques are promising, they have as yet not been implemented in clinic. Studies comparing the feasibility of muscle US as compared to MRI for diagnostic purposes are scarce [32,95,90]. The latter study found that whole body MRI was more sensitive than US to detect muscle abnormalities compatible with IIM. Semi-quantitative US and qualitative US detected abnormalities in the majority of patients while evaluating fewer muscles as compared to MRI. One study compared both techniques during follow-up: after nine weeks of treatment with IVIg monotherapy US showed change over time, while MRI did not show significant change over this relatively short time period [90].

In conclusion, advantages of muscle US comprise that there are no contraindications, that it is widely available in clinical setting, applicable in children and has relatively low costs, while it may show a detailed view of muscle architecture, fascia and subcutis, and enables quantitative analyses. Muscle biopsies can be done US guided. Disadvantages are that the technique is partially machine-dependent and operator-dependent. As compared to WB-MRI, the number of muscles that can be assessed is smaller, mainly depending on time constraints. An important limitation is that currently it is difficult to assess and quantify oedema.

6. Correlation between imaging and other assessment methods of muscle involvement

6.1. Correlation between MRI and muscle strength in adult myositis

Yves Allenbach pointed out that analysis of the correlation between muscle MRI observations and strength measurements is important as regards monitoring of myositis muscle activity on MRI. The currently published data suggest that the results of muscle MRI are indeed correlated with muscle strength during myositis [100]. Semi-quantitative analyses of muscle water T2 signals are mildly correlated with semi-quantitative muscle strength measurements (MMT score) as well as serum CK activity in patients with chronic ASyS [29]. On the other hand, quantitative analysis of the water T2 signal and of muscle strength yields a better correlation [101]. Concerning muscle damage, semiquantitative MRI assessment of fat replacement was shown to be correlated with semiquantitative measurement of muscle strength [29]. Quantitative cross-sectional area and fat fraction measurements of the quadriceps are strongly correlated with knee extension torque in IBM [66].

Together these data suggest that muscle MRI is a promising tool to monitor both disease activity and muscle damage in myositis patients.

6.2. Correlation between muscle imaging and muscle strength/function in juvenile dermatomyositis

Lisa Rider showed that thigh MRI fat-saturated T2-weighted signal intensity is significantly increased in JDM patients with active compared to inactive disease, and significantly lower after therapy [44]. In patients with active disease the fat saturated T2-weighted signal intensity on thigh MRI correlates strongly with muscle strength assessed by MMT, including gluteus, adductors and quadriceps (r_s = 0.8 – 0.90) [44]. In patients with moderately active disease, there is also a moderate correlation of thigh MRI T2 relaxation times with Physician Global Activity, which is stronger than the correlation with muscle strength and physical function assessed by the Childhood Health Assessment Questionnaire

(CHAQ) [46]. Using T2 or fat-corrected T2 quantitative thigh MRI imaging of JDM and adult DM/PM patients, T2- and fat-corrected T2 maps correlated moderately with disease activity measures, including Physician Global Activity, Childhood Myositis Assessment Scale (CMAS), CHAQ, serum creatine kinase (CK) and aldolase activity, and the muscle component of the Myositis Disease Activity Assessment Tool [30]. Generally, correlations were slightly lower with the mapped T2 values compared to semiquantitative STIR muscle scores. T1 semiquantitative scores and T1 fat fraction maps of thigh muscle MRI correlated strongly with muscle damage assessed by the Myositis Damage Index and moderately with Physician Global Damage and with muscle strength. Fat fraction scores were comparable in their correlations with the semi-quantitative scores.

Muscle oedema correlates moderately with Physician Global Activity and serum lactate dehydrogenase levels, greater than the degree of correlation with CMAS, whereas skin and subcutaneous MRI oedema, as determined by MRI, correlate moderately to strongly with serum aldolase levels. Skin MRI oedema correlates with skin global activity, while fascial oedema correlates moderately with aldolase and inversely with serum CK activity [47,58]. Subcutaneous oedema on thigh MRI also has predictive validity, in that the presence of subcutaneous oedema at diagnosis has been associated with a chronic illness course [102], and oedema in this tissue compartment has been documented to predate the development of calcinosis [47].

