The value of qualitative muscle MRI in the diagnostic procedures of myopathies: a biopsy-controlled study in 191 patients

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Abstract

Background and aims: The role of muscle magnetic resonance imaging (MRI) in the diagnostic procedures of myopathies is still controversially discussed. The current study was designed to analyze the status of qualitative muscle MRI, electromyography (EMG), and muscle biopsy in different cases of clinically suspected myopathy.

Methods: A total of 191 patients (male: $n = 112$, female: $n = 79$) with suspected myopathy who all received muscle MRI, EMG, and muscle biopsy for diagnostic reasons were studied, with the same location of biopsy and muscle MRI (either upper or lower extremities or paravertebral muscles). Muscle MRIs were analyzed using standard rating protocols by two different raters independently.

Results: Diagnostic findings according to biopsy results and genetic testing were as follow: non-inflammatory myopathy: $n = 65$, inflammatory myopathy (myositis): $n = 51$, neurogenic: $n = 18$, unspecific: $n = 23$, and normal: $n = 34$. The majority of patients showed myopathic changes in the EMG. Edema, atrophy, muscle fatty replacement, and contrast medium enhancement (CM uptake) in MRI were observed across all final diagnostic groups. Only 30% of patients from the myositis group ($n = 15$) showed CM uptake.

Discussion and conclusion: The study provides guidance in the definition of the impact of muscle MRI in suspected myopathy: despite being an important diagnostic tool, qualitative MRI findings could not distinguish different types of neuromuscular diagnostic groups in comparison with the gold standard histopathologic diagnosis and/or genetic testing. The results suggest that neither muscle edema nor gadolinium enhancement are able to secure a diagnosis of myositis. The current results do not support qualitative MRI as aiding in the diagnostic distinction of various myopathies. Quantitative muscle MRI is, however, useful in the diagnostic procedure of a suspected neuromuscular disease, especially with regard to assessing progression of a chronic myopathy by quantification of the degree of atrophy and fatty replacement and in exploring patterns of muscle group involvements in certain genetic myopathies.

Keywords: electromyography, histopathology, muscle biopsy, muscle MRI, myopathy

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Introduction

The differential diagnostic process of suspected neuromuscular disorders is known to be challenging. Key elements of the diagnostic work-up include personal and family history, detailed clinical assessment, determination of creatine-kinase (CK)-levels, neurophysiological studies, and histopathological findings in muscle biopsy.[1] Muscle magnetic resonance imaging (MRI) has increased its impact in that process over the last decade and plays an important role in the diagnostic work-up of acquired and inherited

neuromuscular diseases, that is, (I) identifying genetically different conditions, (II) helping the clinician select appropriate genetic and biochemical diagnostic investigations, and (III) guiding which muscle should be targeted for histopathological studies.[2,3]

The use of a combination of sequences allows for the analysis of different aspects of the muscle.[2] In general, protocols include T1-weighted (T1W) and a fluid-sensitive, T2-weighted (T2W) or short-tau inversion recovery (STIR) sequence.[4] T1W images allow the assessment of muscle architecture and anatomy, particularly in reference to normal surrounding fat, including hemorrhage and abnormal fat deposition (e.g. muscle fatty replacement).[4] T2W or STIR sequences are primarily used to characterize muscle edema.[4] Furthermore, STIR sequences provide the advantage of homogeneous fat suppression. Gadolinium (contrast medium; CM)-enhanced fat-suppressed T1W imaging (Gd-T1WI) is known to reflect fascial edema or inflammation.[5] A specific MRI pattern has already been established for single neuromuscular disorders, for example, idiopathic inflammatory myopathies (IIMs), including dermatomyositis, polymyositis, and inclusion body myositis.[5,6] Muscle MRI is also helpful in genetically determined myopathies like facioscapulohumeral dystrophy (FSHD)[7] and other muscular dystrophies,[8] showing a specific pattern of affected muscles based on fat replacement recognizable on MRI. However, many of these patterns are overlapping[9] and critical to interpretation.[4]

Muscle MRI is considered to be the imaging modality of choice in routine diagnostic work-up of inherited neuromuscular disorders and to be often able to identify a distinctive pattern of muscle involvement so that muscle MRI may narrow down the genes to be sequenced and evaluated.[10] Due to the increasing impact of muscle MRI in the diagnostic work-flow of suspected myopathies, a muscle T1W MRI-based artificial intelligence-empowered tool has recently been established for muscular dystrophies.[9] However, several questions are still open, especially the association of qualitative MRI categories (CM enhancement, muscle fatty replacement, and edema) with certain myopathies and myositis. Despite the fact that MRI has been used to detect affected muscles by muscle fatty replacement and to establish a landscape of involved muscles in an individual, it is still unknown whether the diagnosis based on the MRI findings can provide more than localizing information. To address these questions, the findings of muscle MRI were analyzed in 191 patients together with electromyography (EMG) and muscle biopsy results performed for diagnostic reasons.

