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Neuromuscular imaging in inherited muscle diseases

Mike P. Wattjes
Rudolf A. Kley
Dirk Fischer

M. P. Wattjes (✉)
Department of Radiology,
VU University Medical Center,
De Boelelaan 1117, 1081 HV
Amsterdam, the Netherlands
e-mail: m.wattjes@vumc.nl
Tel.: +31-204-440341
Fax: +31-204-440397

R. A. Kley
Department of Neurology, Neuromuscular
Centre Ruhrgebiet,
Klinken Bergmannsheil, Ruhr-University,
Bochum, Germany

D. Fischer
Department of Neurology,
University Hospital of Basel,
Basel, Switzerland

D. Fischer
Department of Neuropaediatrics,
University Children's Hospital Basel,
Basel, Switzerland

Abstract Driven by increasing numbers of newly identified genetic defects and new insights into the field of inherited muscle diseases, neuromuscular imaging in general and magnetic resonance imaging (MRI) in particular are increasingly being used to characterise the severity and pattern of muscle involvement. Although muscle biopsy is still the gold standard for the establishment of the definitive diagnosis, muscular imaging is an important diagnostic tool for the detection and quantification of dystrophic changes during the clinical workup of patients with hereditary muscle diseases. MRI is frequently used to describe muscle involvement patterns, which aids in narrowing of the differential diagnosis and distinguishing between dystrophic and non-dystrophic diseases. Recent work has demonstrated the usefulness of muscle imaging for the detection of specific congenital myopathies, mainly for the identification of the underlying genetic defect in core and centronuclear myopathies. Muscle imaging demonstrates characteristic patterns, which can be helpful for the differentiation of individual limb girdle muscular dystrophies. The aim of this review is to give a comprehensive overview of current methods and applications as well as future perspectives in the field of neuromuscular imaging in inherited muscle diseases. We also provide diagnostic algorithms that might guide us through the differential diagnosis in hereditary myopathies.

Keywords Inherited muscle diseases · Muscular dystrophy · Congenital myopathy · Limb girdle muscular dystrophy · Myotonic dystrophy · Muscle MRI

Introduction

During the past few years, substantial progress in the genetic diagnosis of inherited neuromuscular diseases has led to new insights into the pathological understanding of the disease. This in turn has led to the identification of numerous new genetic abnormalities associated with dystrophic or non-dystrophic disease of the striated muscles. In addition to the neurological examination and neurophysiological assessment, neuromuscular imaging is increasingly becoming an important diagnostic tool in detecting muscular involvement as well as describing the degree and pattern of involvement. Neuromuscular imaging can therefore be helpful in supporting the clinical diagnosis, limiting the complex range of differential diagnoses and guiding interventional diagnostic procedures such as muscle biopsy. Since the introduction of ultrasound in the early 1980s as a diagnostic tool in neuromuscular diseases, the dynamic field of neuromuscular imaging techniques has become more fascinating but also complex.

Recent reviews have given a first overview concerning imaging techniques and clinical applications in patients with inherited, metabolic and inflammatory muscle diseases [1–4]. Given the dynamic development in this field of research, the aim of this review is to give a

comprehensive overview of the available techniques and present an update of clinical neuromuscular imaging applications in patients with inherited muscle diseases. Furthermore, we would like to try to give some guidelines about how and to what extent neuromuscular magnetic resonance imaging (MRI) can lead us in the right direction in terms of narrowing the differential diagnosis and making the right diagnosis prior to interventional diagnostic procedures such as muscle biopsy.

Imaging techniques

Before discussing the diagnostic value of different imaging techniques in the detection of muscle abnormalities in patients with inherited muscle disorders, we have to be aware that striated muscle is a dynamic tissue that is influenced by many factors such as exercise, age and gender [5]. These physiological changes can be observed across all imaging techniques and have to be distinguished from pathological changes.

Age is one of the most important factors influencing muscle tissue appearance [6]. During childhood, muscle thickness increases rapidly and is not relevantly influenced by gender. After puberty, the gender-specific muscle development starts (men develop thicker muscles after puberty than women), reaching a peak of muscle volume between 25 and 40 years of age, followed by a subsequent decrease in muscle volume. The influence of age and gender is, however, not constant and differs slightly for each muscle group [6–9].

Ultrasound

Ultrasound (US) is a well-established and validated diagnostic imaging method in the evaluation of patients with suspected muscle disorders [10]. It is a relatively cheap and easily applicable method, allowing the visualisation of striated muscle with a high temporal resolution (>0.1 mm). The major advantage of US is the lack of any radiation exposure, which makes it the perfect imaging method for the evaluation of children. It even allows dynamic imaging of contracting muscles and can visualise pathological muscle activity such as fasciculation [11–13].

A major drawback of US is that its application is limited to superficial muscle groups. Sound wave reflection and absorption lead to difficulties in displaying the deeper structures. This effect becomes even more pronounced when multiple muscle groups overlap. Another disadvantage is the relatively low inter-observer agreement and intra-observer agreement (depending on the level of experience), which makes a strictly standardised examination (e.g. according to certain anatomical landmarks) crucial [2, 14]. However, ultrasound is a reliable

method concerning the measurement of muscle thickness and muscle echo intensity. In addition, by measuring muscle echo intensity it is possible to further characterise age-related or pathological changes of the striated muscles with special regard to dystrophic changes in terms of fatty degeneration and replacement of muscle by connective tissue (Fig. 1). In order to quantify the degree of fat deposition there are several ratings scales available (e.g. the Heckmatt score) as well as computed-assisted quantification methods of muscle echo intensity [15–19].

Ultrasound applications are widely and routinely used in neuromuscular disorders in terms of assessment of changes in muscle morphology (atrophy, hypertrophy, changes in muscle architecture). In particular it is a useful screening tool during the initial diagnostic phase, especially in children. Depending on the disease entity, the sensitivity of detecting dystrophic changes ranges from 25% in non-dystrophic myopathies up to 100% in dystrophic myopathies (Duchenne muscular dystrophy) [10, 19, 20]. The detection of pathological changes can be helpful in guiding muscle biopsy, and the description of the muscle involvement pattern might help in the differential diagnosis [10, 21].

Computed tomography

Computed tomography (CT) has been widely used in the past in order to evaluate the presence and extent of change in the striated muscles in patients with hereditary neuromuscular disorders [2, 22–24]. CT is a fast imaging method that is easy to apply and allows a good and standardised assessment of the aspect and shape of the muscles as well as dystrophic changes (in particular fatty degeneration). CT is also relatively operator-independent and allows the evaluation of deeper muscle groups, and newer CT methods using multi-detector rows provide improved imaging possibilities in terms of spatial resolution and multi-planar reconstructions. However, CT has substantial drawbacks leading to an almost complete replacement of this imaging technique by US and MRI. One of the most relevant disadvantages of CT compared with US and MRI is the relatively high radiation dose, which makes the application obsolete, especially in children. Because of the high radiation dose, whole-body applications in order to describe the pattern of muscle involvement are not desired. Another drawback of CT is the limited soft tissue contrast, which substantially impairs the sensitivity in the detection of inflammatory changes (e.g. oedema) that can precede muscle dystrophy.

