Workshop report

TREAT-NMD workshop: Pattern recognition in genetic muscle diseases using muscle MRI
25–26 February 2011, Rome, Italy

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1. Introduction

The TREAT-NMD workshop on pattern recognition by magnetic resonance imaging (MRI) of skeletal muscle is one in a series of workshops that have been organised by TREAT-NMD to discuss the application of MRI in neuromuscular diseases. In recent years MRI has become more widely used in patients with neuromuscular diseases because the extent and localisation of muscle pathology can provide useful information for the diagnostic workup of patients. In a number of diseases the pattern of selected muscle involvement detected by MRI can almost be pathognomonic and can therefore guide genetic testing, besides the advantage of targeting the optimal muscle for biopsy. Various groups have now reported their experience with muscle MRI in defined patient cohorts and have started to delineate specific patterns of muscle pathology. Muscle pathology in degenerative diseases can be described on T1 weighted axial images of the pelvic girdle and leg muscles and refers to fatty replacement of skeletal muscle tissue. There is still fairly little experience in describing muscle pathology by whole-body MRI or MRI of the truncal and upper limb muscles, although several centres are now starting to explore these applications more systematically.

The degree of muscle pathology can be described semi-quantitatively using various scales that have been suggested in the literature \cite{1} and more and more also quantitatively with a variety of different sequences. For pure diagnostic purposes there is no need to describe the pattern of muscle pathology in a quantitative fashion, because this correlates with the duration of the disease, but rather to focus on the involvement of distinct muscles. Most patient series that have been described so far by muscle MRI are rather small and we still know fairly little about the spectrum of pathology detected by MRI in larger cross-sectional studies. It is currently unclear how many MRI scans one would need to collect before it is possible to speak of a disease-specific pattern of muscle pathology. There are still a number of questions that need to be addressed: When do the first signs of muscle pathology start? What is the degree of progression of pathology assessed by muscle MRI? What is the spectrum of pathology in a homogenous patient population? Are there gender or ethnic differences? Does the pattern of muscle pathology vary with the type of mutation in a given gene? Does exercise influence the extent and localisation of muscle pathology? Answers to these questions will not only help us in our diagnostic approach to muscle diseases but will also provide us with useful information about the general pathophysiology of these diseases. Knowledge about the pattern and progression of muscle pathology can also help to select muscles for quantitative MRI assessments and outcome measure development.

The workshop in Rome brought together neuromuscular clinicians, radiologists and MRI physicists from Finland, France, Germany, Italy, the Netherlands, Spain, Switzerland and the United Kingdom. The participants had specific expertise in a number of muscle diseases, which were discussed sequentially. The main objectives of the workshop were to share expertise about the application
of muscle MRI, to better define the pattern of muscle pathology detected by MRI in a number of genetic muscle diseases, to agree how to collect data more systematically, to develop differential diagnoses for patterns of skeletal muscle pathology and to develop collaborative projects. The workshop also served to provide an idea of the number of muscle MRI scans that are currently available for specific diseases and to identify areas in which more scans need to be collected. The collection of data from different centres could ultimately be used to produce a “diagnostic atlas” for muscle MRI. The workshop report only includes MR scans and schematic figures for those diseases where a selective pattern of muscle involvement seems to have emerged.

2. Pattern recognition in congenital myopathies by MRI

The congenital myopathies - Central Core Disease (CCD), Multi-minicore Disease (MmD), Centronuclear Myopathy (CNM) and Nemaline Myopathy (NM) - are the group of diseases that have remarkably benefitted from the application of muscle MRI for diagnostic purposes [2–6]. Clinically this genetically very heterogeneous group of muscle diseases shows a lot of overlap and muscle pathology can often be very unspecific. Even in the case of distinct structural abnormalities on muscle biopsies, it can still be challenging to identify the underlying genetic cause of the disease. Moreover, many of the genes responsible for congenital myopathies are rather large and sequencing is often not routinely available. The application of muscle MRI and the characterisation of patterns of muscle pathology have helped to improve the diagnostic workup in a number of congenital myopathies.

2.1. RYR1-related myopathies

Heinz Jungbluth reported on the London experience using muscle MRI in congenital myopathies associated with mutations in the skeletal muscle ryanodine receptor (RYR1) gene. The RYR1-related myopathies present a real diagnostic challenge because of the marked clinical and histopathologic variability associated with mutations in this gene. Heinz Jungbluth introduced the clinical and pathological spectrum of the RYR1-related myopathies and explained the different underlying pathogenetic concepts related to ryanodine receptor (RyR1) dysfunction and protein reduction, respectively. Different mutations can have different effects on the receptor protein. RYR1 mutations have now been implicated in most congenital myopathies except nemaline myopathy but the phenotypical spectrum is still expanding. Clinically, severity of RYR1-related myopathies ranges from profoundly affected neonates within the fetal akinesia spectrum to mildly affected adults with a predisposition to exertional myalgia and rhabdomyolysis but no muscle weakness. Pathologically, in addition to the central cores, the “classical” feature, a much wider spectrum of associated muscle biopsy findings has recently emerged, ranging from type I predominance or uniformity, congenital fibre type disproportion, increased internal nuclei and multi-minicores to almost dystrophic features [7]. Muscle MRI on the other hand often shows a very distinctive pattern in RYR1-related myopathies and therefore has a clear place in the diagnostic workup of these patients [8].