A study of WB-MRI using a semi-quantitative scoring system of 42 muscle groups in 41 patients with JDM revealed a strong correlation of muscle oedema with muscle strength and functional measures, as well as with Physician Global Activity and the Disease Activity Score, and moderate correlation with serum muscle enzymes [45]. Subcutaneous and myofascial oedema correlates moderately with Physician Global Activity, the cutaneous component of the Disease Activity Score, and with function assessed by the CHAQ [45]. WB-MRI has good discriminant validity, in that JDM patients with higher STIR T2-weighted muscle oedema scores had active disease, and those with inactive disease by the pediatric Rheumatology International Trials Organisation (PRINTO) criteria and control subjects had significantly lower scores. WB-MRI muscle oedema scores were also sensitive to change, with a high standardized response mean (SRM) of 1.56, in contrast to a moderate responsiveness for clinical measures such as the CMAS (with SRM of 0.56). Nine patients also resolved their muscle oedema, and 5 of these met the PRINTO criteria for clinically inactive disease [45].

In conclusion, in active JDM more than inactive disease there is correlation between various MRI measurements and muscle strength or other disease activity measures.

6.3. Correlation between MRI and muscle histology

Werner Stenzel and **Corinna Preusse** showed selected cases of IIMs and genetic mimickers, focusing on the detailed histological features and comparing them with MRI features that were analysed at time of biopsy from the very same ‘cases’. While the broad alterations of the epimysium and the fascia as well as the perimysium and the endomysium are described by signal increase on T2 as well as T1 fat replacement, the more detailed alterations cannot be visualised [26,103]. Conversely the MRI exam has the major advantage that it allows for visualization of the whole muscle bulk of any given extremity and even of the whole body allowing for description of patterns of involvement in different diseases, and longitudinally, as the disease progresses. However, repeat biopsies are usually not performed.

In two cases of acute and subacute DM as well as one case of a DM relapse at adulthood after start of the disease in childhood, different degrees of fatty tissue on T1 weighted images as well as oedematous signal enhancement on fat saturated T2 weighted images were found (personal observation). In addition, the asymmetry of the process and the relative sparing of adductor as well as ischiocrural muscles were highlighted on MRI. This was compared to a patient who was treated for HIV-related IBM during 12 years with IVIg every 5 months and who was clinically relatively stable during that time with a sudden decline of muscle force and severe atrophy developing over some months after 12 years prompting a second biopsy (personal observation). The biopsy showed that the inflammation was well treated with barely any Major Histocompatibility Complex (MHC) class I and -II positivity of fibres left and very little inflammatory infiltrates. However, the degenerative features continued to worsen with many muscle fibres being replaced by fat as well as severely atrophic fibres and many fibres showing mitochondrial damage with loss of cytochrome-C oxidase (COX).

Of note, there are many relevant inflammatory myopathy mimickers, exemplified by the case of a child with genetically confirmed dysferlinopathy and juvenile arthritis showing the typical alterations of the caput mediale of the gastrocnemius muscles initially without signs of active inflammation and a repeat MRI showing severe atrophy of these muscle regions. However, the morphological phenotype was severely inflammatory with myofibre necrosis, endomysial lymphocytic infiltrates, prominent MHC class I positivity of the sarcolemma and very prominent complement deposition on the sarcolemma as well, while dysferlin protein was entirely absent from the sarcolemma (personal observation). Another mimicker may be lipid myopathies such as Riboflavin-responsive Lipid Myopathy (MADD), where also numerous pre-necrotic and necrotic myofibres can occur and macrophage infiltrates as well as some degree of MHC class I stain could point to a necrotizing myopathy of immune origin. However, MRI revealed no signs of oedema or inflammation and a conspicuous involvement of the posterior thigh compartment while the anterior compartment was relatively spared [104]. Finally, two examples of a predominant epimysial or fascia-predominant inflammatory skeletal muscle disease were shown. Those comprised Shulman syndrome, where the fascia rather than the muscle is strongly hyperintense on T1-weighted images (personal observation). Also, a myofascial involvement of immune checkpoint inhibitor myositis was shown: a contrast-enhanced MRI of the lower legs showing nearly symmetric epi– and perifascial fluid collections in all compartments, in particular around the gastrocnemius muscle. Corresponding endomysial signal enhancement in adjacent muscles was considered a sign of accompanying myositis. Histopathologically this was translated in prominent inflammatory infiltrates in the endomysial muscle compartment as well as in the fascia (personal observation).