Magnetic resonance imaging

MRI is increasingly being used in the evaluation of patients with suspected or proven inherited or metabolic neuromuscular disorders. MRI provides a high soft tissue contrast allowing excellent assessment of striated muscles

Fig. 1 Ultrasound images of the quadriceps muscle in normal control (**a**) and a patient with Duchenne muscular dystrophy (**b**). In the healthy subject (**a**), muscle appears largely black with few perimysial septa. Note the increased homogeneous fine granular echogenicity of muscle due to increased replacement of normal muscle by connective and fatty tissue in the patient with muscular dystrophy (**b**)
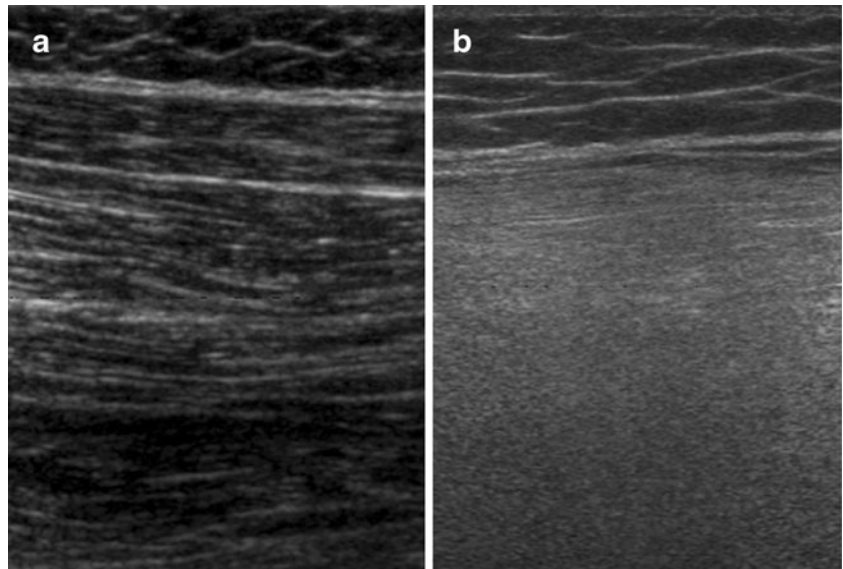
concerning shape, volume (hypotrophy, hypertrophy) and tissue architecture [1, 2]. Because of the lack of ionising radiation, MRI has become a valuable imaging method in children, although sometimes sedation might be necessary. Basically, MRI is performed as a multi-sequence imaging protocol including T1-weighted (T1W) and T2-weighted (T2W) (turbo) spin echo as well as fat-suppressed (short tau inversion recovery or spectral fat suppression techniques) T2-weighted sequences (T2WFS). The image acquisition is performed in the axial plane with a slice thickness of 5-7 mm. If necessary, additional images in other anatomical planes (coronal, sagittal) can be easily acquired.

Dystrophic changes such as fatty degeneration can be easily and sensitively detected using the T1W and T2W sequences. In addition, inflammatory changes such as muscle oedema can be depicted on the T2WFS sequences (Fig. 2). It has been conclusively shown that MRI has a higher sensitivity in the detection of dystrophic changes compared with CT [22, 23]. MRI can be performed and rated in a standardised manner suggesting a good inter-rater agreement and intra-rater (during follow-up) agreement. The degree of muscular dystrophy in inherited muscle diseases is rated according to rating scales [25–27]. Most of the established rating scales are based on the amount of fatty degeneration ranging from normal appearance to complete fatty degeneration (Table 1). The evaluation of the muscle MRI using standardised rating scales allows a fast and reproducible assessment of the degree of involvement of each muscle. Initially, muscle MRI protocols were developed to evaluate certain anatomical areas such as the lower extremities and pelvis. More recent whole-body imaging protocols have been established allowing the evaluation of almost all relevant striated muscle groups. Pattern recognition of muscle involvement is sometimes helpful in narrowing the differential diagnosis and leading to the most probable diagnosis before muscle biopsy. Because of the lack of any radiation exposure, muscle MRI has become an important diagnostic technique for the evaluation of children [3]. In addition, whole-body MR imaging protocols allow evaluation of tissues and organs beyond the striated muscle such as the parenchymatous organs in the abdomen, the oesophagus and heart, all of which can be affected in patients with inherited neuromuscular diseases [28, 29] (Fig. 3).

Using T2WFS sequences, MRI can sensitively detect discrete toxic, metabolic and inflammatory changes that are reflected by muscle oedema, which normally precedes dystrophic changes in terms of fatty degeneration. Therefore, MRI is able to detect ongoing disease activity in the muscle tissue and can be helpful in guiding muscle biopsy (Fig. 2).

The diagnostic value of contrast-enhanced (CE) MR imaging protocols has not been investigated so far. Late contrast enhancement may be a valuable option for the assessment of connective tissue that replaces normal muscle tissue in degenerative myopathies. However, this assessment is associated with a substantial increase in examination time. Therefore, CE MR imaging should not been performed on a regular basis. Recently performed animal studies with more specific contrast agents entering affected muscle tissue have shown that CE MRI might be helpful in distinguishing normal non-affected muscles from damaged muscles and further describe the extension and mechanism of muscular damage in dystrophic disorders [30, 31]. However, more prospective studies are necessary before the clinical application of such imaging protocols in humans during the diagnostic workup.

Quantitative MRI methods such as T2 relaxation time measurements, muscle fat quantification using the 3-point
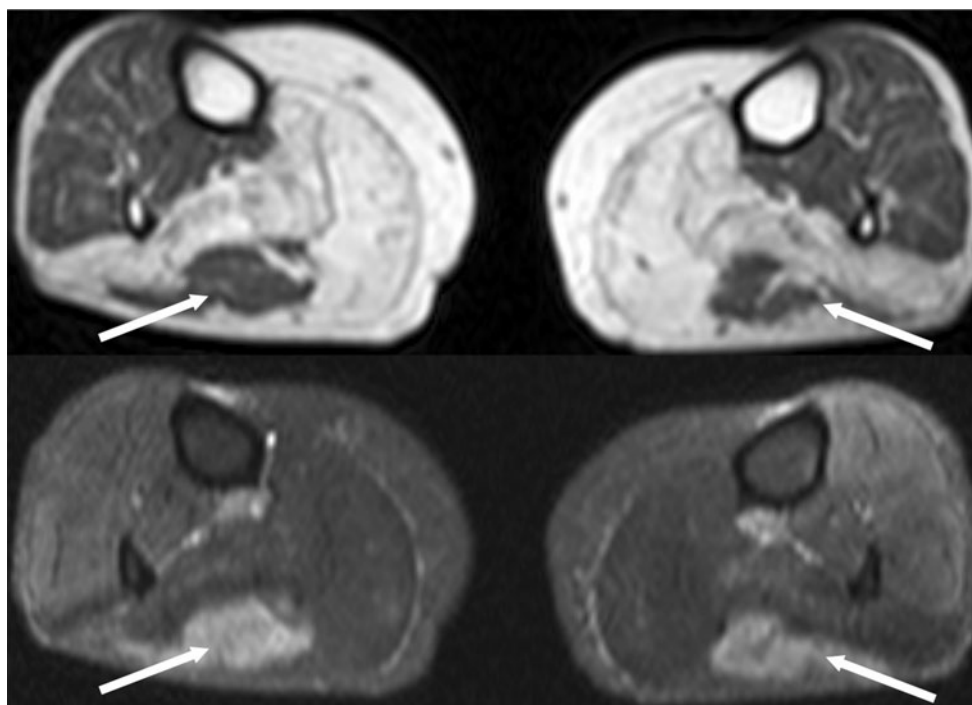
Fig. 2 Transverse T1-weighted (upper row) and spectral fat-suppressed T2-weighted MR image (bottom row) of the thighs of a 48-year-old woman presenting with myotonic dystrophy type 1. Note the different degrees of fatty degeneration within the gastrocnemius muscle. The medial head shows an end-stage fatty degeneration (grade 4 according to the Mercuri and Fischer scale, grade 3 according to the Kornblum scale, Table 1). The muscle tissue is completely replaced by fat. The lateral head shows a moth-eaten appearance with scattered small areas of increased signal (fatty degeneration grade 2 according to the rating scales established by Mercuri et al., Kornblum et al. and Fischer et al., Table 1). The fat-suppressed T2-weighted image shows a high signal in the medial head of the gastrocnemius muscle indicating oedema because of inflammatory changes before and during the degenerative disease stages