On T1 weighted (T1w) axial images through the thigh and the calf in patients with the “classical” form of autosomal dominant (AD) CCD, prominent involvement of the vasti compared to the rectus femoris muscle and of the adductor magnus compared to the adductor longus muscle are typical (Fig. 1a), although the distinction between these muscle groups can be more pronounced in some patients than others. Differential involvement of the rectus femoris compared to the vastus intermedius muscle can easily be

Fig. 1. The figure shows panels of axial T1 weighted MR images through the left thigh and calf of various myopathies and corresponding drawings that illustrate the selective muscle involvement in shades of gray, with white being most severely affected and black being normal. RYR1, autosomal dominant ryanodine receptor 1 associated myopathy; SEPN1, selenoprotein 1 associated congenital myopathy; Bethlem, autosomal dominant Bethlem myopathy caused by collagen VI mutations; DNM2, dynamin 2 associated centronuclear myopathy, LMNA, laminopathy. The MR images provide examples of selective muscle pathology in individual patients, whereas the drawings summarize typical patterns of muscle pathology according to current knowledge.
picked up on muscle ultrasound, even in small children [9,10]. The sartorius is often more affected than the gracilis, which may cause differential diagnostic problems with SEPN1-associated myopathies (see below). The anterior compartment of the thigh is generally more severely affected than the posterior compartment, where the semitendinosus and/or the semimembranosus are variably preserved. In the calf, the soleus muscle is often the most severely affected, while both the lateral and medial head of the gastrocnemius muscles are variably involved (Fig. 1a). The peroneus longus is more severely affected than the tibialis anterior muscle. Overall there appears to be little progression of muscle pathology as detected by MRI in the disease, and the pattern may often look the same in parents and their children harbouring the same RYR1 mutation.

Patients with recessively inherited RYR1-related myopathies are often more severely affected clinically, and this is also reflected in their MRI scans. In particular those with extraocular muscle involvement may show more diffuse muscle MRI involvement corresponding to overall more diffuse weakness. There are a number of additional RYR1-associated phenotypes, e.g. with predominant paraspinal muscle pathology, that are not yet very well defined and whose muscle MRI doesn’t follow the typical pattern of an RYR1 myopathy but may show marked involvement of the paraspinal muscles [11]. Patients with the malignant hyperthermia susceptibility (MHS) trait due to RYR1 mutations may have a normal muscle MRI or even feature overt muscle hypertrophy.

Following a general overview, Heinz Jungbluth presented three cases that illustrated the diagnostic value of muscle MRI in patients with RYR1-related myopathies. In each of these cases, the pattern of selective involvement on muscle MRI was more predictive of the genetic cause of the disease than the muscle biopsy findings which were non-specific. Vice versa, he also demonstrated that without the typical RYR1-associated muscle MRI pattern, core-like structures on muscle biopsy are most likely not caused by RYR1 mutations.

Francesco Muntoni presented data from a series of 37 scans in patients with RYR1 mutations [8], half of whom had dominant and half recessive mutations. The pattern of muscle pathology was fairly consistent throughout the longitudinal axis of the muscle, although variability was detected in paraspinal muscles, the sartorius and the gracilis. Susana Quijano-Roy reported on the experience of the Paris group with RYR1 patients, which was very similar to that of the London group [5]. On whole-body MRI scans the Paris/Garches group also detected involvement of facial muscles, including the tongue, and of the masseter and temporalis muscles. The biceps brachii muscles were also more frequently affected in RYR1-associated myopathies than in other congenital myopathies.

The most important differential diagnosis for RYR1-associated myopathies are congenital myopathies caused by SEPN1 mutations. In SEPN1 patients the sternocleidomastoid muscles seem to be most severely affected, whereas (in contrast to RYR1-associated myopathies) other facial or masticatory muscles appear to be spared. There is currently limited experience with ultrasound investigations in these diseases, but the changes in the sternocleidomastoid muscles in SEPN1 or the biceps brachii muscles in RYR1-related myopathies may well be detectable by muscle ultrasound. It is primarily at the severe end of the clinical spectrum that there is most difficulty distinguishing between SEPN1- and RYR1-related myopathies by muscle MRI. A muscle MRI pattern similar to that of patients with RYR1-related myopathies can also be found in patients with SMA III, in whom hypertrophy of the adductor longus can be quite prominent, and in patients with X-linked myotubular myopathy [12].

2.2. Nemaline myopathies

Patients with genetically confirmed nemaline myopathies have not been characterised in great numbers by muscle MRI. A first study using muscle imaging was published by Carina Wallgren-Pettersson more than 20 years ago, when the underlying mutations of the patients were unknown [13]. It is now known that 11 of the 12 originally reported patients have NER mutations and only one has an ACTA1 mutation. The rectus femoris and vastus intermedius muscles seem to be most severely affected in nebulin patients. The tibialis anterior muscle is often more severely affected than one would expect from the clinical picture, although patients with nebulin mutations can also present with a distal myopathy. Bjarne Udd presented patients with homozygous missense mutations in the nebulin gene that presented with a distal myopathy and severe involvement of the tibialis anterior muscles on MRI [14]. These patients did not show nemaline rods in their muscle biopsies and on muscle MRI the thigh muscles showed little pathology. This is also in keeping with findings in a small series reporting muscle MR imaging findings in patients with NER-related nemaline myopathy and mild to moderate clinical severity, where tibialis anterior involvement was the earlier sign before any significant thigh involvement [15]. Susana Quijano-Roy presented whole-body MRI scans from severely affected patients with nebulin mutations. In the lower leg, the tibialis anterior and soleus muscles were affected, whereas the gastrocnemius muscles were well preserved. Thigh muscles were diffusely affected without selectivity on muscle MRI, whereas in the masticatory muscles a selective and striking involvement of the lateral pterygoid muscle was observed, while all other masticatory muscles were well preserved. Francesco Muntoni also reported on a patient with one nebulin mutation that clinically showed profound foot drop and presented with distinct pathology in the tibialis anterior and the vastus intermedius muscles on MRI.

Patients with ACTA1 mutations seem to show less involvement of the anterior compartment muscles in the
lower leg than patients with nebulin mutations, but there is not yet sufficient experience for a consistent pattern to be evident. The clinical spectrum of ACTA1-related patients is also very broad.

Larger systematic muscle MR imaging studies are clearly required in different forms of nemaline myopathy with different genetic backgrounds.

