Muscle MRI for Neuromuscular Disorders

Using muscle MRI to diagnose neuromuscular conditions requires awareness of different patterns of muscle involvement.

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Muscle MRI can provide information that is complementary to clinical, histologic, genetic, and laboratory findings for the diagnosis of neuromuscular disease. Muscle MRI allows the identification of edema and fatty replacement of muscle tissue. Most commonly it is used for diagnosis of inherited myopathies that have distinctive patterns of muscle involvement on MRI. These patterns are established by the identification of preferentially involved and preferentially spared muscles, which may not always be clinically observable. Certain patterns are specific for a particular myopathy and others are common to multiple disorders. Distinctive MRI findings are also seen in some inflammatory myopathies and spinal muscular atrophy (SMA). Muscle MRI can also be helpful in selecting a muscle for biopsy and there is growing interest in using muscle MRI to assess response to treatment in clinical trials and practice.

We review the clinical use of muscle MRI with an emphasis on the basic aspects of muscle MRI interpretation and different patterns of muscle involvement in various myopathies.

Practical Use of Muscle MRI

In practice, muscle MRI is most commonly used diagnostically, especially for inherited myopathies. Diagnostic algorithms incorporating imaging and clinical findings, have been proposed to direct genetic testing. This approach, however, has been largely superseded by the advent of next-generation gene panels and whole-exome sequencing. An adjunctive role for MRI remains; for example, there are distinctive imaging findings that can support the pathogenicity of a variant of uncertain significance (VUS) or direct attention to a gene that may have been overlooked. In this regard, certain imaging patterns are more specific and informative than others. In the few studies evaluating the diagnostic accuracy of muscle imaging, it has been shown to help identify the molecular basis of myofibrillar myopathies,[1] muscular dystrophies with rigid spine,[2] and distal myopathies,[3] but the ability to distinguish between most limb-girdle muscular dystrophies (LGMD) on imaging was poor.[4]

Suitable targets for muscle biopsy can sometimes be more easily identified with MRI, especially for inflammatory myopathies with patchy distribution of inflammation that results in high rates of sampling error and nondiagnostic biopsies. Edema seen on MRI correlates with inflammation, and biopsy yield can be enhanced by targeting the muscle with the greatest amount of edema and the least fatty tissue replacement.[5] In some circumstances, MRI is more sensitive than clinical examination for detecting muscle abnormalities,[6] suggesting it may be helpful for evaluation of subclinical muscle involvement in individuals with either nonspecific symptoms (eg, myalgia and fatigue) or with an elevated creatine kinase (CK) level. The ability to differentiate between myopathic and neuropathic processes on muscle MRI remains limited.

Basic Principles for Muscle MRI

Muscle MRI can detect abnormal muscle volume, abnormal muscle signal (fatty infiltration or edema), mass lesion, and abnormal anatomy. A frequently used MRI protocol includes both T1-weighted images and sequences that identify water in tissue (eg, T2-weighted images, with or without fat-signal suppression, or short-tau inversion recovery [STIR]). The T1-weighted images can be used to assess muscle anatomy; detect fatty infiltration, which reflects remote damage and muscle loss; and crudely assess muscle volume for atrophy or hypertrophy. Although endomysial fibrosis, which reflects muscle fiber loss and replacement by connective tissue, is a better indicator of muscle function loss than fatty tissue infiltration, there is no reliable imaging modality for muscle fibrosis yet.[7] Ongoing muscle damage, seen as increased water content

or edema, is best imaged by STIR or T2-weighted images. Fatty infiltration of muscle tissue is reflected by increased signal intensity on T1-weighted images, whereas edema is seen as hyperintensity on T2-weighted and STIR sequences. Postcontrast sequences are not routinely performed because these sequences have limited use in the diagnosis of inherited myopathies. Postcontrast sequences can be of use for detecting fasciitis in inflammatory myopathies or evaluating a mass lesion. In neurologic practice, the most relevant anatomic anomaly is the absence or complete atrophy of a muscle, such as the sternocleidomastoid or semimembranosus in selenoprotein N (SELENON)-related myopathies.[8]