Subjects and methods

Patients
A total of 191 patients (male: $n = 112$, female: $n = 79$) were included into the study group. All patients had been referred to the Department of Neurology, University Clinic of Ulm, Germany for diagnostic procedures for a suspected myopathy between the years 2014 and 2017. Age at inclusion ranged from 18 to 88 years (median: 53 years, 25% percentile: 43 years, 75% percentile: 62 years). Information about their disease history and characteristics, comorbidities, medication, neurological, and cardiac symptoms were obtained in structured personal interviews addressing the presentation of muscle weakness, muscle cramps, myalgia, and family history. All patients included into the study received extensive clinical work-up including blood samples for CK, muscle MRI, EMG, and muscle biopsy for diagnostic reasons. In all patients assessed, the locations of biopsy and muscle MRI were the same (either upper or lower extremities or paravertebral muscles).

EMG studies
EMG studies (Toennies universal amplifier, Erich Jaeger GmbH, Hochberg, Germany & DasyLab, v 13, measX GmbH und Co. KG, Mönchengladbach, Germany) were performed during the diagnostic work-up prior to muscle biopsy and genetic confirmation of the disease. EMG results were obtained from individually selected muscles according to clinical findings and patients' history. The reports were evaluated for description of spontaneous activity fibrillation potentials, positive sharp waves and complex repetitive discharges, motor unit action potentials and recruitment during maximum innervation. According to comparison with norm values,[11] EMG results were classified into (I) myopathic, (II) neurogenic, (III) combined myopathic and neurogenic, or (IV) normal.

Muscle histopathology and molecular genetic testing

Histopathological analysis of all muscle biopsies [vastus lateralis muscle ($n=139$), biceps brachii muscle ($n=15$), gastrocnemius muscle ($n=11$), deltoid muscle ($n=7$), paravertebral muscles ($n=7$), semimembranosus muscle ($n=5$), tibial anterior muscle ($n=3$), gluteus maximus muscle ($n=2$), psoas major muscle ($n=1$), triceps brachii muscle ($n=1$)] were performed according to standard protocols.[12] The muscle specimens were frozen and stored at –80°C. Ten-micron frozen sections were stained with hematoxylin and eosine, Gomori trichrome, nicotinamide adenine dinucleotide dehydrogenase, cytochrome c oxidase/succinate dehydrogenase, acid phosphatase, elastica-van Gieson, periodic-acid Schiff , adenosine triphosphatase at pH 4.3, 4.6, and 10.35, respectively, and oil-red O.[12] Histopathological findings were categorized as (I) inconspicuous, (II) unspecific myopathic, (III) degenerative myopathic, (IV) inflammatory myopathic, or (V) neurogenic.[13,14] Biopsies with myopathic alterations were differentiated between inflammatory and non-inflammatory myopathies, comprising hereditary muscular dystrophies and associated disorders (i.e. congenital myopathies, myofibrillar myopathies, metabolic myopathies except from mitochondrial myopathies and ion channel disorders).

Myopathic changes were qualitatively and quantitatively evaluated concerning shape and size, caliber variation of muscle fibers, position of nuclei, structural defects or changes in individual muscle fibers, acid phosphatase activity, distribution of connective and adipose tissue, fiber type distribution, splitting, presence of lymphozytic infiltration, vacuoles, glycogen, lipid droplets, and oxidative reactions as described by Dubovitz and Sewry.[13] Isolated mitochondrial myopathies were not included in the analysis. Accompanying mitochondrial disturbances in inflammatory myopathies were accepted.

I. Normal skeletal muscle was evaluated when routine histological stainings showed neither structural deficits, lipid storage, glycogen storage, neurogenic or myopathic changes, nor mitochondrial disturbances with oxidative abnormalities or ragged red fibers.