### 2.3. SEPN1-related myopathies

Susana Quijano-Roy introduced the clinical picture of SEPN1-associated myopathies. Patients typically present with generalised weakness, spinal rigidity, scoliosis and respiratory problems. Clinically many show atrophy of the sartorius muscles, which is also a hallmark of the muscle MRI pattern (Fig. 1b). Sometimes it can even be difficult to detect the sartorius muscle on MRI scans at all. In the anterior compartment of the thigh, the rectus femoris is normally well preserved, while the vasti may be affected in the most severe cases. In the medial compartment of the thigh, the adductor magnus is the most severely affected muscle, with the adductor longus and gracilis muscles being spared. The posterior compartment of the thigh shows often fatty degeneration of the biceps femoris and semitendinosus muscles with the semimembranosus muscle usually being spared (Fig. 1b). The gluteal muscles can also be severely affected in SEPN1-related myopathies, whereas there is relatively little involvement of the lower leg muscles. In case of lower leg pathology, the soleus and gastrocnemius muscles seem to be the first muscles to be affected, but normally less than e.g. in RYR1-related myopathies (Fig. 1a,b). On whole-body MRI selective atrophy of the sternocleidomastoid muscles is clearly visible in the neck. The thoracic paraspinal muscles are the first muscle with abnormal MRI signals and the intercostals muscles are also involved early in the course of the disease. The arm and masticatory muscles are in contrast to patients with RYR1-related myopathies very well preserved.

Eugenio Mercuri demonstrated that at early stages of the disease only the sartorius and gluteal muscles may be affected. In very mild SEPN1 cases it can be difficult to detect muscle pathology by sequential MRI of the pelvic and lower limbs at all, if the sartorius isn’t affected. At later stages the pattern of muscle pathology can become more diffuse and the vasti may also become involved, although the sartorius always appears to be the most severely affected muscle. Overall, the posterior compartment in the thighs is relatively well preserved in SEPN1-related myopathies. One major difference between typical SEPN1- and typical RYR1-related myopathies is that the vasti are often relatively well preserved in SEPN1 patients (Fig. 1b). In patients with lamin A/C (LMNA)-associated muscle diseases, which can be difficult to diagnose on purely clinical grounds, the sartorius muscle seems always to be spared.

Francesco Muntoni pointed out that the overlap in the muscle MRI pattern between SEPN1 and RYR1 patients may also be related to the overlap in the pathomechanisms of the diseases. Both diseases have been reported to show an abnormal redox potential. Interestingly, patients with selenocysteine (Sec) insertion sequence-binding protein 2 (SBP2)-related myopathy also show sartorius involvement [16], not dissimilar to primary SEPN1 myopathy, but the patients also have endocrinological problems.

### 2.4. Collagen VI-related disorders

In one of the first more comprehensive publications on sequential muscle MRI in patients with collagen VI-related myopathies [17] it was pointed out that the medial thigh muscles are less severely affected than the lateral thigh muscles and that the rectus, sartorius and gracilis muscles are normally spared. In Bethlem myopathy the periphery of the muscles, especially the vasti, is more affected than the central part (concentric atrophy) (Fig. 1c). The peripheral muscle involvement is also visible in the calf, where one of the first signs is often a “rim” of fatty infiltration between the soleus and gastrocnemius muscles (Fig. 1c). Eugenio Mercuri presented data from 40 cases that have recently been published [18]. He pointed out that there is a clear overlap in the muscle MRI pattern between Ullrich congenital muscular dystrophy (UCMD) and Bethlem myopathy. In UCMD patients the soleus is often very strongly affected. Bethlem patients on the other hand frequently show an “internal shadow” (fatty infiltration) in the central part of the rectus femoris muscle (Fig. 1c). Susana Quijano-Roy presented whole-body MRI scans from patients with UCMD. In contrast to some of the congenital myopathies, the patients did not show any involvement of tongue or masticatory muscles. Neck extensors were moderately affected whereas the periscapular muscles showed diffuse involvement with the anterior serratus, latissimus dorsi and the subscapularis muscles being most severely affected. On whole-body MRI an almost pathognomonic striped pattern could be detected in lower limb muscles, the deltoid, subscapularis, triceps, paraspinal and gluteal muscles. Only one young mild case showed a different pattern with mild abnormal signal in the lumbar paraspinal, gluteal and thigh muscles. Robert Carlier showed MRI scans of the arm muscles with a similar pattern to the thigh muscles with predominant peripheral involvement and central preservation of the tissue. The calf muscles may be very well preserved.

Overall, muscle MRI is a very good diagnostic tool to guide molecular testing in collagen VI-related myopathies. From the London experience it was suggested that muscle MRI might be more helpful than fibroblast analysis (skin biopsy) or muscle biopsy analysis for collagen VI expression. The pattern of muscle involvement in collagen VI related myopathies is probably pathognomonic on whole-body MRI. However, similar MRI changes in the lower limb muscles have been observed in a few cases with mild laminin 22 chain deficiency (MDC1A), calpain 3-deficiency and dysferlin-associated muscle diseases.
2.5. Centronuclear myopathies

Centronuclear myopathies (CNM) can be caused by mutations in a number of genes, namely MTM1 (X-linked), DNM2 (AD), BIN1 (AR) and RYR1 (AR), and are primarily defined by the appearance of centrally located myonuclei [19]. Of these, most muscle MRI data have been collected in DNM2-related CNM [20], although sufficient data are not yet available in any of the CNMs for a typical pattern to be suggested. Dirk Fischer described the clinical picture of patients with CNM and pointed out that patients with dynamin 2 (DNM2) mutations in particular may show a very broad spectrum of clinical severity. On muscle MRI a more distal than proximal involvement is often found in patients with DNM2 mutations. In the thigh, the posterior muscles (SM, biceps, ST) are more severely affected than the anterior muscles (Fig. 1d). The same is true for the calf muscles, of which the medial gastrocnemius and the soleus muscles are most severely affected (Fig. 1d). The tibialis anterior and the muscles of the lateral compartment do show some pathology, but less than the soleus and gastrocnemius muscles. The gluteal muscles are frequently severely affected. Both the gracilis and sartorius muscles are relatively spared. The rectus femoris muscle is also in most cases spared, but has been reported to be affected in a few cases [21]. Whole-body MRI scans have shown that the masticatory and axial muscles are also involved in DNM2-associated CNM, whereas the gluteal muscles are normally spared [22].