Qualitative analysis or visual assessment of MRI sequences is sufficient for neuromuscular diagnosis. After a general overview of image sequences to evaluate for the aforementioned MRI abnormalities, the next step is to ascertain a pattern of abnormalities by identifying which muscles are preferentially affected vs preferentially spared. This is particularly helpful in hereditary myopathies, as discussed later in this review. In advanced stages, however, this pattern may be lost, as muscles that had been spared may become involved. A comparative approach is therefore preferable. For example, in the majority of people with ryanodine receptor 1 (RYR1)-related myopathies, the rectus femoris is less affected than the vasti and the soleus is more affected than the gastrocnemius.[9] These relative differences may still hold true at advanced stages, when the rectus femoris and gastrocnemius are involved. Semiquantitative approaches, such as the 6-grade Mercuri scale, have been established to visually grade the fat content of individual muscles.[10] Early in the disease process, affected muscles have a moth-eaten appearance on T1-weighted images (stage 1). Signal abnormalities subsequently become increasingly confluent, comprising less than 30% (stage 2a) or 30% to 60% of the muscle (stage 2b). More advanced pathology is characterised by a washed-out appearance with little (stage 3) or no (stage 4) remaining muscle tissue. This grading only allows a crude evaluation of progression over time with limited sensitivity for mild changes.[11] Quantitative methods are needed for muscle MRI to be useful as an outcome measure for disease progression or treatment response, especially in clinical trials. Quantitative muscle imaging will not be discussed in this article, but details can be found elsewhere.[7-12]

Anatomy

Most studies of muscle MRI have focused on the lower limbs, where the pattern of muscle involvement is usually established with 1 cross-section from the thigh and 1 cross-section from the lower leg (Figure 1). This is in part because the upper limbs are technically more challenging to image, but also because of the greater frequency of lower limb involvement in myopathies. Whole-body MRI would offer a more comprehensive evaluation with additional cross-sections from the upper limbs, axial, and sometimes cranial muscles.[13]

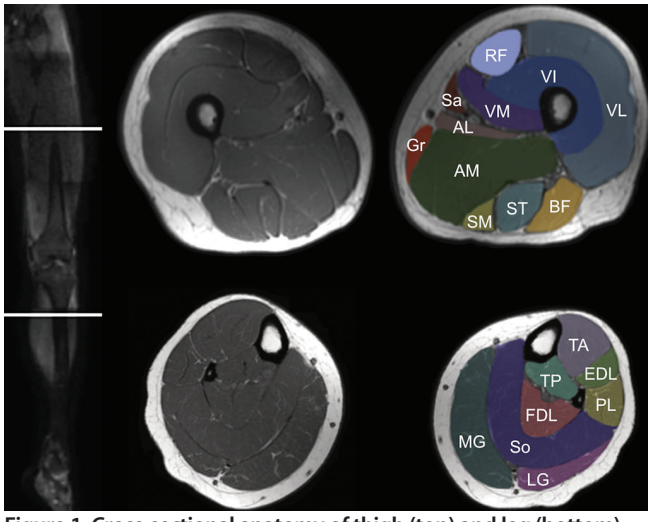

Figure 1. Cross-sectional anatomy of thigh (top) and leg (bottom) muscles. Abbreviations: AL, adductor longus; AM, adductor magnus; BF, biceps femoris; EDL, extensor digitorum longus; FDL, flexor digitorum longus; Gr, gracilis; LG, lateral gastrocnemius; MG, medial gastrocnemius; PL, peroneus longus; RF, rectus femoris; Sa, sartorius; SM, semimembranosus; ST, semitendinosus; VI, vastus intermedius; TP, tibialis posterior; VL, vastus lateralis; VM, vastus medialis.