II. As "unspecific" abnormalities, we considered mild abnormalities like internal nuclei in <5% of muscle fibers, scarce necrotic, whorled fibers, or targetoid muscle fibers without any other abnormalities.

III. Myopathic changes were obtained when histopathology was abnormal in a combination of increased fiber size variability with endomyseal fibrosis, high amount of central nuclei, fiber splitting, and whorled fibers, rounded fiber shape, necrosis, and phagocytosis. Distinctive pathological changes implying a certain myopathy as well as an increased amount of adipose tissue were also included in finding the final histopathological diagnosis, addressed as "myopathy" in this study.

IV. Inflammatory myopathies were indicated as myopathic changes in combination with inflammatory lymphocyte infiltration in immunohistochemistry as well as specific features like perifascicular atrophy in dermatomyositis or rimmed vacuoles in inclusion body myositis. These diagnoses were summarized as "myositis" in this study.

V. Neurogenic atrophy consisted of atrophic fibers of both types in reticular distribution or small/large groups of atrophic fibers of both fiber types without any myopathic changes.[13,14]

Genetic studies were performed according to standard protocols.[15]

Muscle MRI

All patients underwent an MRI examination of either bilateral upper or lower limbs or the paravertebral muscles according to the patients' symptoms using a 1.5 T MRI scanner (Magnetom Symphony, TIM, Siemens Healthcare, Erlangen, Germany). The routine MRI examination was conducted with the patient lying supine using a phased array body coil. All images were acquired in axial scan planes using fast-spin echo T1W (TR/TE, 932/10; number of signal averages, 2; FOV: 439.1 mm × 330 mm), STIR (TR/TE, 7310/56; inversion time 140 ms; number of signal averages, 1; FOV: 439.1 mm × 330 mm) and T1W fat saturated post contrast (TR/TE, 831/10; number of signal averages, 2; FOV: 439.1 mm × 330 mm) for all patients except 15 patients in whom contrast was not applied because of renal impairment and low glomerular filtration rate (<30%). For contrast application 0.1–0.2 ml/kg of Prohance contrast medium (Bracco, Italy) was injected

Table 1. Inter-rater reliability for all muscle magnetic resonance imaging scores according to Cohen's κ.

	Cohen's κ
Muscle atrophy	$\kappa = 0.616$, $Z = 11.3$, $p < 0.001$
Muscle fatty replacement	$\kappa = 0.663$, $Z = 13.8$, $p < 0.001$
Muscle edema	$\kappa = 0.696$, $Z = 13.5$, $p < 0.001$
CM uptake	$\kappa = 0.779$, $Z = 14.1$, $p < 0.001$

CM, contrast medium.

automatically at a rate of 1 ml/s followed by 10 ml saline using automatic injector (Medrad, Bayer, Germany). Examinations were conducted from the level of the shoulders to the wrists in the case of upper limb evaluation and from the level of the hips to the ankles in the case of lower limb evaluation. Both arms were scanned separately in different acquisitions, while both thighs/legs and paravertebral muscles were scanned together in the same acquisition.

Two blinded raters independently reviewed and scored the images; rater 1 with 10 years of experience in musculoskeletal radiology and rater 2 with 7 years of experience in musculoskeletal radiology. Both raters were blinded to each other's results and to the clinical data of the patients.

For qualitative MRI evaluation, four different findings were evaluated, that is, muscle size/atrophy, muscle fatty replacement, muscle edema (STIR/T2 hyperintensity), and extent of contrast enhancement of the involved muscles. To this end, we used a previously published definition and grading score.[16] Accordingly, atrophy was defined as visual loss of muscle volume and graded according to a four-point visual scale: grade 0, no atrophy; grade 1 mild atrophy (<30% of the total muscle volume), grade 2 moderate atrophy (>30% and <60% of the total muscle volume), and grade 3 severe atrophy (>60% of the total muscle volume). Muscle fatty replacement was then graded according to a five-point visual scale,[17,18] as follows, grade 0 normal; grade 1 just some fatty streaks; grade 2 <50% fatty infiltration of the involved muscle; grade 3 as much fat as muscle; and grade 4, more fat than muscle. Muscle edema was evaluated in STIR/T2W images as abnormally increased signal (hyperintensities) within the muscle. It was graded

according to a previously proposed three-point visual scale:[19] grade 0, normal muscle with no abnormally increased signal; grade 1 abnormally hyperintense signal involving one-third or more of the muscle volume; and grade 2 abnormally hyperintense signal in more than one-third of the muscle. According to the four-point visual atrophy grading scale, we proposed a similar visual scale for contrast enhancement of the muscles, where grade 0 corresponds to no muscle enhancement and grades 1, 2, and 3 correspond to muscle enhancement of ≤30%, 30–60%, and >60% of the involved muscle, respectively.