One of the genes that has more recently been recognised to cause a histological picture of CNM and congenital fibre type disproportion is the RYR1 gene. Most patients are compound heterozygous for a missense and a nonsense mutation. Heinz Jungbluth pointed out that patients with recessive RYR1-related CNM can clinically resemble patients with congenital myotonic dystrophy type 1, considering the shared feature of temporal muscle wasting, and patients with MTM1-related myotubular myopathy, considering the shared feature of extraocular muscle involvement. Corresponding to findings in other recessive RYR1-related myopathies, the pattern of selective muscle involvement in the few reported cases with RYR1-related CNM [23] is similar but more diffuse than the pattern observed in typical dominant RYR1-related CCD. Interestingly, the muscle MRI pattern seen in RYR1-related myopathies shows some overlap with that reported in X-linked myotubular myopathy, probably reflecting the shared pathomechanism of primary and secondary RyR1 disturbance. Dirk Fischer presented the clinical picture of MTM1-associated CNM and the muscle MRI pattern found in this X-linked condition and highlighted the similarities to the pattern observed in RYR1-related CNM. In addition to the obvious similarities between the two genetically distinct conditions, it was pointed out that in MTM1-related CNM the rectus femoris and the biceps femoris muscles might be more severely affected than in RYR1-related CNM.

Only a small number of MRI scans have been published for patients with BIN1 mutations [24]. The pathology looks different to the pattern described for RYR1 and DNM2-associated CNM, with the tibialis anterior being most severely affected. Robert Carlier presented whole-body MR images from a patient with BIN1 mutations with fairly diffuse fatty infiltration in almost all muscles. The semitendinosus muscles were slightly more affected than the other thigh muscles. The arm and forearm were also involved, whereas the masticatory muscles were well preserved. It is still too early to make any statements about a muscle MRI “pattern” for patients with BIN1-related CNM.

2.6. Laminopathies

The spectrum of clinical phenotypes in laminopathies is very broad, and this is reflected in the fairly unspecific muscle MRI findings [18,25]. Muscle involvement can be severe and diffuse at early stages and occasionally there might be reduced fat around muscles. Eugenio Mercuri explained that there is a recognisable muscle MRI pattern (Fig. 1e), but that inter- and intra-familial variability can be broad. Involvement of the thigh muscles is variable and findings may even be normal. The vastus lateralis is often the most severely affected muscle (Fig. 1e), while the medial thigh muscles are normally less affected. In the calf the medial gastrocnemius is most prominently involved (Fig. 1e), along with the soleus. Overall it can be very difficult to use muscle MRI findings to aid the diagnosis of a laminopathy.

Susana Quijano-Roy presented a severe case of congenital laminopathy with respiratory failure, distal weakness in the leg and proximal weakness in the arm muscles. Whole-body MRI showed that there were almost no limb or trunk muscles visible at 10 years of age. Only the forearm and psoas muscles were spared. She also presented a patient with late onset LMNA-associated Emery Dreifuss muscular dystrophy who was less affected and didn’t show any involvement of the medial gastrocnemius muscle. Jorge Diaz presented muscle MRI findings in a laminopathy family with five affected members. The patients showed different degrees of muscle pathology with involvement of the paravertebral muscles, which showed signs of atrophy. The findings in the calves and thighs were similar to the findings reported by Eugenio Mercuri. Some patients showed concentric wasting of the vastus lateralis muscles. Bjarni Udd also presented a case with similar MRI findings in the vastus lateralis muscle. The pathology looked very much like the pathology in Bethlem myopathy, but with a normal rectus femoris structure.

Robert Carlier presented the MRI findings from 25 laminopathy cases. He also found that atrophy was very obvious in the thighs. In his series of cases the posterior compartment in the thigh showed more involvement than the anterior compartment. In the calves of his patients the medial gastrocnemius was also more severely affected than the lateral gastrocnemius. The paraspinal muscles...
were generally involved, whereas interestingly the neck muscles and the arm muscles were only very little affected. He did not find any involvement of the masticatory muscles.

3. Pattern recognition in limb girdle muscular dystrophies by MRI

The limb girdle muscular dystrophies (LGMDs) are a very heterogeneous group of genetic muscle disorders that have a more proximal than distal phenotype. The vast majority of LGMDs are inherited in an autosomal recessive fashion and show a progressive disease course with predominant involvement of the shoulder and pelvic girdle muscles. Many other neuromuscular diseases not classified as LGMDs can also present with progressive limb girdle weakness and the diagnostic workup of patients with progressive limb girdle weakness can therefore be rather challenging. Over recent years muscle imaging has been applied to many of the LGMDs to see whether there is any added diagnostic value [4,28–30].

3.1. Limb girdle muscular dystrophy 2A (LGMD2A, calpainopathy)

Mutations in the CAPN3 gene are in many countries the most common cause of autosomal recessive LGMD. Clinically, many patients present with a classical pattern of progressive proximal weakness. Dirk Fischer presented muscle MRI data from patients with LGMD2A. Typically, all patients show prominent involvement of the gluteal and posterior compartment muscles of the thigh (Fig. 2a). The gluteus maximus muscle can be atrophic. Pathology seems to start in the adductor magnus muscle and spreads to the semitendinosus and thereafter to all the hamstring muscles. The posterior compartment is also more severely affected in the lower legs. Even in advanced stages of the disease, the tibialis posterior muscle is in most cases very well preserved. There can be some overlap with collagen VI-related disorders in that the atrophy and fatty replacement of muscle starts peripherally [29,31].