Common Neuromuscular Disorders

Acquired Myopathies

The use of muscle MRI to differentiate types of inflammatory myopathy is limited. The predominant finding in these disorders is increased T2 signal (Figure 2), except in inclusion body myositis in which fatty infiltration predominates.

Inclusion Body Myositis. Diagnosed clinicopathologically, inclusion body myositis (IBM) features predominant weakness of finger flexors and knee extensors. Imaging studies show preferential involvement of the flexor digitorum profundus and quadriceps. In the thigh, there is a proximal to distal gradient of fatty infiltration, with distal segments being most involved.[14] There is also involvement of the gracilis and gastrocnemius. This pattern has good sensitivity and specificity for IBM, although MRI findings have yet to be incorporated into accepted diagnostic criteria.[15] Asymmetry is more common in IBM than in most other myopathies and can be seen clinically and on MRI. In the affected muscles, fatty infiltration generally predominates over edema, which is usually sparse and patchy.

Other Inflammatory Myopathies. In necrotizing autoimmune myopathy, proximal and axial muscles are most affected, and edema is prominent.[16,17] The severity of the MRI findings correlates with antibody status and is

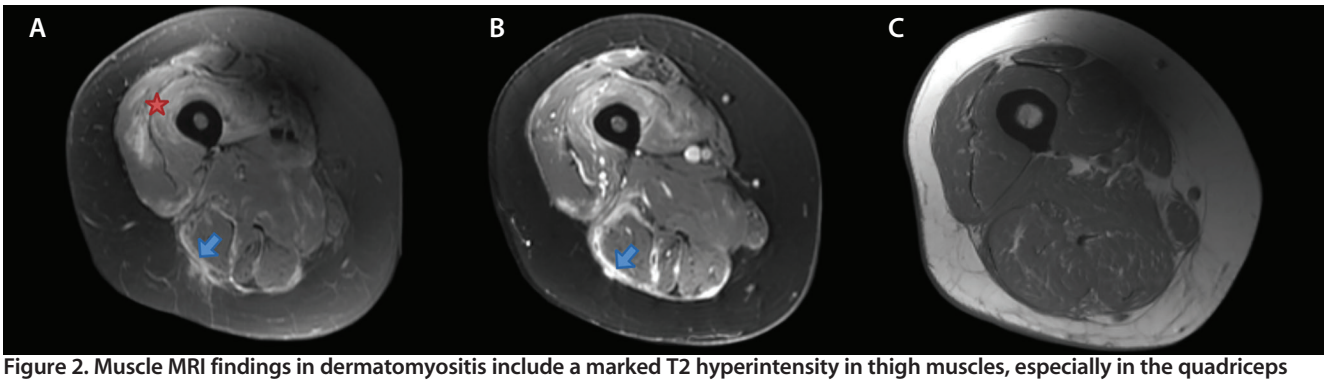

Figure 2. Muscle MRI findings in dermatomyositis include a marked T2 hyperintensity in thigh muscles, especially in the quadriceps (star), and along the fascial layers, especially in the biceps femoris (arrow), with evidence of subcutaneous fat edema on a T2-fat suppressed sequence (A). A post-gadolinium sequence (B) shows marked peripheral enhancement along the fascial planes (arrow). A T1-sequence (C) shows no significant abnormality.

generally more pronounced than in other inflammatory myopathies. In dermatomyositis, the subcutaneous tissue and fascia may also be prominently involved (Figure 2).[18] These findings, however, are not pathognomonic for dermatomyositis because they can also be seen in other types of inflammatory myopathies.[17] Sarcoid myopathy may also display a typical imaging pattern in some patients, consisting of nodular muscle involvement.[19]

Inherited Myopathies

The commonly described MRI patterns in inherited myopathies are summarized in the Table. The semimembranosus, adductor magnus, long head of the biceps femoris, and posterior leg compartment muscles are most frequently reported as preferentially involved, whereas the muscles most commonly spared include the gracilis, sartorius, and tibialis posterior.