The final score for each finding and each patient was estimated according to the most affected muscle. Inter-rater reliability was evaluated to assess reproducibility.

Statistical analysis and inter-rater reliability
All statistical analyses and visualizations were performed using Prism Version 7 (GraphPad, San Diego, CA, USA). The inter-rater reliability of qualitative assessments of muscle MRI was determined by Cohen's κ. For further analysis, MRI-values of both raters were averaged and decimal places ≥0.5 have been rounded up.

Ethical statement
This study was conducted according to the Helsinki Declaration. All included patients gave informed written consent prior to study inclusion. The study was approved by the local University of Ulm ethics committee (reference no. 12/09).

Results

Inter-rater reliability for MRI interpretation
Calculation of Cohen's κ for two raters in 191 cases (except CM uptake: $n = 179$) resulted in a proportion κ >0.6 in all scores, as a proportion of match beyond chance. Results of inter-rater reliability are shown in Table 1. Inter-rater reliability was evaluated as "good" for all scored MRI categories.[20]

Clinical findings and histopathological results
The majority of patients out of all diagnostic groups reported myalgia. Subsequently, paresis and crampi were observed (Table 2). Interestingly, myalgia, crampi, and paresis together were only seen in

Table 2. Clinical findings of *N* = 191 patients in correlation to the final diagnosis. Numbers are given as total numbers of patients and percentages of the respective diagnosis subgroups. Multiple symptoms could be reported.

	Myalgia	Crampi	Paresis	Myalgia, crampi, and paresis	Number of patients with CK elevation
Final diagnosis					
Myopathy, *n* = 65	50 (77%)	12 (18%)	36 (55%)	5 (8%)	46 (71%)
Myositis, *n* = 51	33 (65%)	6 (12%)	31 (61%)	0	41 (80%)
Neurogenic disease, *n* = 18	11 (61%)	5 (28%)	8 (44%)	0	13 (72%)
Unspecific, *n* = 23	22 (96%)	5 (22%)	13 (57%)	0	13 (57%)
Normal, *n* = 34	30 (88%)	4 (12%)	9 (26%)	0	16 (47%)
CK, creatine kinase.					

Table 3. Electromyographic findings of *N* = 191 patients according to the final diagnosis; combined = myopathic and neurogenic electromyography findings. One patient may have >1 clinical finding. Numbers are given as total numbers of patients and percentages of the respective diagnosis subgroups.

|	Myopathic	Neurogenic	Combined	Normal
Final diagnosis				
Myopathy, *n* = 65	30 (46%)	8 (12%)	2 (3%)	25 (38%)
Myositis, *n* = 51	27 (53%)	5 (10%)	2 (4%)	17 (33%)
Neurogenic disease, *n* = 18	4 (22%)	10 (55%)	–	4 (22%)
Unspecific, *n* = 23	7 (30%)	–	–	16 (70%)
Normal, *n* = 34	17 (50%)	5 (15%)	1 (3%)	11 (32%)

patients with myopathy. CK elevation (>145U/l) was present in 129/191 patients. EMG was normal in 73/191. Next to combined EMG patterns, exclusively myopathic changes were found in 85/191 and exclusively neurogenic changes (polyphasic potentials increased in amplitude and reduced recruiting) were observed in 28/191. Five patients showed combined myopathic and neurogenic changes (Table 3). The final diagnosis according to biopsy results and genetic testing were: myopathy *n* = 65, myositis *n* = 51, neurogenic disease *n* = 18, unspecific *n* = 23, and normal *n* = 34. Out of the myopathic group, genetic testing led to the following diagnoses: metabolic myopathies were diagnosed most frequently (24/65), followed by myoadenylate deaminase deficiency (3/65), core myopathy (2/65), and limb girdle muscular dystrophy (2/65). One patient was defined as a Duchenne carrier. In all diagnostic groups, biopsy results defined the final diagnostic group.