Eugenio Mercuri also presented muscle MRI data that confirmed the involvement of the adductor magnus muscle at early stages of the disease. In the vastus intermedius muscle the peripheral involvement might start from the medial part and less from the lateral.

3.2. Limb girdle muscular dystrophy 2B/Miyoshi myopathy (LGMD2B, dysferlinopathy)

Patients with mutations in the DYSF gene can present with either more proximal (LGMD2B) or more distal muscle involvement (Miyoshi Myopathy, MM). Over the course of the disease these phenotypes often overlap and patients show both proximal and distal involvement, especially of the leg muscles. Almost every muscle can be affected in LGMD2B. Jorge Diaz presented muscle MRI data from 29 patients (14 MM, 12 LGMD2B, 1 asymptomatic hyperCKemia, and 2 symptomatic carriers). The MM and LGMD2B patients showed no difference in their rate of disease progression [32]. In the thigh, muscle pathology generally seems to start in the adductor magnus muscle and then affects the semimembranosus and the vastus lateralis muscles (Fig. 2b). Similarly to many of the other LGMDs and to Pompe disease, the rectus, gracilis, and sartorius muscles were normally spared. In the calf there was no big difference between MM and LGMD2B patients. The posterior compartment was predominantly affected. Overall there was no clear correlation between disease onset, disease progression and muscle MRI findings. Muscle pathology in dysferlinopathy can be asymmetric.

Jorge Diaz also presented STIR abnormalities in a 3 year old patient with dysferlinopathy who had been diagnosed with a high serum CK activity. The STIR signal was

Fig. 2. The figure shows panels of axial T1 weighted MR images through the left thigh and calf of various forms of autosomal recessive limb girdle muscular dystrophy (LGMD2) and corresponding drawings that illustrate the selective muscle involvement in shades of gray, with white being most severely affected and black being normal. The MR images provide examples of selective muscle pathology in individual patients, whereas the drawings summarize typical patterns of muscle pathology according to current knowledge.
abnormal in the adductor magnus and the medial gastrocnemius muscle. These findings have also been confirmed in adult patients with dysferlin mutations and high CK levels. Francesco Muntoni did also present a case of an early diagnosed dysferlinopathy patient with abnormal STIR images.

Maggie Walter presented muscle MRI data from her Munich cohort of dysferlinopathy patients and showed that muscles of both the anterior and posterior compartment can be diffusely affected. Interestingly, she didn’t find a clear difference in the extent of thigh muscle pathology between MM and LGMD2B patients. In the calf the gastrocnemius medialis and lateralis and the soleus muscles were most severely affected (Fig. 2b). Overall, the pattern of muscle involvement is very variable in dysferlinopathy patients and the calf muscles seem to be the earliest and most severely affected in both LGMD2B and MM. As seen in many other of the LGMDs, the tibialis anterior muscles were well preserved until late stages of the disease. The gluteus minimus muscle is almost always affected in patients with dysferlinopathy, whereas the gluteus maximus might sometimes be spared [33].

3.3. Sarcoglycanopathies

Although the four autosomal recessive sarcoglycanopathies (LGMD2C-2F) are among the best clinically characterised LGMDs, there are very few muscle MRI data available. Dirk Fischer summarized the MRI findings for the sarcoglycanopathies. Similar to Duchenne and Becker muscular dystrophy the most severe changes are seen in the anterior compartment of the thigh with very little pathology in the lower legs (Fig. 2c).

Bjarne Udd presented MRI images of a 22-year-old female patient with the common SGCA (R77C) mutation, who was just ambulant. Except for the sartorius and the gracilis muscles all of her thigh muscles were almost completely replaced by adipose tissue. Interestingly, in her calf the tibialis anterior muscle was affected. The same pattern of muscle involvement was found in a 21-year-old non-ambulant patient with sarcoglycanopathy (LGMD2D, common SGCA mutation), who also showed tibialis anterior involvement. In a 27-year-old female patient with the same mutation almost all muscles except the lateral gastrocnemius muscles were replaced by adipose tissue. Francesco Muntoni presented a case that showed both gastrocnemius and peroneal muscle involvement.

Other muscle MRI scans from patients with sarcoglycanopathies showed that at earlier stages of the disease the calf muscles are normally not involved. Susana Quijano-Roy presented a whole-body MRI scan from a 12-year-old patient whose arm muscles were very well preserved whereas the shoulder girdle muscles were affected.

3.4. Limb girdle muscular dystrophy 2I (FKRP, LGMD2I)

Most patients with autosomal recessive LGMD2I are affected by a homozygous founder mutation in the FKRP gene (c.826C > A). The mutation has the highest prevalence in Northern Europe and North America. Clinically, the age of onset, rate of progression and degree of severity varies greatly in LGMD2I patients.

Volker Straub presented muscle MRI data from a multi-centre study that was conducted in Newcastle upon Tyne, London, Copenhagen and Paris using both T1w and 3 point Dixon images. The study included 38 adult patients (19 male; 19 female) with the homozygous FKRP founder mutation (Fig. 2d). It had previously been reported that there is initial posterior involvement of the thigh muscles with gradual infiltration anteriorly as the disease progresses [28,30]. In the multi-centre study the biceps femoris (long head) muscle was most severely affected, with the semimembranosus and the semitendinosus muscles coming next (Fig. 2d). The vastus lateralis muscle was generally spared until late in the disease process. Fatty infiltration showed a reverse of the pattern in collagen VI-related disorders, with the lateral portion of the vastus lateralis being less involved. The sartorius and gracilis muscles were relatively spared and had a stippled appearance with hypertrophy when affected. The rectus femoris was also relatively spared with gross hypertrophy in less severe patients. Atrophied recti were seen in patients with more extensive changes, a feature noticed in several of the LGMDs. In the lower leg, involvement of the gastrocnemii and soleus muscles was most noticeable with relative sparing of the tibialis anterior muscle until a late stage (Fig. 2d). The study also identified gender differences that had not previously been reported for LGMD2I. In the anterior thigh of males, in contrast to females, median fat infiltration in the vastus medialis muscle was significantly more than in the vastus lateralis muscle. Diffuse fat infiltration of the gastrocnemii muscles was demonstrated in females, whereas in males more fat infiltration was detected in the medial than the lateral gastrocnemius.