Dixon technique, magnetic resonance spectroscopy and perfusion imaging might be helpful to further analyse the degree of pathological changes in the striated muscles [32–34]. In particular blood flow measurements in the striated muscle based on either dynamic contrast-enhanced T1-weighted MRI, arterial spin labelling or blood oxygen-dependent MRI can be helpful to distinguish between inflammatory (increase of microvascular perfusion) and

Table 1 Summary of the well-established rating scales on MRI concerning the visual rating of dystrophic change of striated muscle tissue

| Grade	Mercuri et al. 2002 [25]	Kornblum et al. 2006 [27]	Fischer et a. 2008 [26]
0		Normal appearance	Normal appearance
1	Normal appearance	Discrete moth-eaten appearance with sporadic T1 hyperintense areas	Mild: traces of increased signal intensity on the T1-weighted MR sequences
2	Mild involvement: Early moth-eaten appearance with scattered small areas of increased signal or with numerous discrete areas of increased signal with beginning confluence, comprising less than 30% of the volume of the individual muscle	a. Moderate moth-eaten appearance with numerous scattered T1 hyperintense areas b. Late moth-eaten appearance with numerous confluent T1 hyper-intense areas	Moderate: increased T1-weighted signal intensity with beginning confluence in less than 50% of the muscle
3	Moderate involvement: Late moth-eaten appearance with numerous discrete areas of increased signal with beginning confluence, comprising 30-60% of the volume of the individual muscle	Complete fatty degeneration, replacement of muscle by connective tissue and fat	Severe: increased T1-weighted signal intensity with beginning confluence in more than 50% of the muscle
4	Severe involvement: Washed-out appearance, fuzzy appearance due to confluent areas of increased signal or an end-stage appearance, with muscle replaced by increased density connective tissue and fat, and only a rim of fascia and neurovascular structures distinguishable		End-stage appearance, entire muscle replaced by increased density of connective tissue and fat
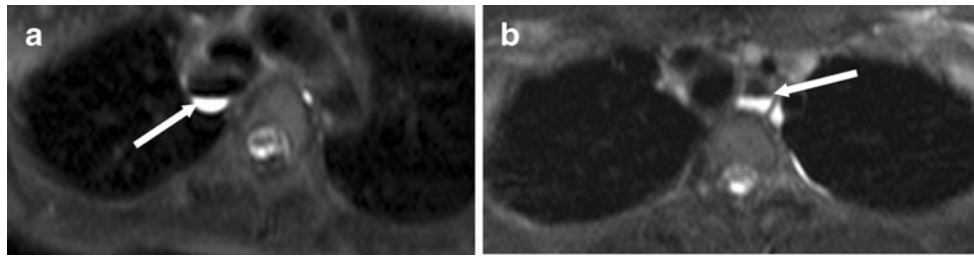
Fig. 3 Transverse spectral fat-suppressed T2-weighted images obtained from two patients presenting with a myotonic dystrophy type 1 (A: 37-year-old woman; B: 16-year-old boy). The images were obtained during a multi-sequence whole-body muscle MRI protocol. In both patients, dilatation of the oesophagus in the proximal segment with the air-fluid level could be diagnosed, which was clinically reflected by dysphagia

degenerative/dystrophic changes [4, 35]. However, there have been only a limited number of studies with low numbers of included subjects available up to now. Therefore, these techniques remain experimental for this purpose and should not be considered a standard imaging tool in the clinical routine setting.

Muscle imaging in muscular dystrophies

Muscular dystrophies are characterised by permanent and progressive muscle weakness. Clinical, pathological and genetic classifications are overlapping and heterogeneous. However, the most common separation is made according to the age of onset and the pattern of involved (e.g. facial, proximal, distal) muscles.

In dystrophinopathies, onset of (proximal) weakness is in the first decade of life. Limb-girdle muscular dystrophies (LGMD) are a group of autosomal dominantly or recessively inherited muscular dystrophies that also present with primary proximal (limb-girdle) muscle weakness. However, most LGMDs start in the second decade of life. Myofibrillar myopathies (MFM) are a group of adult-onset myopathies, often beginning in the third or fourth decades of life. In contrast to LGMD, muscle weakness often starts in the distal muscles. Other dystrophies such as myotonic dystrophy or FSHD have often a characteristic pattern of clinical weakness but can start at any age.

Early onset (proximal) LGMD and dystrophinopathies

In western and central Europe, LGMD2I, LGMD2A and LGMD2B are probably the most common LGMD forms. A muscle biopsy including protein expression analysis is usually necessary to distinguish among LGMD subtypes [36, 37]. LGMDs also present with different patterns of muscle involvement on imaging that might help in the genetic diagnosis. An illustration of different muscle imaging findings in LGMD patients is provided in Fig. 4.

FKRP-related myopathies (LGMD2I)

A few years ago, a novel gene encoding a putative glycosyltransferase, fukutin-related protein (FKRP), was found to be responsible for both a novel form of congenital muscular dystrophy (MDC1C) and for a form of limb girdle muscular dystrophy (LGMD2I) [38, 39]. Recently, we performed a systematic clinical and muscular MRI assessment in several LGMD2I patients and compared these findings with those of other patients with genetically confirmed diagnosis of other forms of autosomal recessive LGMDs or dystrophinopathies [40].