MRI findings
A total of *n* = 94 patients out of all diagnostic groups showed edema. In 71% of these patients (*n* = 67), MRI also displayed gadolinium enhancement. Edema was observed across all pathologies, most often in myopathies, less in neurogenic muscle disease (Table 3). Gadolinium enhancement was not specific but observed across all diagnostic groups. Representative examples of the qualitative MRI patterns are given in Figure 1. More than two-thirds of patients from the myositis group showed muscle fatty replacement, which was most commonly observed in patients with myopathy (Table 4; Figure 2). In patients with myopathy and myositis as the final diagnosis, highest cumulative MRI scores were observed for muscle fatty replacement, followed by edema, CM uptake, and muscle atrophy (Figures 2 and 3). Interestingly, CM uptake has only been observed in 30% of patients with myositis. The majority of patients with
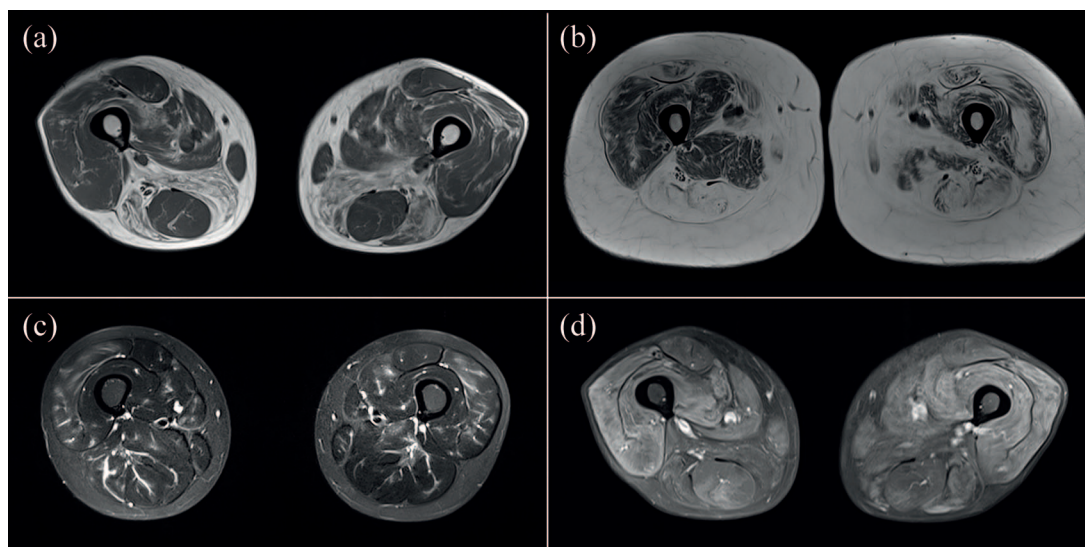
Figure 1. Representative examples of thigh magnetic resonance imaging (MRI) (a) atrophy and (b) muscle fatty replacement in T1-weighted images (c) edema in short-tau inversion recovery, and (d) gadolinium enhancement in fat saturated T1-weighted MRI with contrast medium.

Table 4. Magnetic resonance imaging findings [atrophy, muscle fatty replacement, edema, and contrast medium (CM) uptake] given as % according to the appearance in each diagnostic group (myopathy, myositis, neurogenic disease, unspecific, and normal).

	MRI findings			
	Atrophy	Muscle fatty replacement	Edema	CM uptake
Myopathy, $n = 65$	23 (35%)	53 (82%)	37 (57%)	33 (51%)
Myositis, $n = 51$	12 (24%)	31 (63%)	24 (47%)	15 (29%)
Neurogenic disease, $n = 18$	2 (11%)	8 (44%)	5 (28%)	3 (17%)
Unspecific, $n = 23$	7 (30%)	15 (65%)	11 (48%)	8 (35%)
Normal, $n = 34$	10 (29%)	22 (65%)	17 (50%)	11 (35%)

myositis as a final diagnosis showed muscle fatty replacement (63% of patients) followed by edema (47% of patients) (Figure 2). Combined MRI findings (edema, CM uptake, atrophy, and muscle fatty replacement) were detected in all diagnostic groups except the neurogenic disease group.