Bjarne Udd presented muscle MRI data from LGMD2I patients with the common founder mutation. The first and most severely affected muscles in the thigh were the adductor magnus and the long head of the biceps femoris. Upper body MRI scans revealed involvement of the latissimus dorsi, pectoralis and serratus anterior muscles. Francesco Muntoni presented a 12-year-old boy with a homozygous founder mutation in whom the gluteal muscles and the adductor magnus muscles were also the first and most severely affected muscles. At this early stage of the disease the calf muscles were almost completely normal. The same pattern was found in an 8-year-old boy who was compound heterozygous for the founder mutation. A 24-year-old male patient did also show mild involvement of the tibialis anterior.

3.5. Limb girdle muscular dystrophy 2J (TTN, LGMD2J)

Limb girdle muscular dystrophy 2J due to mutations in the gene encoding titin is a rare form of autosomal recessive LGMD with the highest prevalence in Finland due to a founder mutation. Bjarne Udd reported that patients with the homozygous TTN founder mutation did not show...
a distinct muscle MRI pattern at the late stage of the disease when all muscles were involved, whereas involvement of the tibialis anterior muscle is a hallmark of the disease in heterozygous patients [36]. He also presented one newly diagnosed LGMD2J case of a 12-old girl with the homozygous mutation who did not show any clear MRI pathology despite clinical symptoms of proximal weakness and markedly elevated CK levels.

3.6. Limb girdle muscular dystrophy 2L (anoctamin 5 deficiency)

Over the last two years it has become evident that limb girdle muscular dystrophy 2L (LGMD2L), caused by mutations in the 
\(^{\text{ANO5}}\) gene, is one of the most common forms of autosomal recessive LGMD in Northern Europe and probably also in North America. It is an adult-onset condition with very high serum CK activity that predominantly affects male patients [34,35]. Volker Straub presented the clinical features and muscle MRI data of eight patients, six of whom presented with proximal and two with distal weakness in the legs. Disease duration at the time of examination ranged from 10–34 years. In contrast to other autosomal recessive LGMDs, the gluteal muscles are only moderately affected. Similarly to patients with LGMD2B, patients with LGMD2L may show asymmetric muscle involvement with both muscle atrophy and hypertrophy. In the thigh, the muscles of the posterior compartment are predominantly affected, especially the adductor magnus, semimembranosus and semitendinosus muscles (Fig. 2e). The gracilis, sartorius and short head of the biceps femoris muscle appear to be less affected or were only involved at later stages of the disease (Fig. 2e). The femoral quadriceps muscle also showed patchy fatty infiltration at more advanced stages of the disease with moderate involvement of the rectus femoris muscle. Calf muscle involvement was similar to that seen in patients with LGMD2A and LGMD2B, with severe atrophy of the medial gastrocnemius and soleus muscles. There was no or only minor involvement of the anterior and lateral compartment. Overall, the LGMD2L patients presented by Volker Straub showed a rather homogenous pattern of muscle involvement by MRI. Both proximal and distal muscles were affected in all individuals and no major differences were noticeable between patients with a more proximal or distal clinical presentation or different \(^{\text{ANO5}}\) mutations. Patients at different stages of the disease showed a more pronounced posterior involvement of the thighs and lower legs. There is a clear overlap of the muscle MRI pattern between LGMD2B and 2L (Fig. 2e).

Bjarne Udd presented 20 LGMD2L patients with a similar pattern to that of the Newcastle cohort. Although the gracilis and sartorius muscles were well preserved overall, there was more pathology in the gracilis muscle. On STIR (Short TI Inversion Recovery) images there were also clear abnormal signals in the vastus muscles. A few of the Finnish cases did show asymmetric involvement of the tibialis anterior muscle. One 63-year-old female patient (homozygous R758C mutation) who was first diagnosed with muscular dystrophy at 35 years of age because of a CK activity of ~3,000 U/l showed far less muscle pathology by MRI than her affected brother, with only mild involvement of the medial gastrocnemius muscles. A similar muscle MRI pattern was detected in another female patient of 48 years of age and her sister of 61 years of age. Udd assumed that LGMD2L will be found to be the most common form of LGMD in Finland, with a far broader mutation spectrum than seen in other LGMDs.

Robert Carlier presented the whole-body MRI of a 45-year-old male patient with LGMD2L with very asymmetric involvement in the thighs and calves and very well preserved gluteal muscles.

4. Pattern recognition in myofibrillar myopathies by MRI

The group of autosomal dominant myofibrillar myopathies (MFMs) is one of the best characterised groups of muscle diseases with regard to muscle MRI patterns [37–39]. One reason for this is the helpful application of MRI in the diagnostic workup of the different MFMs, which can be caused by mutations in a number of different genes, namely CRYAB, DES, LDB3, MYOT and FLNC. There is very little expertise in muscle MRI for patients with \(^{\text{BAG3}}\) mutations. Dirk Fischer summarized the clinical presentation and the muscle histology findings of patients with MFMs. He then presented the muscle MRI findings in a large cohort of MFM patients [37].