All LGMD2I patients had a characteristic muscular phenotype on MRI of the lower extremities that demonstrated marked signal changes in the adductor muscles, the posterior thigh and posterior calf muscles. Furthermore, data of patients with different clinical disease severity pointed towards a specific temporal pattern. At the pelvic level, the gluteus maximus was involved earlier and more severely than the gluteus medius. At the thigh level the earliest and most severe changes were observed in the adductor (magnus) muscles and the biceps femoris. With further progression degenerative changes were noticed in the remaining hamstring muscles and to a lesser degree in the vastus lateralis and vastus intermedius muscles. Involvement of the vastus medialis and rectus femoris was only observed in the patient with advanced disease, while the sartorius and gracilis muscles were relatively spared. In the lower legs relatively diffuse changes in the medial head of the gastrocnemius and the soleus muscle were observed early in the disease, while involvement of the anterior compartment muscles was only observed in later stages of the disease. The tibialis anterior muscle was usually spared and often hypertrophied.

Calpainopathies (LGMD2A)

Compared with LGMD2I, in patients with LGMD2A, caused by mutation in the calpain-3 gene, we observed a very similar and consistent clinical and muscle imaging phenotype. As in LGMD2I, muscle MRI images have confirmed the clinical observation that in LGMD2A there
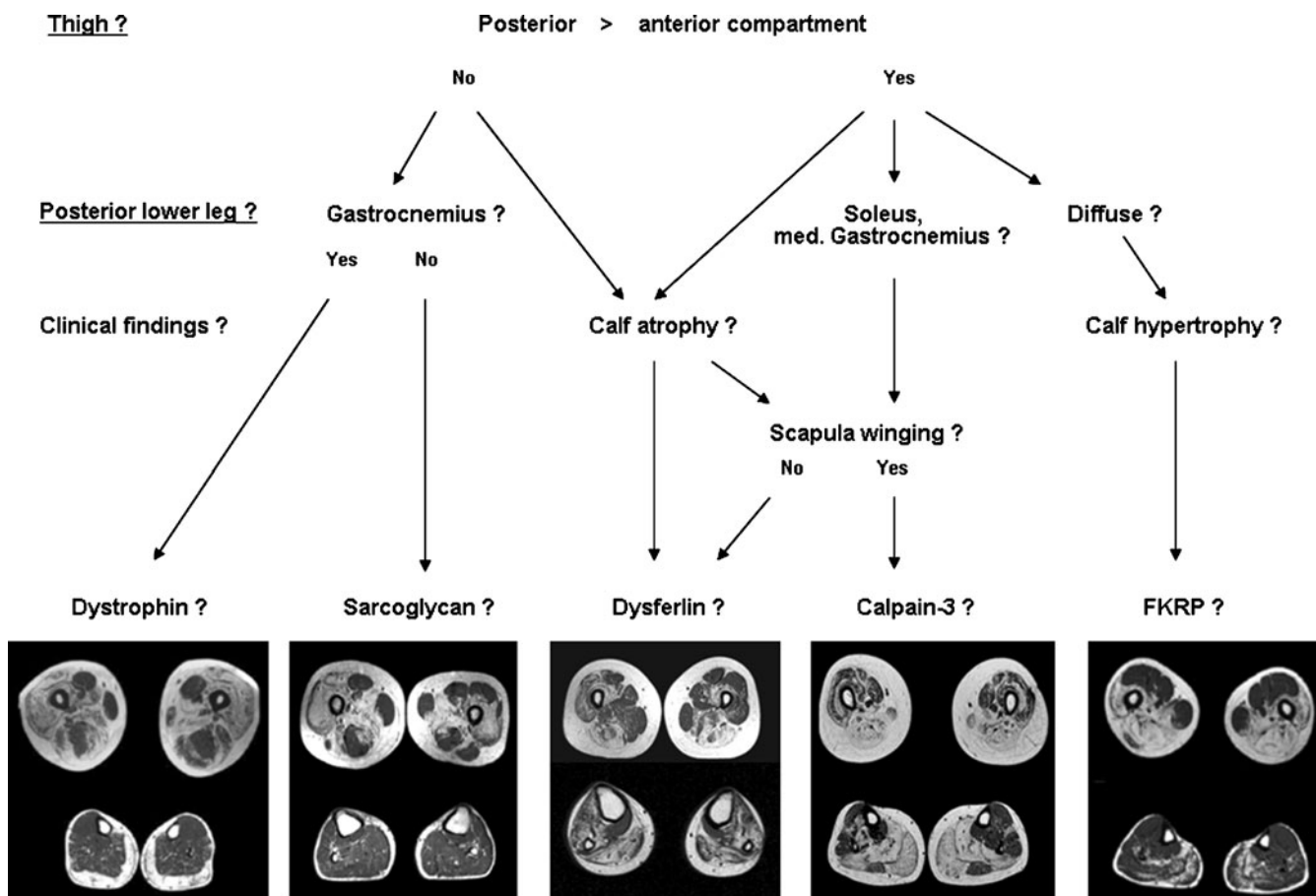
Fig. 4 Flowchart showing the approach to LGMD. Most LGMD patients have greater affliction of the posterior rather than the anterior thigh compartment muscles. On the other hand, patients with dystrophinopathy and sarcoglycanopathy often have significant affliction of the quadriceps muscle. Dystrophinopathy often presents with early and marked changes in the gastrocnemii muscles, while patients with sarcoglycanopathy show no affliction of these muscles. Patients with dysferlinopathy most often show posterior thigh and posterior lower leg involvement with sparing of the sartorius, gracilis and biceps femoris. However, muscle affection can be variable, but clinically calf atrophy and absence of scapular winging are commonly present. Calpain-3 and FKRP patients present with predominant posterior thigh and posterior lower leg involvement. Calpain-3 patients usually show marked involvement of the soleus and medial gastrocnemius muscles. Furthermore, calf atrophy and scapular winging are usually observed. Conversely, FKRP patients have a more diffuse involvement of the posterior lower leg muscles, while the tibial anterior muscle is often spared or even hypertrophied

is early and predominant involvement of posterior compartment muscles such as the gluteus maximus in the pelvis, semimembranosus, biceps femoris and adductor muscles in the thigh, with relative sparing of the vastus lateralis, sartorius and gracilis. These findings were also later confirmed by others [41]. Contrary to LGMD2I, there are, however, some important differences: the vastus lateralis is spared more in LGMD2A compared with LGMD2I; the medial gastrocnemius and soleus muscles are much more selectively involved compared with the diffuse affliction seen in LGMD2I, and hypertrophy of the tibialis anterior muscle is only rarely present in LGMD2A.

Dysferlinopathies (LGMD2B)

Dysferlinopathies, which are genetically characterised by mutations in the dysferlin gene lead to LGMD 2B, distal Miyoshi myopathies and a form of distal anterior compart-

ment myopathy [42, 43]. On MRI, symptomatic patients with dysferlinopathies present with severe dystrophic changes in the anterior and posterior compartments of the thighs with a characteristic sparing of the gracilis and sartorius muscles. In the lower legs, dysferlinopathies predominantly affect the posterior compartment with a relative sparing of the medial head of the gastrocnemius muscle [44–46]. This distinct pattern is different from muscle involvement in LGMD2I and LGMD2A patients in which dystrophic changes in the posterior thigh and posterior calf muscle can frequently be observed [40].