Discussion

Neuromuscular imaging with muscle MRI is increasingly being used for the diagnostic work-up of patients with suspected acquired or inherited muscle diseases.[21,22] Despite the low specificity,[23] several MRI patterns (affected muscle pattern) have already been established in the clinical algorithms.[4,6,7,21,24] MRI is reported to have a sensitivity of approximately 90% to detect abnormal muscles in IIMs.[22] In hereditary muscular disorders, MRI has also been proposed as a tool for identifying patterns of muscular involvement and as a biomarker of disease progression.[2,25–27] However, it remains an unsolved question whether MRI findings can provide enough information to deduce a diagnosis. Since the underlying pathophysiology cannot be differentiated, muscle MRI can qualitatively only differentiate severity and distribution of morphological changes in size and shape, severity and
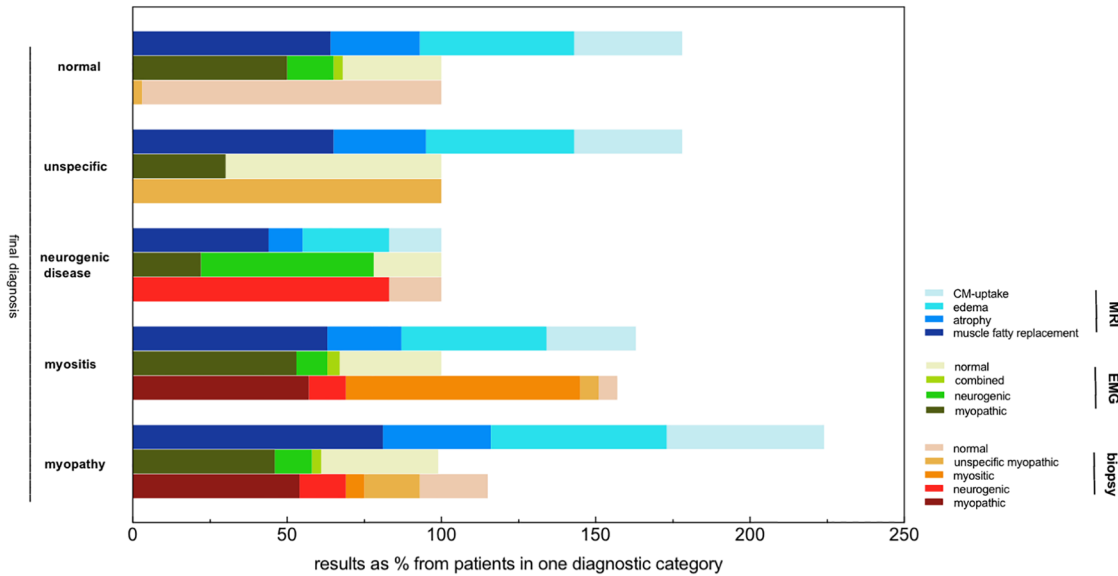
Figure 2. Combined results of biopsy, electromyography (EMG), and magnetic resonance imaging (MRI) according to each diagnostic category. Values given as % of patients in each diagnostic group. Given that one patient may have >1 finding, especially in biopsy and MRI, percentage may exceed 100%.
CM, contrast medium.
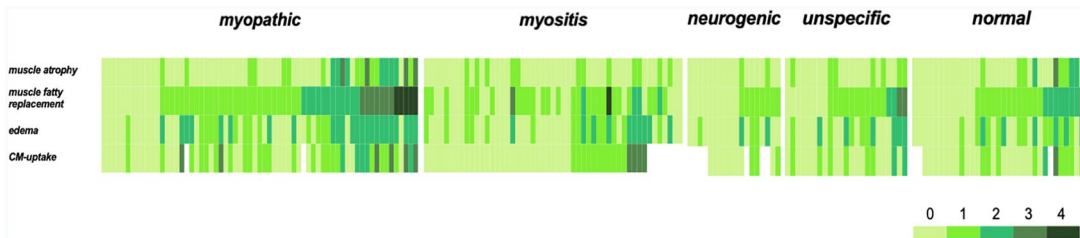
Figure 3. Heatmap showing the individual magnetic resonance imaging (MRI) scores for each MRI category analyzed according to each diagnostic group. Atrophy (four-point visual scale): grade 0 no atrophy; grade 1 mild atrophy (<30% of the total muscle volume), grade 2 moderate atrophy (>30% and <60% of the total muscle volume), and grade 3 severe atrophy (>60% of the total muscle volume). Muscle fatty replacement (five-point visual scale): grade 0 normal; grade 1 just some fatty streaks; grade 2 <50% fatty infiltration of the involved muscle; grade 3 as much fat as muscle; and grade 4, more fat than muscle. Muscle edema (three-point visual scale): grade 0, normal muscle with no abnormally increased signal; grade 1 abnormally hyperintense signal involving one-third or more of the muscle volume; and grade 2 abnormally hyperintense signal in more than one-third of the muscle. Contrast enhancement (four-point visual scale): grade 0 no muscle enhancement, grade 1 muscle enhancement of ≤30%, grade 2 muscle enhancement of 30–60%, and grade 3 muscle enhancement of >60%.
CM, contrast medium.