7. Evaluation of extramuscular activity by imaging

7.1. Evaluation of swallowing impairment in inclusion body myositis

In this last session, **Jens Schmidt** highlighted that dysphagia is present in about two-thirds of the IBM patients and leads to a reduced quality of life. Risk of aspiration and malnutrition, death by aspiration pneumonia is increased in IBM. Dysphagia is often overlooked by patients and caregivers since swallowing difficulties may go unnoticed because of the slow progression of the disease or since dysphagia may not be perceived as disease-related but attributed to ageing. The standard imaging techniques to evaluate swallowing include flexible endoscopic evaluation of swallowing (FEES) and videofluoroscopy (barium swallow assessed by X-ray). Research-based techniques include real-time MRI with pineapple juice as contrast agent that contains natural manganese,

ultrasound and manometry. Standardised assessments are lacking so far. Parameters for detailed analysis of swallowing times in real-time MRI include oral transport time (OTT), pharyngeal constriction time (PCT), pharyngeal transport time (PTT) and oeseophageal opening time (EOT). Significant differences in OTT and PTT were found in a comparative analysis between healthy controls and IBM patients [105]. In addition, in the latter a functional stenosis ('cricopharyngeal bar') was found which is higly specific for IBM and considered a risk factor for acquiring aspiration-associated pneumonia [106,107].

In conclusion, there are different techniques which may be used to evaluate swallowing difficulty in IBM. Real-time MRI may be a promising tool for future assessment of swallowing, particularly in longitudinal analysis in clinical trials, but has not yet been implemented as a routine examination in daily clinic.

7.2. Evaluation of myocarditis in adult myositis

Louise Diederichsen reported that there is an increased mortality of 75% in IIMs compared to the general population [108]. Cardiovascular diseases account for up to 55% of death in IIMs, which makes cardiac evaluation fundamental. Different cardiac imaging techniques exist including echocardiography (ECHO), CMR and nuclear imaging modalities as cardiac SPECT-CT and PET-CT [109]. In daily clinical practice, heart function is assessed by two-dimensional ECHO and Tissue Doppler Imaging. Three-dimensional speckle-tracking ECHO is a more recent development, which is however as yet not a routine tool in the clinical arena [110]. While many studies assess the left ventricular systolic function ECHO lacks the ability to detect finer structural changes within the myocardium.

The gold standard for detecting myocardial inflammation and fibrosis has been endomyocardial biopsy. However, CMR can assess morphological abnormalities including tissue characterization of the peri– and myocardium and as well as functional abnormalities [109]. The International Consensus Group on CMR Diagnosis of Myocarditis - founded in 2006 to achieve consensus amongst CMR experts and develop recommendations on the current state-of-the-art use of CMR for myocarditis – established diagnostic CMR criteria for myocarditis in 2009, the Lake Louise Criteria [74]. Myocardial oedema and fibrosis are visualised by conventional CMR including gadolinium-enhanced T1-weighted images and T2-weighted images.

The prevalence of myocarditis in IIMs is largely unknown. Clinical overt myocarditis is probably rare. Only few IIM case reports with clinical myocarditis – visualized by CMR – have been reported. However, non-controlled case series have reported subclinical myocarditis in up to 75% of IIM patients, detected by late gadolinium enhancement [111–113]. The lack of control groups and of CMR standardized reference intervals should be taken into account for interpretation of these findings. A case-control study could not confirm a significant difference in CMR T2-weighted images between newly diagnosed IIM patients and healthy controls [114].