Dystrophinopathies (DMD/ BMD) and sarcoglycanopathies (LGMD2C, D, E and F)

While sarcoglycan deficiencies (LGMD2C, D, E and F) are relatively rare, dystrophinopathies [type Duchenne (DMD) and type Becker (BMD)] are the most common

muscular dystrophies worldwide. Therefore, late onset BMD patients or sporadic symptomatic female carriers of DMD often enter the differential diagnosis in sporadic LGMD patients. Furthermore, recently published studies emphasised an overlap between LGMD2I and the group of dystrophinopathies mainly as both often have calf or generalised muscular hypertrophy, and respiratory and cardiac involvement [38, 39]. However, on muscle imaging all our patients with BMD and alpha-sarcoglycanopathy showed pronounced signal changes in the anterior rather than the posterior thigh muscles (as present in LGMD2I patients). In accordance with our results, a predominant affliction of the anterior thigh compartment has been observed in dystrophinopathy and LGMD2D [47–49]. Thus, the relation between knee extensor and flexor involvement might be useful in distinguishing dystrophinopathies and sarcoglycan deficiencies from LGMD2I on muscular MRI. Finally, alpha-sarcoglycanopathy can be differentiated from BMD patients by the greater extent of upper limb involvement [47] and by the different pattern in the lower limbs on muscular MRI [50].

Late onset (distal) myofibrillar myopathies

MFMs are histopathologically characterised by aberrant desmin aggregation and ultrastructurally by myofibrillar degeneration, which led to the introduction of the term 'myofibrillar myopathy' (MFM). Mutations in the human desmin gene (DES) were first shown to be associated with MFM; another form is associated with mutations in the gene encoding αB-crystallin (CRYAB). More recently, mutations in the human Z-disc proteins myotilin (MYOT), ZASP (LDB3) and filamin C (FLNC) have also been shown to cause MFM [51]. Practically, a definitive determination of the MFM subtype can only be established by direct gene sequencing. However, muscle imaging in combination with clinical information is very helpful for separation of distinct MFM subtypes and in scheduling of genetic analysis.

Recently, we performed muscle imaging in 46 MFM patients (19 desminopathy, 12 myotilinopathy, 11 filaminopathy, 1 αB-crystallinopathy and 3 ZASPopathy patients) and observed two major characteristic patterns of muscle involvement [26]. In desminopathy patients, at the thigh the semitendinosus was the most affected muscle, being more affected than the biceps femoris and semimembranosus muscles. Furthermore, the sartorius and gracilis muscles were often involved earlier and more severely than other thigh muscles. At the lower legs, peroneal muscles were more involved than the tibialis anterior muscle or at least equally as involved. Muscle imaging findings in a patient with a R120G αBC mutation were very similar to those in desminopathy patients. The most frequently involved muscles were the gluteus maximus, semitendinosus, sartorius, gracilis and the peroneal muscles.

Highly contrarily, all other MFM patients (caused by mutations of the Z-disc protein-encoding genes myotilin, filamin c and ZASP) showed an opposite posterior thigh affliction with more involvement of the biceps femoris, semimembranosus and the adductor magnus than the semitendinosus muscle. In filaminopathy, the gracilis and sartorius muscles were often relatively equally spared, while in myotilinopathy the sartorius muscle was slightly more involved than the gracilis muscle. In the lower legs, the soleus and the medial gastrocnemius were the most frequently affected muscles, and in the anterior compartment the tibialis anterior muscle was the most frequently affected. Differences among these three MFM subforms were much more subtle, but detectable on statistical analysis. This revealed highly sensitive and specific criteria (Fig. 5) that may be very useful for the detection of individual MFM forms.

Other muscular dystrophies

Diagnosis of common muscular dystrophies such as myotonic dystrophy type 1, facio-scapulo-humeral muscular dystrophy and oculopharyngeal muscular dystrophy is usually based on classical clinical findings. Therefore, in these muscular dystrophies the role of muscle imaging has yet to be defined. Recent studies performed on these myopathies suggested that some characteristic findings are present, even if there is less diagnostic value compared with CM, LGMD and MFM (Fig. 6).

Myotonic dystrophy

Myotonic dystrophy types 1 and 2 (DM1, DM2) are autosomal dominantly inherited multisystem disorders and genetically characterised by pathogenic repeat mutations. DM1 is—with an estimated prevalence of 1 in 8,000—the second most common muscular dystrophy worldwide [52]. The clinical phenotype and pattern of muscle affliction differ between DM1 and DM2 (or proximal myotonic myopathy = PROMM) but also show some overlap. Almost all DM1 patients show signs of fatty degeneration and/or oedematous changes in the striated muscles on muscular MRI. Most of the patients show severe fatty degeneration of the proximal and distal lower limb muscles. There is a predominant affliction of the anterior compartment of the thighs compared with the posterior compartment with a relative sparing of the rectus femoris muscles [27, 53, 54]. Particularly, the vastus muscles frequently show a semilunar peri-femoral area of fatty degeneration [53, 55]. In the lower legs of DM1 patients, the gastrocnemius muscles show early and frequent involvement, whereas the posterior tibial muscles are relatively unaffected. In addition, whole-body MRI protocols can frequently detect the involvement
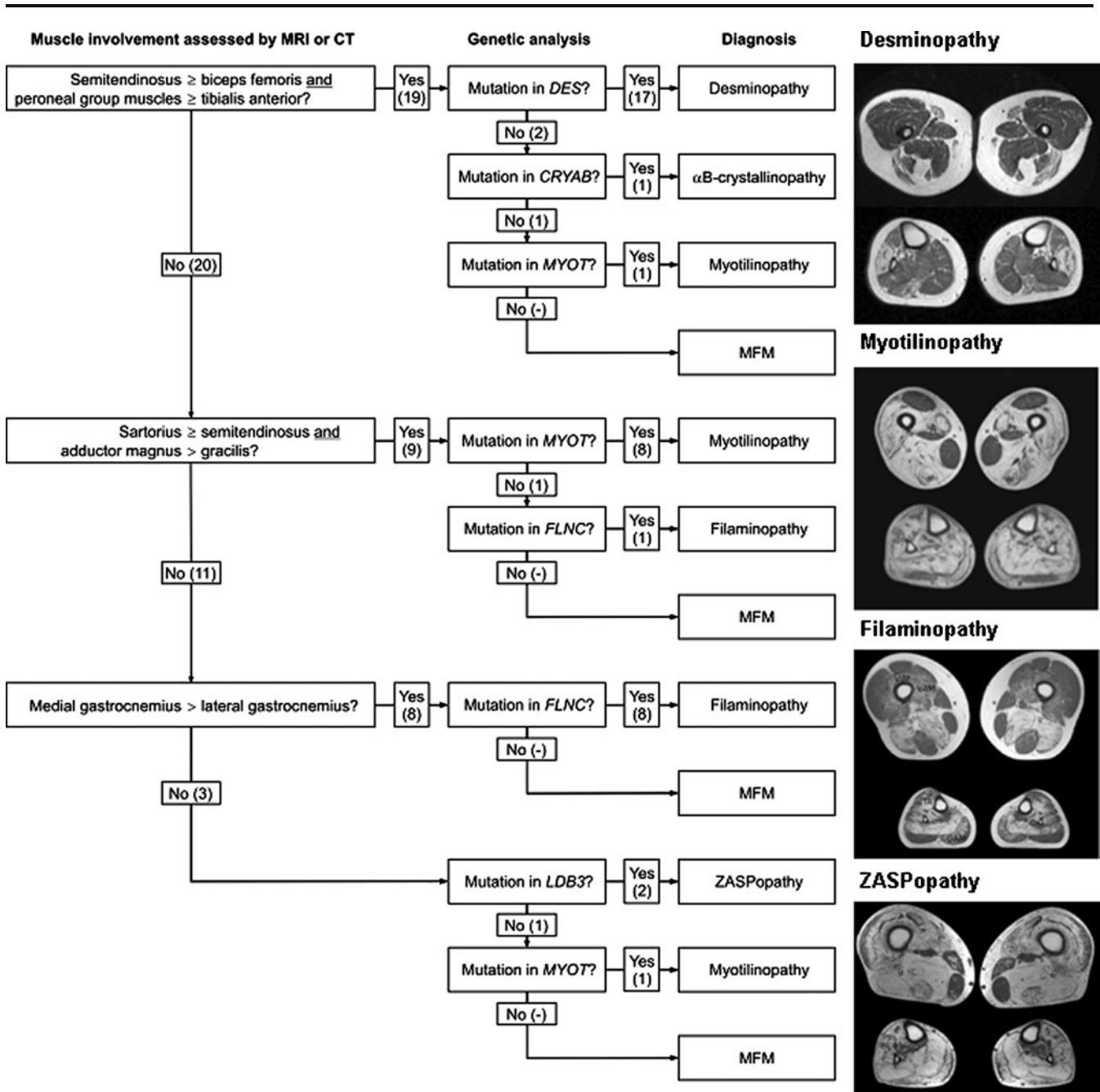
Fig. 5 Muscle imaging differences in myofibrillar myopathies. Highly specific and sensitive statistical criteria were identified in a systematic retrospective muscle imaging assessment in a large series of 43 MFM patients [24]. Equal or greater affliction of the semitendinosus than the biceps femoris and equal or greater affliction of the peroneal group than the tibial anterior muscles is highly specific for primary desminopathy and crystallinopathy (18 out of 19 patients). Those of the remaining patients who had equal or greater involvement of the sartorius than the semi-tendinosus and equal or greater involvement of the adductor magnus than the gracilis usually had a myotilin mutation (eight out of nine patients). All eight patients who did not fulfil the criteria for desmin and myotilin mutations and who had more involvement of the medial than the lateral gastrocnemius showed a filamin C mutation. Two of the three remaining patients had a ZASP and the third a myotilin mutation