Dystrophinopathies. Duchenne muscular dystrophy (DMD) is the most common inherited myopathy. The MRI pattern of DMD is among the most extensively studied, in part because of interest in using MRI as an outcome measure in clinical trials (See *Duchenne Muscular Dystrophy Treatments* in this issue).[20] The pattern of muscle involvement in Becker muscular dystrophy is similar, but the abnormalities are less severe. Dystrophinopathies are characterized by preferential involvement of the glutei and adductor magnus and sparing of the sartorius and gracilis.[21] The quadriceps and biceps femoris are involved at later stages. In the lower leg, the gastrocnemius and peroneus longus are most prominently involved, whereas the tibialis anterior is most commonly spared.

Myotonic Dystrophies. Clinically, myotonic dystrophy type 1 (DM1) is characterized by predominantly distal weakness associated with clinical myotonia. This finding is mirrored by preferential involvement of the flexor digitorum profundus in the upper limb and the gastrocnemius and soleus in the lower limb on muscle MRI.[22-24] The tibialis anterior is less affected, and the tibialis posterior is spared. In the thighs, there is involvement of the vasti and sparing of the rectus femoris. The regions closest to the femur are preferentially affected, leading to a characteristic semilunar appearance.[22] Unlike DM1, the clinical picture of myotonic dystrophy type 2 often overlaps with other inherited myopathies, especially when there is no clinical myotonia; muscle MRI is frequently normal.[22,23]

Facioscapulohumeral Muscular Dystrophy. Clinically, facioscapulohumeral muscular dystrophy (FSHD) predominantly affects periscapular, pectoralis, and leg muscles. Muscle MRI in FSHD is characterized by preferential involvement of the semimembranosus, usually the most severely affected muscle, in the thigh and the medial gastrocnemius and tibialis anterior in the leg. Other anterior leg compartment muscles are preferentially spared.[21] Upper limb MRI shows predominant involvement of the periscapular muscles, with sparing of the deltoid, supraspinatus, infraspinatus, and subscapularis.[25] Unlike most inherited myopathies, FSHD frequently presents with asymmetric weakness, and MRI findings are likewise often asymmetrical.

Limb-Girdle Muscular Dystrophies. The LGMDs form a group of more than 30 myopathies with dominant or recessive inheritance that predominantly affect proximal upper- and lower-limb muscles. Posterior thigh muscles, adductors, and glutei are predominantly affected in most LGMDs, including those related to mutations in *calpain-3* (*CAPN3*), *dysferlin* (*DYSF*), *fukutin-related protein* (*FKRP*) and *anoctamin-5* (*ANO5*) (Table).[26] In the leg, posterior compartment muscles are most affected, with the exception of FKRP-related muscular dystrophy, in which there may be more diffuse involvement.[27,28] It is difficult to differentiate most LGMDs with MRI, but imaging remains valuable for distinguishing them from other myopathies (eg, dystrophinopathies and collagen VI-related myopathies).[4] However,