distribution of lipomatous changes, and presence of muscle edema.[24,28,29]

In the current study, 191 patients (male: $n=112$, female: $n=79$) with suspected myopathy received muscle MRI, EMG, and muscle biopsy for diagnostic reasons. The majority of patients were diagnosed with non-inflammatory myopathy, followed by myositis. Muscle biopsy was histologically normal in 18% and showed unspecific findings in 12%. A primary neurogenic disease was detected in 9% of our cohort. Muscle edema, atrophy, muscle fatty replacement, and gadolinium enhancement in MRI were observed in all final diagnostic groups.

The earliest change at MRI of inflamed muscles is muscle edema, generally observed in both T2W

and STIR sequences, which is thought to be caused by increased intracellular and/or extracellular water content.[24,30] It has already been shown that 56% of patients with active dermatomyositis and 15% of those with active polymyositis have muscle edema in MRI.[31] The sensitivity of MRI in showing muscle edema in active myositis is about 80–90%.[30] However, the specificity of muscle MRI is known to be more limited, since muscle edema can be noted in a whole array of different conditions (e.g. intense muscle exercise, infections, early neuropathy, ischemia, injury, neoplasm, radiation, and compartment syndrome).[24,30,32] Consistent with recent findings,[22,23] the majority of patients with myositis as the final diagnosis showed muscle fatty replacement (63% of patients), followed by edema (47% of patients) and CM uptake (29% of patients). In the myositis group, highest MRI scores were observed for muscle fatty replacement, followed by edema and CM uptake (Figure 3). Gadolinium enhancement is reported to be mainly present in subcutaneous and fascial areas in inflammatory myopathies[5] as a form of myofasciitis. Our findings support the notion that edema and muscle fatty replacement are key findings in muscle MRI of patients with suspected myopathies. Qualitative muscle MRI was not able to distinguish between myositis and degenerative myopathy as the final diagnosis and is therefore of limited value for proposing the underlying disease entity in diagnostics, as previously reported.[33] The finding of muscle fatty replacement in 63% of patients with myositis as final diagnosis indicates that chronic myositis leads to fatty replacement of the affected muscles, as in degenerative myopathies.

In inflammatory myopathies, the diagnosis is based on characteristic clinical findings, elevated serum skeletal muscle enzymes, electromyography, and muscle biopsy. However, MRI is known to accurately document the extent and intensity of muscle abnormalities.[23] Specific findings may differ between the acute/active (edema, high signal intensity on STIR, and fat-saturated gadolinium-enhanced T1W images) and chronic phase (atrophy and muscle fat replacement on T1W images).[22,23,30]

Recent studies showed gadolinium depositions following serial administrations of gadolinium-based contrast agents for MRI examinations in various parts of the brain in animal models and humans.[34–36] Subsequently, even though no clinical correlates of the deposits are known yet, an intensive discussion about safety and impact of contrast agents followed. In the investigated cohort, CM uptake has only been observed in 30% of patients with myositis and was as well observed in all other final diagnostic groups. In line with the upcoming discussion of gadolinium deposits,[37–39] our study further underlines the question of whether there is a diagnostic value of contrast enhancement in comparison with STIR sequences in suspected myositis.