of other organs in DM1 patients. Dypshagia is a common clinical finding in DM1 patients, which is reflected by a substantial dilatation of the oesophagus that can be easily detected and rated on MRI (Fig. 2).

Contrary to DM1, patients with DM2 are less affected based on MRI findings. A recently published whole-body MRI study including DM1 and DM2 patients showed that most of the DM2 patients showed no fatty degeneration,
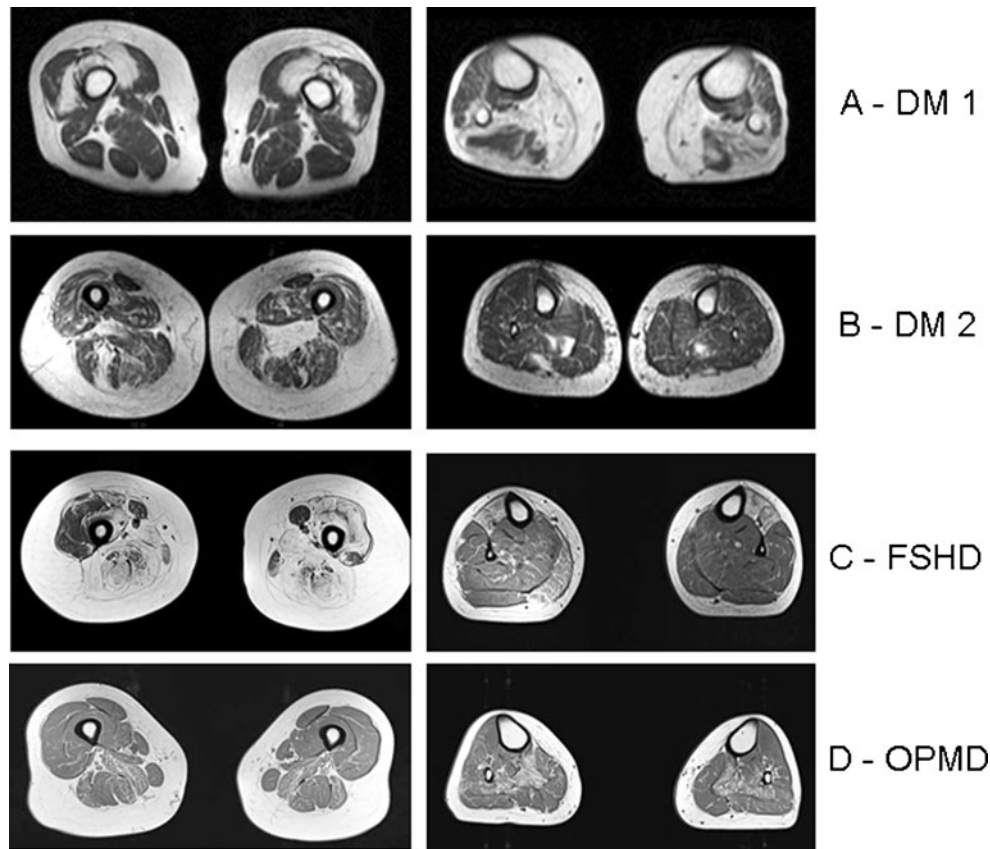
Fig. 6 Muscle MRI of lower extremities in other muscular dystrophies. Myotonic dystrophy type I (**a**) is typically characterised by distal more than proximal muscle involvement showing predominant affliction of the soleus, medial gastrocnemius and proximally the anterior thigh compartment with relative sparing of the rectus femoris. Patients with myotonic dystrophy type II (or proximal myotonic myopathy = PROMM) (**b**) are often less affected and show no fatty degeneration. Affected patients show more involvement of the proximal muscles with affliction of the quadriceps and sparing of the rectus femoris and gracilis muscles. FSHD (**c**) patients are often characterised by marked asymmetry with the adductor magnus, hamstrings, rectus femoris and tibial anterior being the most frequently affected muscles. OPMD (**d**) patients show predominantly posterior thigh (adductor magnus, semimembranosus and biceps femoris muscles) and posterior lower leg (soleus) muscle involvement

and none of the patients showed any inflammatory changes. The affected patients were exclusively men and showed damage predominantly of the trunk muscles (such as the erector spinae and gluteus) and in some cases involvement of the proximal and lower leg muscles with sparing of the rectus femoris and gracilis muscles in all DM2 patients [27].