TABLE. PATTERNS OF LOWER LIMB MUSCLE INVOLVEMENT IN SELECTED INHERITED MYOPATHIES

Type of muscular dystrophy or myopathy	Duchenne	Myotonic type 1	Myotonic type 2	Facioscapulohumeral	Oculopharyngeal	Limb-girdle					Congenital				Myofibrillar			
Gene	*DMD*	*DMPK*	*CNBP*	*DUX4*	*PABPN1*	*CAPN3*	*DYSF*	*SGCA-SGCD*	*FKRP*	*ANO5*	*SELENON*	*RYR1*	*DNM2*	*COL6 A1-3*	*DES*	*CRYAB*	*MYOT*	*FLNC*
Gluteus maximus	I	V	V	V	V	V	V	V	I	V	I	V	I	V	I	I	V	V
Gluteus medius	I	V	V	V	V	I	V	I	V	V	V	V	V	V	V	V	I	V
Gluteus minimus	I	V	V	V	V	I	I	I	V	V	S	V	V	V	V	V	I	V
Vastus lateralis	I	V	V	V	S	V	V	V	V	V	I	V	V	I	V	I	V	S
Vastus intermedius	I	V	V	V	V	V	V	V	V	V	V	V	V	I	V	I	I	I
Vastus medialis	I	V	V	V	V	V	V	V	V	V	V	I	V	I	V	I	I	I
Rectus femoris	V	S	V	V	S	V	S	V	S	S	V	S	V	V	S	I	S	S
Adductor magnus	I	V	V	I	I	I	I	I	I	I	I	I	I	V	V	V	I	I
Adductor longus	S	S	V	V	V	I	I	V	I	I	S	S	I	S	V	V	I	I
Gracilis	S	S	V	V	S	V	S	S	S	S	S	S	S	S	I	I	S	S
Sartorius	S	V	V	V	V	S	S	S	V	S	I	I	S	S	I	I	S	S
Biceps femoris	V	V	V	I	I	I	I	V	I	I	V	V	I	V	V	V	I	I
Semitendinosus	S	V	V	I	V	I	I	V	I	I	S	V	I	V	I	I	S	S
Semimembranosus	S	V	V	I	I	I	I	V	I	I	I	V	I	V	S	S	I	I
Gastrocnemius	I	I	V	I	V	I	I	S	V	I	V	V	V	I	I	I	I	I
Soleus	I	I	V	I	I	I	I	S	V	I	I	I	I	I	I	V	I	I
Tibialis posterior	S	S	V	S	V	S	V	S	S	S	S	S	S	V	V	V	I	V
Tibialis anterior	S	V	V	I	S	S	V	S	S	S	S	S	I	S	V	I	I	I
Peroneus longus	V	V	V	S	V	S	V	S	V	S	V	V	V	V	I	I	I	V

Abbreviations: I, preferentially involved; S, preferentially spared; V, variably involved or without sufficient data.

sarcoglycanopathies may have a distinct pattern. The leg muscles are most commonly spared.[4,29] When markedly affected, the vastus lateralis is usually still spared distally, creating a distal-to-proximal gradient, unlike the proximal-to-distal gradient seen in IBM.[29] Although originally considered helpful for distinguishing sarcoglycanopathies from other LGMDs, predominant involvement of the quadriceps varies; more commonly, the adductor magnus and glutei are the first and most severely affected muscles.[4,29] In addition to LGMD, mutations in *DYSF* can also lead to distal myopathy, and both clinical phenotypes have similar imaging findings.[30] In contrast, different *titin* (*TTN*) mutations can lead to different clinical and MRI patterns.[31]

Congenital Myopathies and Muscular Dystrophies. The congenital myopathies and muscular dystrophies are highly heterogeneous both clinically and genetically. *Collagen VI* (*COL6A1-3*), *SELENON*, and *RYR1* are among the most common causative genes and are associated with characteristic MRI findings. The collagen VI-related myopathies (Bethlem myopathy and Ulrich congenital muscular dystrophy) have among the most distinctive MRI appearances, with involvement of the periphery of the vasti, soleus, and gastrocnemius, giving these muscles a tigroid or "rolled-cake" appearance.[2] This pattern is not pathognomonic of collagen VI-related myopathies, however, because it has also been described in merosinopathy.[32] An inverse pattern

(involvement of the central portions of muscles, with peripheral sparing) has been described in protein-O-glucosyltransferase 1 (POGLUT1)-related myopathy.[33]

A typical distribution of muscle involvement has also been reported in SELENON-related myopathies. The sternocleidomastoid, semimembranosus, and sartorius are most often involved and are frequently severely atrophied.[2,8] Involvement of the sartorius is notable, considering that this muscle is spared in most other inherited myopathies. Lower leg muscles are less severely affected without a consistent pattern of muscle involvement.[2]

Although mutations in RYR1 have been associated with a wide spectrum of clinical phenotypes and histologic findings, the vast majority of RYR1-myopathy patients share a common pattern of muscle involvement on MRI.[9] In the thigh, the vasti are always more involved than the rectus femoris. Additionally, the adductor magnus and sartorius are commonly involved, whereas adductor longus and gracilis are spared. In the leg, the soleus is more affected than the gastrocnemius, and the peronei more than the tibialis anterior.