4.1. Desmin and alpha-B crystalline-related myofibrillar myopathies

The muscle MRI pattern caused by mutations in the juxtasarcromeric proteins desmin and alpha-B crystalline looks very similar. The majority of patients that have been imaged showed mutations in the \(^{\text{DES}}\) gene, whereas experience in patients with alpha-B crystalline-related MFM is still fairly limited. Both diseases are generally adult-onset myopathies with predominantly distal and proximal muscle involvement and cardiac abnormalities. Patients with desminopathy show a fairly typical pattern of muscle pathology in their thighs (Fig. 3a). On T1w MRI scans the semitendinosus, sartorius and gracilis are the most severely affected muscles. This pattern is very different from the autosomal recessive LGMDs or the congenital myopathies and together with a corresponding clinical picture is highly suggestive of a \(^{\text{DES}}\) mutation. The biceps femoris can also be affected but to a lesser extent and a later stage of the disease. In the calf, the peroneal muscle group is typically more severely affected than the tibialis anterior muscle. The gluteal muscles are also affected.

Maggie Walter presented a cohort of desminopathy patients with a broad clinical spectrum of severity in whom the muscle MRI pattern was nevertheless in accordance with the typical pattern described by Dirk Fischer [40].
Francesco Muntoni presented a 19-year-old patient with a desmin mutation who showed no pathology on muscle MRI, even though he also had a mutation in LMNA.

The MRI findings in patients affected by a primary alpha-B crystallinopathy seem to be very similar to the pattern described for desminopathy patients, but because of the rarity of the disease, experience is very limited.

Robert Carlier presented whole-body MRI of a 46-year-old desminopathy patient with a clinically mild presentation. Whole-body MRI revealed some changes in the iliopsoas and semitendinosus muscles and fairly severe involvement of the peroneal muscle. The head and arms did not show any involvement.

Giorgio Tasca presented a case with semitendinosus, gracilis and sartorius muscle involvement, a pattern typically seen in patients with either DES or CRYAB mutations. Interestingly, mutations in those genes were excluded in these patients, which suggested that there are other diseases that can show a similar muscle MRI pattern.

4.2. Myotilin, filamin C and ZASP-related myofibrillar myopathies

Myotilin, filamin C and ZASP (encoded by the LDB3 gene) are all proteins of the Z-disc and therefore show great overlap in their MRI pattern of muscle pathology. Patients with mutations in the MYOT gene generally have a later disease onset than desminopathy patients, are clinically more variable and show cardiac involvement less frequently. Both distal and proximal muscles are affected in patients with MYOT mutations, whereas patients with filamin-C related MFM [41] show a more proximal and patients with ZASP related MFM a more distal muscle involvement. Similarly to patients with desminopathy, muscle MRI findings are very distinct in Z-disc related MFMs and can also help to guide genetic testing. In contrast to desminopathies though, the semitendinosus muscle is far less severely affected, whereas the semimembranosus muscle shows very prominent pathology (Fig. 3). Other thigh muscles that can be severely affected are the adductor magnus and the biceps femoris (long head) muscle. In filaminopathy, in contrast to desminopathies, the gracilis and sartorius muscles are often spared (Fig. 3d), whereas in myotilinopathies the sartorius is more severely involved than the gracilis muscle (Fig. 3b). The findings in the lower leg are less specific, with the soleus and the medial gastrocnemius being the most frequently affected muscles in the posterior compartment and the tibialis anterior being the most frequently affected muscle in the anterior compartment at a later stage. Overall, the muscle pattern for the three Z-disc-related MFMs is very similar.

Maggie Walter presented a patient with a MYOT mutation and severe limb girdle weakness (LGMD1A) in whom muscle pathology was too advanced to recognise a clear pattern [42].

Only a few muscle MRI studies have been performed in patients with BAG3 mutations, another disease within the MFM group, and it is too early to draw any conclusions about a specific pattern of pathology. The same is true for autosomal dominant inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD) caused by mutations in the VCP gene. Although quite a number of muscle MRI scans have been analysed, the clinical phenotype of patients is very heterogeneous, as is the pattern of muscle pathology. Bjarne Udd presented IBMPFD patients with a pure distal muscle phenotype and selective involvement of the anterior compartments in the lower leg [43], and another patient with a proximal phenotype in whom the thigh muscles were completely replaced by adipose tissue.

5. Pompe disease

Clinically, Pompe disease can often be difficult to diagnose, and even muscle biopsy findings can be very unspecific and do not always show glycogen accumulation. Muscle imaging has therefore been considered a helpful
diagnostic approach in adults with Pompe disease. Anna Pichiecchio presented muscle MRI findings from 11 patients with late-onset Pompe disease [26]. The paraspinal muscles are often the first ones to show pathology. Five of the patients were clinically mildly affected and showed muscle pathology of the adductor magnus, semimembranosus and to a lesser extent the semitendinosus muscles. The patients that were clinically more severely affected also showed predominant involvement of the posterior compartment of the thigh and in addition some fatty infiltration in the vastus muscles (Fig. 3e). Even in patients that were clinically severely affected there was sparing of the gracilis and sartorius muscles on MRI. The calf muscles are generally spared (Fig. 3e).

Jorge Diaz presented muscle MRI findings from four patients with Pompe disease, all presenting with moderate weakness and none being ventilator-dependent. The paravertebral and abdominal muscles were always affected. There was moderate involvement of the gluteal and iliopsoas muscles and in the thighs the posterior compartment was more severely affected than the anterior compartment. Again there was no involvement of the calf muscles.

Robert Carlier presented whole-body MRI data from 20 patients, 11 males and 9 females aged 37–75, three of whom had been followed over a 2-year period [27]. Although the facial and masticatory muscles were well preserved, most patients showed involvement of the tongue muscles, which may be the only sign in very mildly affected patients. Patients showed little neck muscle involvement but very prominent involvement of the subscapularis muscles, while other shoulder girdle and arm muscles were spared. The discrepancy between the preservation of the arm muscles and the clear pathology of the truncal muscles was very obvious. The gluteus medius muscle was the most severely affected of the gluteal muscles. Interestingly, according to Robert Carlier’s patient series there was no clear pattern of muscle pathology in the leg muscles. Muscles of both the anterior and posterior compartment may be affected. The best-preserved muscles were the sartorius, rectus and gracilis (Fig. 3e). The data clearly showed that whole-body MRI can be very helpful to diagnose patients with Pompe disease. Susana Quijano-Roy pointed out that clinically Pompe disease can resemble congenital muscular dystrophy with rigid spine syndrome (SEPN1), but that the involvement of the tongue is typical for Pompe patients.