Facio-scapulo-humeral muscular dystrophy

Facio-scapulo-humeral muscular dystrophy (FSHD) is the third most common muscular dystrophy (worldwide prevalence 1:20,000) [52]. FSHD is characterised by asymmetric loss of strength and atrophy of muscular tissue starting in the face and shoulder region [56]. These typical clinical findings are also mirrored on muscle imaging, which shows marked asymmetry and involvement of the medial gastrocnemius, the tibial anterior and the soleus muscles in the lower legs. At the thigh, the most frequently involved muscles are the semimembranosus, followed by the biceps femoris, the semitendinosus muscle and the adductor group muscles [57, 58].

Oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is a late-onset autosomal dominant dystrophy, and is clinically characterised by slowly progressive ptosis, dysphagia and dysphonia. Proximal limb weakness often develops subsequently [59]. There are few reports on muscle imaging in OPMD. Abnormal fatty infiltration of the tongue, masseter, neck, shoulder girdle, lumbar paraspinous and the gluteus muscles have been described [60].

Muscle imaging in non-dystrophic myopathies

In contrast to muscular dystrophies, the weakness in congenital myopathies (CM) is usually not progressive

over time. Presentation of hypotonia and weakness is "congenital" at birth or in the first years of life with delayed motor milestones. CMs are classified according to the predominant structural abnormality in skeletal muscle. In contrast to CM, most other non-progressive hereditary myopathies present with intermittent, episodic muscular symptoms as weakness (as episodic weakness in channelopathies) or exercise-related muscle pain and fatigue (as in metabolic myopathies related to disturbances of glucose, fat or mitochondrial metabolism.)

Congenital myopathies

CMs show distinctive morphological abnormalities such as rods, an abnormal number of central nuclei or (central or multiple) cores. Often these findings guide the physician to the correct genetic diagnosis. However, some pathological overlap between genetically distinct disorders has been described, making a genetic diagnosis sometimes difficult. Recently, different muscle imaging patterns in CM have been identified, which can be of help in the differential diagnosis.

Muscle imaging in patients with central core disease (CCD) caused by mutations in the ryanodine receptor 1 gene (RYR1) shows a characteristic pattern with main involvement of the gluteus maximus in the pelvis. At the thigh level, the most severe changes are observed in the medial compartment (adductor magnus) and in the anterior compartment muscles (vastus lateralis, vastus intermedius). Sparing of the adductor longus, gracilis and biceps femoris muscles is common. In the distal lower leg muscles, the soleus and the lateral head of the gastrocnemius muscles are most severely involved [61, 62]. This pattern seems to be highly characteristic, as muscular involvement in other congenital myopathies caused by mutations in the SEPN1, ACTA1, NEB or collagen VI encoding (COL6A1, COL6A2 and COL6A3) genes is different [1]. In addition to RYR1, patients with Ullrich CMD or Bethlem myopathy related to collagen VI encoding genes also present with dominant affliction of the anterior thigh compartment. These patients show an early and selective involvement of the centre of the rectus femoris and vastus lateralis muscles. In addition, in the lower legs there is often a rim of degenerative changes between the soleus and the gastrocnemius muscle, a pattern not observed in other CMs [63, 64].

Contrary to RYR1- and collagen 6A-related disorders, which have marked affliction of the anterior thigh, in most other CM forms the posterior rather than anterior thigh compartment muscles are affected. SEPN1 patients, often presenting as a rigid spine (multi-minicore) myopathy, typically show a selective affliction of the sartorius and posterior compartment muscles and a relative sparing of the quadriceps and the gracilis muscle [25]. In patients with dynamin 2-related autosomal dominant centronuclear myopathy (DNM2-CNM), muscle imaging shows predominantly distal lower leg muscle affliction (medial head of the gastrocnemius, soleus), milder involvement of the

posterior thigh compartment (mostly the biceps femoris and semimembranosus muscles) and the gluteus minimus muscle. The sartorius and gracilis are often spared [65]. Congenital (nemaline) myopathies related to ACTA1 gene mutations show predominantly distal anterior lower leg and mild diffuse thigh compartment involvement. On the other hand, nebulin gene-associated nemaline myopathies often spare the thigh muscles and show selective distal involvement of the soleus and tibial anterior muscles [66]. A useful flowchart for the differential diagnosis of CM using muscle imaging is provided in Fig. 7.

Muscle channelopathies and metabolic myopathies

Compared to the increasing data regarding the diagnostic value of neuromuscular MRI in patients presenting with dystrophic myopathies or non-dystrophic congenital myopathies, data concerning MRI findings in muscle channelopathies or metabolic myopathies are rather limited. A recently published study focussed on patients with myotonia congenital type Becker, a non-dystrophic generalised myotonia caused by mutations in the muscle chloride gene. Although all patients presented with a severe disabling myotonia, no fatty degeneration or muscle oedema could be detected by using a whole-body high-field MRI protocol [67]. These findings suggest that conventional MRI techniques are less sensitive in the detection of changes in channelopathies. Recent experimental studies using ^{23}Na-MRI instead of or in combination with ^{1}H-MRI have shed some light on the muscle cell function and disease process in Na-channelopathies by demonstrating Na-accumulation during episodes of weakness [33, 68].