Some myopathies present with a typical phenotype which allows targeted molecular genetic analysis to secure the diagnosis without muscle biopsy, for example, FSHD. Furthermore, neurogenic diseases are generally diagnosed based on clinical and electrophysiological findings without biopsy. However, in the majority of cases, the diagnosis of myopathies still requires a thorough analysis of the phenotype combined with EMG findings and histopathological changes. Several studies have already shown that muscle MRI is a useful tool in the diagnostic procedures of neuromuscular disorders, especially in uncertain cases and monitoring of disease progression in myositis, in addition for the identification of a moderately involved muscle for biopsy to increase quality and diagnostic output.[2,3,22]

Although potentially useful in pointing to specific viable muscles for biopsy, it is possible within a severely affected muscle to take a specimen from a very atrophic fascicle that will show "end-stage atrophy" because the biopsies are not MRI-guided. A very careful clinical examination with functional assessment of the muscle strength and palpation of the candidate muscle before proceeding to the biopsy remains essential.

Our study confirmed that muscle MRI can serve as a diagnostic tool for the selection of the biopsy area; however, the qualitative changes in MRI cannot achieve a prediction of the histological diagnosis with neither of the detected qualitative MRI subgroups. Since biopsy can also be made after thorough clinical examination and selection of a non-atrophic paretic muscle, skeletal muscle MRI, especially whole body muscle MRI, is used as a quantitative evaluation for myopathies with a selective involvement pattern for genetic testing.[40] There are also hereditary myopathies where identical clinical or histopathological features may be caused by a variety of genes or, in contrast, a genetic defect may lead to variable clinical phenotypes.[1]

Conclusion

It is already known that the sensitivity of muscle MRI is higher than its specificity, especially in detection of inflamed muscles.[30] In the studied cohort, combined MRI findings (edema, CM uptake, atrophy, and muscle fatty replacement) were detected in all diagnostic groups with the exception of the neurogenic disease group, which might be seen as a possible indicator of high sensitivity with limited specificity. Consistent with recent studies, high MRI scores were found for edema and muscle fatty replacement in myositis patients. However, the data show that edema is not specific for inflammation but can also be detected as denervation edema[4] and in certain forms of genetic myopathies. Muscle fatty replacement has been observed across all final diagnostic groups and therefore cannot be regarded as a marker for a neurogenic disorder.

Given that each recognized MRI pattern was observed across all histopathological diagnoses, qualitative MRI patterns were not able to predict the final diagnosis. Out of all diagnostic groups, the highest median MRI scores for muscle fatty replacement and edema were observed in patients with myopathy, indicating that the simultaneous occurrence of edema and muscle fatty replacement can be considered to be an MRI-based indicator for chronic myopathies (either genetic or inflammatory). Its value has to be seen in exploring the extent of muscle groups affected but not in histopathology forecast.

Gadolinium uptake was observed in all diagnosis groups, although less frequently than edema, even in the myositis group. These findings underline the limited value of gadolinium in suspected myopathies. The present study provides important information on the impact of muscle MRI in suspected myopathy. Neither muscle edema nor gadolinium enhancement could distinguish between histologically proven diagnosis groups so that these findings are therefore unable to secure a diagnosis of myositis. Although a final diagnosis cannot be made based on MRI findings alone according to the current results, muscle MRI might have value in the diagnostic procedure of a suspected neuromuscular disease, including the selection of a location for a muscle biopsy. Being qualitatively non-specific, the additional value has to be reevaluated in terms of cost-effectiveness and contribution to the individual disease prior to biopsy. On the other hand, muscle MRI can distinguish between similar diseases in form of pattern recognition. Therefore, it serves as a tool for advanced selective questions in distinguishing variable phenotypes of a genetic myopathy or in addressing long-term follow-up and therapy evaluation in inflammatory myopathies.

In muscle disease, MRI can detect signal changes or atrophy of muscles, not only in clinically affected muscle groups but also in subclinical involvement. The quantitative analysis of muscle involvement, especially in quantitative whole body MRI, can help to refine a certain diagnosis. It can be useful in assessing progression of a chronic myopathy by quantitating the degree of atrophy and fatty replacement and for research purposes in exploring patterns of muscle group involvements in certain genetic myopathies. Muscle MRI can be used to identify suitable muscles for biopsy, which is also possible after clinically established working diagnosis and thorough examination.

The use of MRI therefore can be used for specific questions, but the expansive use, especially with gadolinium exposure, should be critically reconsidered.

Author contributions
Conception and design: ACL, JK, and AR. Data acquisition and analysis: DLU, MM, JK, and AR. Drafting of the manuscript: DLU, MM. Figures and statistical analysis: DLU. Revision of the manuscript: ACL, JK, and AR.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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