Since 2009, even more sensitive CMR mapping techniques have been developed, which detect inflammation and fibrosis by quantifying myocardial relaxation times; T1 mapping/extracellular volume (ECV) and T2 mapping [101]. T1- and T2-mapping techniques have now been included in the updated Lake Louise Criteria from 2018 [115]. All subsequent CMR studies using these mapping techniques have found abnormalities in IIM patients, including subclinical cardiac disease. In several Asian case series of IIM patients with preserved systolic heart function without cardiovascular (CV) symptoms, higher T1 mapping values were found in IIM patients vs. healthy controls [116–119]. Recently, Xu et al. showed significant reduction in abnormal myocardial T1 and T2 values of IIM patients at CMR follow-up after one year of immunosuppressive treatment [120]. A multimodality screening algorithm for myocarditis – including Troponins and CMR – has recently been suggested in newly diagnosed patients with IIM, however standardized screening strategies are still lacking from this patient group [121].

Few studies of cardiac SPECT-CT or PET-CT in IIM exist. Increased cardiac tracer uptake was detected in 57% of IIM patients, which correlated with inflammation in myocardial biopsy [122]. In another study, the increased cardiac tracer uptake in patients with IIM correlated with heart function [123]. Additionally, biopsy proven myocarditis was revealed by CMR and by cardiac PET-CT in a recent case report [124].

In conclusion, CMR is the preferred non-invasive imaging modality to diagnose overt myocarditis. New CMR sensitive mapping techniques might detect and monitor subclinical myocarditis in IIM. Recently, IIM-associated myocarditis has casuistically been detected by cardiac PET-CT. Taken together, these findings might point to fused cardiac PET/MR imaging as a promising technique in the future. The prognostic value of CMR and cardiac PET-CT in IIM has yet to be proven.

8. General discussion & recommendations

During the second part of the workshop on September 9–10, 2022 we aimed to achieve consensus on the topics that were formulated at the beginning of the first workshop and which were discussed extensively: a standardized protocol for the evaluation of skeletal muscle images in various types of IIMs; the exact parameters, anatomical localizations and MRI/MRS techniques; assessment methods in the different IIM subtypes; the pattern of muscle involvement in IIM subtypes; the application of MRI as a biomarker for disease activity and disease damage in follow-up studies and clinical trials, and the place of MRI in the evaluation of swallowing difficulty and cardiac manifestations.

In order to facilitate the discussion prior to this workshop a questionnaire was distributed amongst the 12 physicians attending the workshop. The following recommendations were formulated:

8.1. When is imaging needed? For diagnostic imaging

8.1.1. Recommendations

In patients with suspected IIM, muscle imaging is highly recommended to be part of the initial diagnostic workup and baseline assessment

- To aid in the diagnosis of IIM distinguishing IIM mimics such as muscular dystrophy e.g., dysferlinopathy, anoctaminopathy and FSHD
- It may be useful to distinguish subtypes, especially IBM
- To target muscle biopsy if performed to maximise yield
- As a baseline evaluation of disease activity and severity
- To aid patient understanding of the disease: visualisation of distribution and severity of muscle involvement

MRI is the preferred imaging modality due to its sensitivity to both oedema and fat accumulation, wide anatomically coverage, and widespread availability. Other modalities, in particular US may be used in specific clinical circumstances such as for suspected IBM where both the increase in echointensity and involvement of specific muscles (forearm flexors, quadriceps) is useful. Otherwise, it may be considered if with contraindications to MRI - depending on local expertise. US requires a highly experienced examiner and is still an area of active research.

8.1.2. Research agenda

Prospective large international cohorts of well phenotyped patients using current disease classification, with more extensive anatomical coverage and standardized protocols.