Future perspectives

During the past 5 years an abundant amount of data has been published concerning the degree and pattern of striated muscle involvement in inherited muscle disease. These data have led to a new era in the non-invasive diagnosis of neuromuscular diseases. The diagnostic flowcharts presented in this review are based on these data collected during the past few years. However, this is just a beginning, and we have still a long way to go. Continuously new genetic disease entities leading to muscle dystrophy can be identified and described by using new diagnostic tools. Therefore, the role of neuromuscular imaging has to be considered as a dynamic field of research that will gain even more importance in the near future. While the first imaging approaches focussed mainly on certain muscle groups primarily of the lower limbs, current and future imaging protocols should consider a "whole-body approach" such as whole-body muscle MRI including the muscle of the trunk, shoulder girdles and upper extremities. This can extend the possibilities for pattern description and recognition.
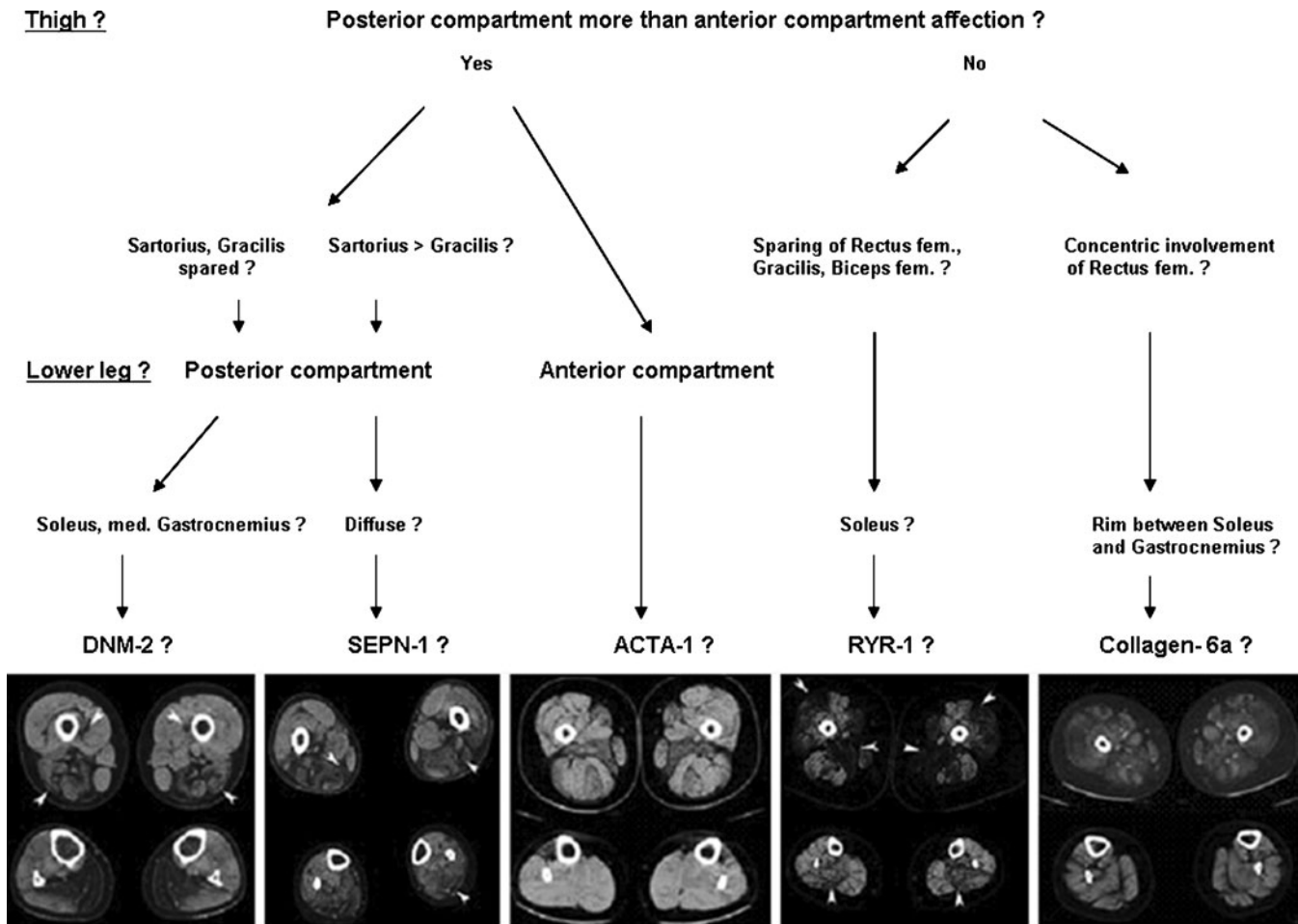
Fig. 7 Flowchart showing a useful approach to the differential diagnosis of congenital myopathies. We highly recommend systematically analysing muscle imaging findings beginning with the thigh muscles. The first distinction should be made according to the relation of posterior to anterior thigh muscle involvement. Most CMs show greater affliction of the posterior rather than the anterior thigh muscles. In the second step, the same relation should be assessed in the lower legs. Predominant posterior thigh and posterior lower leg involvement with sparing of the gracilis and sartorius but marked affliction of the soleus and medial gastrocnemius is observed in DNM2-CNM. Predominantly posterior thigh with marked affliction of the sartorius and predominantly diffuse posterior lower leg involvement are typical findings of SEPN1-related CM. Posterior thigh but anterior leg involvement was observed in CM patients with ACTA1 mutations. On the other hand, marked anterior thigh affliction is seen in RYR1- and collagen 6A-related CM. In addition, RYR1 patients show sparing of the rectus femoris, gracilis and biceps femoris and often marked affliction of the soleus muscle, while patients with a collagen 6A defect show a special rim with the beginning of degeneration within the rectus femoris muscle and a degenerative rim between the soleus und gastrocnemius muscles. Typical muscle imaging findings of patients with proven mutations in the DNM2, SEPN1, ACTA1, RYR1 and collagen 6A1 are provided

In addition to the available cross-sectional data, it would be interesting to gain more longitudinal data in order to understand the disease evolution and the prognostic role of subclinical changes detected by MRI or ultrasound. In particular, the possible role of imaging for treatment monitoring is of great interest, and first approaches in metabolic diseases are promising [69, 70].

The potential role of advanced MRI techniques such as perfusion-weighted imaging, diffusion-weighted imaging and MR spectroscopy is currently unknown. It can be suggested that some of these techniques can further increase the sensitivity in the detection of subtle changes in the striated muscle and contribute to a better understanding of the underlying pathophysiological mechanism [32–35]. It is of great interest whether these imaging techniques will show additional diagnostic and prognostic value. High-field MRI is increasingly being used in the clinical setting [71, 72]. Due to a substantial increase in the signal-to-noise ratio, in vivo imaging at higher magnetic field allows faster image acquisition and higher spatial resolutions. The first whole-body high-field muscle MRI protocols have been recently described [27, 51, 67]. Future studies have to investigate whether structural and quantitative (perfusion MRI, MR spectroscopy) high-field MRI protocols do have added value in the diagnosis of hereditary, metabolic or inflammatory muscle disease.

The role of contrast-enhanced imaging US and MRI techniques is still unclear. The first imaging studies using gadolinium(Gd)-based contrast-enhanced MRI have been published in denervated muscles and inherited dystrophic

muscle disease [31, 73]. However, whether Gd-based contrast MRI leads to be an improvement in the diagnosis of hereditary muscle dystrophies is not clear. Perhaps more specific contrast media agents such as small iron oxide particles (SPIO) can contribute to a better visualisation and understanding of inflammatory and degenerative changes in striated muscles.

Conclusion

The importance of clinical muscular imaging is becoming increasingly obvious in patients with suspected or proven inherited muscle diseases. Musculoskeletal US is a well-established, easily applicable and cost-effective screening technique for the detection of dystrophic changes in the striated muscle, particularly in young children. However, MRI is becoming the technique of choice in the diagnostic workup of patients with suspected hereditary muscle diseases. The role of MRI goes far beyond the pure detection of inflammatory and/or dystrophic changes. Using whole-body MRI protocols, we are able to identify muscle involvement per muscle and quantify the degree of dystrophic changes according to established rating scales leading to a description of involvement patterns. These sometimes distinct patterns of involvement can further narrow the differential diagnosis and might lead to the correct diagnosis even before invasive diagnostic procedures such as muscle biopsy.

Recently introduced advanced and quantitative MRI methods including T2 relaxation time measurements, muscle fat quantification using the 3-point Dixon technique, magnetic resonance spectroscopy and perfusion imaging are quite promising, but also challenging in terms of the quantification and further specification of the disease process and disease monitoring. In addition, quantification of muscle volume by muscle MRI and advanced quantitative MRI methods may be used for controlling the safety and efficacy of (experimental) treatment. Further in vivo studies are needed to investigate whether these methods are useful for implementation in a clinical routine setting.

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