Distinct muscle imaging patterns in myofibrillar myopathies

D. Fischer, MD*
R.A. Kley, MD*
K. Strach, MD
C. Meyer, MD
T. Sommer, MD
K. Eger, MD
A. Rolfs, MD
W. Meyer
A. Pou, MD
J. Pradas, MD
C.M. Heyer, MD
A. Grossmann, MD
A. Huebner, MD
W. Kress, MD
J. Reimann, MD
R. Schröder, MD
B. Eymard, MD
M. Fardeau, MD
B. Udd, MD
L. Goldfarb, MD
M. Vorgerd, MD
M. Olivé, MD

Address correspondence and reprint requests to Dr. Dirk Fischer, Department of Neurology, University Hospital Basel, Switzerland
fischerdi@uhbs.ch

ABSTRACT

Objective: To compare muscle imaging findings in different subtypes of myofibrillar myopathies (MFM) in order to identify characteristic patterns of muscle alterations that may be helpful to separate these genetic heterogeneous muscular disorders.

Methods: Muscle imaging and clinical findings of 46 patients with MFM were evaluated (19 desminopathy, 12 myotilinopathy, 11 filaminopathy, 1 αB-crystallinopathy, and 3 ZASPopathy). The data were collected retrospectively in 43 patients and prospectively in 3 patients.

Results: In patients with desminopathy, the semitendinosus was at least equally affected as the biceps femoris, and the peroneal muscles were never less involved than the tibialis anterior (sensitivity of these imaging criteria to detect desminopathy in our cohort 100%, specificity 95%). In most of the patients with myotilinopathy, the adductor magnus showed more alterations than the gracilis muscle, and the sartorius was at least equally affected as the semitendinosus (sensitivity 90%, specificity 93%). In filaminopathy, the biceps femoris and semitendinosus were at least equally affected as the sartorius muscle, and the medial gastrocnemius was more affected than the lateral gastrocnemius. The semimembranosus mostly showed more alterations than the adductor magnus (sensitivity 88%, specificity 96%). Early adult onset and cardiac involvement was most often associated with desminopathy. In patients with filaminopathy, muscle weakness typically beginning in the 5th decade of life was mostly pronounced proximally, while late adult onset (>50 years) with distal weakness was more often present in myotilinopathy.

Conclusions: Muscle imaging in combination with clinical data may be helpful for separation of distinct myofibrillar myopathy subtypes and in scheduling of genetic analysis. ***Neurology*® 2008;71:758-765**

GLOSSARY

IF = intermediate filament; **MFM** = myofibrillar myopathies.

Desmin-related myopathy was initially described as a progressive muscular disorder often associated with cardiomyopathy and histopathologically characterized by aberrant desmin aggregation in abnormal muscle fibers.[1] The finding that myofibrillar disintegration was associated with accumulation of many

other proteins besides desmin prompted the non-committal term myofibrillar myopathy (MFM).[2-4] Mutations in the human desmin gene (*DES*) on chromosome 2q35 were first shown to be associated with MFM.[5-7] Desmin is the main intermediate filament (IF) in skeletal and cardiac muscle. It forms a three-dimensional scaffold around myofibrillar Z-discs thereby connecting the myofibrils to the subsarcolemmal cytoskeleton.[8-10] Another MFM form is associated with mutations in the gene encoding αB-crystallin (*CRYAB*), a chaperone that normally stabilizes desmin filaments and prevents their aggregation.[11] More recently, mutations in the human Z-disc proteins myotilin (*MYOT*), ZASP (*LDB3*), and filamin C (*FLNC*) have also been shown to cause MFM.[12-15] If a mutation in one of these five genes can be identified, the MFM subtype is designated according to the affected protein as desminopathy, αB-crystallinopathy, myotilinopathy, filaminopathy, or ZASPopathy.

The diagnosis of MFM is defined by histopathologic criteria.[2-4] However, a differentiation between the MFM subtypes on pathology findings alone is not possible. The time-consuming hsp27-2D-gel electrophoresis has been shown to be a useful diagnostic tool but only for differentiating desminopathies from other forms of MFM.[16] Clinical presentation of MFM has been very variable.[6,12-19] Weakness of proximal and distal muscles of lower and upper limbs may occur in each MFM subtype. Individual distribution pattern of muscle weakness overlaps between the MFM subtypes and large interindividual variation has been observed even in patients with identical mutation.[20] Practically, a definite determination of MFM subtype can only be established by means of direct gene sequencing.

Muscle imaging by MRI or CT has become a very useful tool in clarification of neuromuscular disorders and is performed routinely in many neuromuscular centers. The aim of the present study was to compare muscle imaging findings in desminopathy, αB-crystallinopathy, myotilinopathy, filaminopathy, and ZASPopathy and to search for characteristic radiologic patterns that may help to differentiate subtypes of MFM and to schedule genetic analyses.

METHODS Patients and molecular genetic analysis. A total of 46 patients were examined, including 19 patients with desminopathy from 13 different families, 12 patients with myotilinopathy from 4 unrelated families, 11 filaminopathy patients from 3 families sharing a common founder mutation, 3 patients with ZASPopathy, and 1 patient with αB-crystallinopathy. DNA extraction from blood samples and *DES*, *MYOT*, *FLNC*, *LDB3*, and *CRYAB* mutation analysis were performed by standard procedures as described for each gene.[10-12,15,17] Detailed genetic and clinical data of all patients are given in the table. All patients were fully cooperative and had given written consent for genetic and muscular imaging examinations.