- To answer questions as to the usefulness of baseline scan to predict final diagnosis, prognosis and treatment response
- To create large cohorts of patients to fully describe the spectrum of imaging findings in IIM subtypes, including rarer ones like brachiocervical inflammatory myopathy (BCIM) [125]
- To consider the added benefit of quantitative imaging or more advanced analysis methods including machine learning and deep learning in diagnostic imaging
- To identify imaging features which distinguish IIM as a group versus muscular dystrophy or other disease mimics
- To compare imaging modalities systematically to determine the best modality for different indications
- To define necessary anatomical coverage for diagnostic purpose

8.2. Repeat imaging for treatment or disease monitoring

8.2.1. Recommendations

The role of follow up imaging is debated. Repeat imaging should be considered if patients do not respond to treatment, if there is ongoing diagnostic uncertainty or there is clinical or laboratory evidence of disease relapse. In this setting it can be very helpful to determine the relative contribution of inflammatory disease activity against chronic damage. There may be a lag in imaging improvement, so repeat imaging to assess treatment response before two months is unlikely to be informative. In case of worsening, earlier repeat imaging can be helpful.

8.2.2. Research agenda

Prospective longitudinal studies are required to explore:

- Indications and optimal interval for repeat imaging
- The role of imaging in decisions about treatment intensity, duration or withdrawal
- Individualised prescription of physical therapy

8.3. Muscle imaging as an outcome in clinical trials

8.3.1. Recommendations

Quantitative MRI is established as a sensitive biomarker in IBM and could be included as a primary or secondary outcome measure in early phase clinical trials, or as a secondary outcome measure in late phase clinical trials.

In other IIM, the role of imaging in clinical trials is less studied, but it may be considered as a secondary outcome measure.

Image analysis should be performed blinded to clinical details and treatment group for unbiased assessment.

8.3.2. Research agenda

- Development of a standardized protocol suitable for multi-site, multi-vendor quantitative assessment of muscle water T2 in IIM.
- Inclusion of quantitative (or qualitative) imaging alongside clinical measurements in both open label and randomised therapeutic studies to define the sensitivity and timeframe of imaging versus other treatment response biomarkers
- To understand the relationship between imaging biomarkers including inflammation, fat accumulation and muscle size, and strength and functional assessments
- Research into imaging biomarkers of other muscles, including bulbar muscles, axial muscles, respiratory muscles, distal muscles, upper limbs

We also discussed whether recommendations could be provided on correlations between imaging and other assessment methods of muscle involvement such as muscle strength/function in adult and juvenile DM, and muscle histology. However, the workshop participants concluded that these three assessment methods are complimentary. Assessment of correlation is hampered because of the variation in muscle groups subject to investigation. In addition, in real life muscle imaging usually shows a mixture of disease activity (oedema) and muscle damage (replacement of muscle by fat).

9. Protocol and analysis MRI

	Minimal requirement	Optimal setting	Transversal studies	Longitudinal studies
Imaging sequences	▪ T1W-SE and ▪ STIR-T2W or ▪ TSE-Dixon only	▪ 3D Dixon isotropic PDW and ▪ Multi TE SE	▪ T1W-SE or Dixon FF and ▪ STIR-T2W or Multi TE SE or ▪ TSE-Dixon only	▪ Dixon FF ▪ Multi TE SE
Regions to scan	• Thighs, pelvis	• Whole body	• Thighs (pelvis, lower legs) • Whole body	• Thighs (pelvis, lower legs) • Whole body • Specific region of interest
Tissues to be analyzed	• Muscles • Subcutaneous tissue • Fascia	• Muscles • Subcutaneous tissue • Fascia	• Muscles • Subcutaneous tissue • Fascia • Incidental findings in WB	• Muscles • Subcutaneous tissue • Fascia
Assessment	• Visual scoring of – fat replacement – oedema – trophicity • Distribution • Extent • Severity	• Quantitative evaluation of – FF – CSA (offline) – cCSA (offline) – water T2 (offline) • at the level of – global segment (FF) – muscle groups (FF, water T2, CSA, cCSA) – individual muscles (FF, water T2, cCSA)	• Semi-quantitative scoring of inflammation and fatty replacement or • Quantitative evaluation – see optimal setting	• Quantitative evaluation – see optimal setting • Repeated examinations (at intervals dependent on question)

FF – fat fraction; TE – echo time; SE – spin echo; TSE – Turbo Spin echo; T1W – T1-weighted, T2W – T2-weighted; PDW – proton density weighted; CSA – global cross-sectional area; cCSA – contractile cross-sectional area; WB - Whole Body MRI.

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Declaration of Competing Interest

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