6. Myotonic dystrophy (DM1 and DM2)

Myotonic dystrophy type 1 and 2 are two of the clinically best characterised genetic muscle diseases and molecular diagnosis is easy to perform. The prevalence of DM1 and DM2 differs from country to country, with Finland and Germany having a very high number of DM2 patients whereas the prevalence is much lower in the UK. The consortium participants agreed that muscle MRI does not play a role in the diagnostic workup of patients with DM1 and DM2. Bjarne Udd pointed out that DM2 might be an under-diagnosed disease and that the clinical symptoms can be very unspecific. He did look at the muscle MRI pattern in his cohort of 200 DM2 patients and found that the vastus lateralis is frequently diffusely affected, that there is relative sparing of the rectus femoris in typical patients and that the calf muscles are well preserved. The spectrum of severity can be quite broad, with even older patients exhibiting normal muscle MRI findings.

7. Facioscapulohumeral muscular dystrophy (FSHD)

Autosomal dominant FSHD can sometimes be a diagnostic challenge if there is no family history and if patients don’t show facial weakness. As genetic testing is also not always straightforward in patients with FSHD2, muscle MRI can help to support the diagnosis of FSHD in some patients. Beatris Wokke gave a clinical summary of FSHD and presented muscle MRI results from a previous imaging study [44]. One of the hallmarks of FSHD is asymmetric muscle involvement in both the upper and lower limbs. In the thighs the semimembranosus, biceps femoris, semitendinosus and the adductor muscles are most severely affected, whereas the gluteal muscles are relatively spared. In the calf the tibialis anterior and the medial gastrocnemius muscle are most prominently involved [45]. The extensor digitorum longus can also be affected in the calf whereas the flexor digitorum longus is often spared. Muscle pathology can be variable along the longitudinal axis of the muscles, which makes it more difficult to describe a distinct pattern for FSHD. Wokke also showed that patients with FSHD can have increased signal intensity on turbo inversion recovery magnitude sequences.

Robert Carlier presented a whole-body MRI scan from a 72-year-old woman with FSHD and camptocormia. The erector spinae muscles were severely affected, and interestingly the patient didn’t show any facial involvement on MRI. The arm muscles were also preserved, but the gluteal and adductor muscles in the thighs, as well as the tibialis anterior and medial gastrocnemius muscles in the calves, were diffusely affected. A 60-year-old man with FSHD showed tongue pathology and involvement of the trapezius, intercostals and abdominal muscles. In the thighs, the posterior compartment muscles were generally more severely affected than the anterior compartment muscles. The lower leg generally showed involvement of the tibialis anterior and medial gastrocnemius muscles.

Enzo Ricci presented an impressive series of 225 FSHD cases that had been assessed by muscle MRI [46]. Generally the abdominal, semimembranosus and tibialis anterior muscles were most severely affected. Many of the FSHD patients had follow-up scans and the progression of muscle pathology assessed by MRI clearly correlated with disease progression. This large amount of MRI data allowed Ricci to nicely document the natural history of the muscle pathology. The first sign of muscle pathology on MRI was hypertrophy of otherwise healthy looking muscles.
The first muscles that were abnormal on T1w images were the abdominal and iliopsoas muscles and in some cases the rectus femoris muscle. In other cases the rectus femoris muscle was the only muscle that was spared. Interestingly, there were cases in which the scapular muscles were completely spared. Ricci suggested that severe atrophy of the rectus femoris and fatty replacement of the adductor longus muscles was a frequent sign in FSHD. The pectineus muscle was also involved in the majority of cases. In his large cohort of patients, Ricci did not find a typical pattern of muscle pathology in the lower legs. Involvement of lower leg muscles varied between family members and could be both symmetrical and asymmetrical. It was rarely the case that the anterior compartment in the thigh was more severely affected than the posterior compartment. In one case only TA involvement was detected. A very characteristic MRI finding in FSHD patients was abnormal signals detected using T2 STIR sequences. Increased STIR signal intensity always preceded changes detected on T1w images. The data clearly showed that FSHD is a multifocal disease and that STIR abnormalities allowed the prediction of consecutive fatty degeneration of specific muscles.

8. Summary

Eugenio Mercuri summarized that sufficient muscle MRI data now exists for several genetic muscle diseases to allow a typical pattern of pathology to be identified. The next objective will now need to be the definition of the spectrum of muscle MRI changes. It will also be important to better define when muscle MRI can be helpful in the diagnosis of a disease. For most genetic muscle diseases there is still a lack of MRI data and it will be necessary to collect larger cohorts of patients before any statements about the usefulness of muscle MRI for specific diseases can be made. It will be a task of the TREAT-NMD muscle MRI consortium to coordinate the collation of MRI data and to define typical patterns of muscle involvement and the spectrum of pathology. Pierre Carlier pointed out that another future task would be the collection of cardiac MRI data, which might be relevant for the monitoring of therapeutic interventions.

Most data that were discussed at the workshop were T1w images and as technology is advancing other imaging applications might become more relevant to define and understand disease mechanisms and patterns of pathology. One of the most puzzling finding in muscle MRI studies is the selective involvement of specific muscles in diseases in which the disease-causing gene is ubiquitously expressed. There is currently very little understanding of why distinct muscles are severely affected in one disease but very well preserved in another.

9. Conflict of interest

None.

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Acknowledgment

We would like to acknowledge Rachel Thompson for her help with the organisation of the workshop and for proofreading. The workshop was supported by TREAT-NMD, the EU-funded network of excellence for rare inherited neuromuscular diseases (EC, 6th FP, contract # 036825; www.treat-nmd.eu).

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