Myofibrillar Myopathies. A group of inherited myopathies characterized by aggregation of Z-disc–associated proteins, myofibrillar myopathies are clinically and pathologically similar but have different patterns on imaging studies.[1,34-36] Typical MRI findings in the thigh are shown in Figure 3. In the leg, the peroneal muscles are more affected than the tibialis anterior or posterior compartment muscles in desminopathies, whereas the posterior compartment is predominantly involved in myotilinopathies.

Neuropathies and Motor Neuron Disorders

In neuropathies, MR neurography is the most commonly used modality and allows the evaluation of nerve abnormalities (eg, enlargement, enhancement, or T2 hyperintensity) and identification of possible etiologies of nerve injury (eg, a compressive lesion or nerve entrapment). Evaluation of the muscle involvement pattern can help localize the lesion in focal neuropathies, but as noted, differentiating myopathy from denervation with MRI is limited. Nevertheless, muscle MRI has been studied in SMA because the clinical presentations may mimic myopathies. In survival of motor neuron 1 (SMN1)-related SMA, the distribution of imaging abnormalities varies with the age of onset and disease severity. In the most severely affected individuals, thigh muscles are diffusely involved, with some sparing of the gracilis and adductor longus.[37] In the less severe juvenile form, the iliopsoas and quadriceps are most affected. In the lower leg, the soleus is most severely involved.[37] Mutations in *BICD cargo adaptor 2* (*BICD2*) and *dynein cytoplasmic 1 heavy chain 1* (*DYNC1H1*) cause less common forms of SMA, termed SMA with lower extremity predominance. In both disorders, the anterior compartment of the thigh is most involved, with sparing of the adductors and semitendinosus.[38,39] In contrast, spinobulbar muscular atrophy (Kennedy disease) preferentially affects the posterior compartment of the thigh more than the anterior compartment, also with sparing of the adductors.[40]

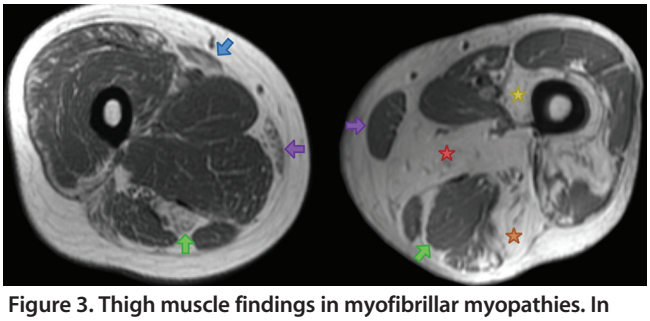

Figure 3. Thigh muscle findings in myofibrillar myopathies. In desminopathies (left), MRI findings show preferential involvement of the semitendinosus (green arrow), sartorius (blue arrow), and gracilis (purple arrow), with sparing of the adductors and other posterior thigh muscles. In contrast, in myotilinopathies (right) and filaminopathies, the biceps femoris (orange star), adductor magnus (red star), semimembranosus (blue star), and vastus medialis (yellow star) are most affected, and the semitendinosus (green arrow), and gracilis (purple arrow) are spared.

Conclusion

In summary, in both acquired and inflammatory myopathies, muscle MRI can provide information that is complementary to clinical, histologic, genetic, and other laboratory findings. For effective use of MRI in the diagnosis of myopathies, clinicians must be aware of the different patterns of muscle involvement in different myopathies, including their distinctive and overlapping features. The role of muscle MRI in neuropathies remains limited. Further studies are needed to improve our ability to detect muscle fibrosis and to distinguish between neuropathic and myopathic processes. ■

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Disclosures

SN and EN have no disclosures reported