Muscle imaging. Muscle imaging data were collected retrospectively in 43 patients and in a prospective manner in 3 patients. Muscle imaging included CT or MRI scans of the pelvis, thigh, and lower leg muscles, with some variations depending on the facilities at the performing radiologic department or individual patient conditions (e.g., pacemaker prohibiting MRI). Scans were performed at the pelvis (middle of the inguinal ligament and 5 cm below), thigh (largest diameter of the thigh and 5 cm below), and calf (largest diameter of the lower leg and 5 cm below) levels. Each muscle was evaluated at both scan levels on both sides to stage the level of muscular involvement.[21-24] The degree of muscle degeneration was evaluated according to a modified 5-point scale.[25-27] Stage 0 is referred to a normal appearance; stage 1 (mild) to traces of decreased signal density on CT or increased signal intensity on the T1-weighted MR sequences; stage 2 (moderate) to decreased signal density on CT increased signal intensity (MRI) with beginning confluence in less than 50% of the muscle; stage 3 (severe) to decreased signal density (CT) or increased signal intensity (MRI) in more than 50% of an examined muscle; and stage 4 (end-stage disease) to a state when the entire muscle is replaced by lower density (CT) or increased signal intensity (MRI).

Statistical analysis. To compare the involvement of different muscles (rated on 5-point scale) within the desminopathy, myotilinopathy, and filaminopathy groups, the Wilcoxon matched pairs test at significance level 0.05 was used. For evaluation of differences between the groups, the scores on the 5-point scale were converted into relative values by dividing these scores by the mean value (on 5-point scale) of all affected muscles, calculated separately for each patient. Thus, values less than one indicated a below average involvement, higher values an above average involvement. For statistical evaluation, the nonparametric Mann–Whitney U test at significance level 0.05 was used. Specificity, sensitivity, and correct classification rate for imaging criteria of desminopathy, myotilinopathy, and filaminopathy were calculated using 2×2 contingency tables. Patients with incomplete imaging data of the muscles included in the criteria were not considered for this analysis (for details see table e-1 on the *Neurology*® Web site at www.neurology.org).

RESULTS Muscle imaging. Details of muscle involvement scores of each patient and mean muscle involvement of each muscle are provided in table e-1. A comparison of absolute and relative muscle involvement between MFM subtypes (desminopathy, myotilinopathy, filaminopathy) is shown in table e-2. Table e-3 shows a comparison of muscles and table e-4 a comparison of muscle groups within the MFM subtypes. Muscle imaging criteria for separation of different MFM subtypes are provided in table e-5.

**Table**   Summary of genetic and clinical data of all patients included

Patient data						Distribution of clinical weakness					Cardiac involvement	
No. (ref.*)	Sex	Age at onset, y	Age at imaging, y	Gene	Mutation (ref.*)	Hip		Knee	Ankle	Distal vs proximal	Cardiomyopathy	Pacemaker
1 (5)	F	†	27	DES	R350P	F	Ab	F	E	D	−	−
2	M	†	18	DES	E245D (33)	F	−	F	E	P = D	−	−
3 (5)	M	†	30	DES	R350P	F > E	Ab	F	E > F	D > P	−	−
4 (34)	M	22	25	DES	P419S	−	−	−	E > F	D	+	−
5 (34)	M	25	27	DES	I367F	−	−	−	E > F	D	+	+
6 (28)	M	14	24	DES	R406W	F	−	F > E	E > F	D > P	+	+
7	F	53	54	DES	E245D (33)	−	−	−	−	−	−	−
8 (29)	F	31	40	DES	D399Y	−	−	−	E	D	−	−
9 (29)	M	43	46	DES	L338R	+	+	+	+	D > P	+	−
10	M	38	42	DES	E245D (33)	F	−	E = F	E > F	D > P	−	−
11 (34)	F	29	49	DES	P419S	−	−	−	E > F	D	+	+
12	M	38	48	DES	S21 (8)	NA	NA	NA	NA	NA	NA	NA
13 (28)	F	16	27	DES	R406W	F	Ab	F = E	E > F	D > P	+	+
14 (5)	F	44	53	DES	R350P	F	NA	+	E > F	P = D	−	−
15 (29)	M	34	39	DES	D399Y	+	+	+	+	D > P	+	−
16	F	41	56	DES	L338R (29)	F	Ab > Ad	F	E	P > D	−	−
17 (30)	F	36	51	DES	Del (Asp366)	F = E	Ab = Ad	F = E	F = E	P = D	+	−
18 (29)	M	41	53	DES	L377P	NA	NA	NA	NA	NA	+	+
19	M	40	57	DES	L338R (29)	F = E	Ab = Ad	F = E	F = E	P > D	−	−
20	F	NA	NA	CRYAB	R120G (11)	NA	NA	NA	NA	NA	NA	NA
21	F	50	53	MYOT	S55F (32)	−	−	−	E > F	D	−	−
22 (12)	M	51	57	MYOT	S55F	−	−	F > E	E > F	D > P	−	−
23 (12)	F	67	72	MYOT	S55F	−	−	−	E > F	D	−	−
24 (12)	M	51	62	MYOT	S55F	F > E	Ab > Ad	F = E	E > F	P > D	−	−
25 (12)	F	69	76	MYOT	S55C	F	Ab	F = E	E > F	D > P	−	−
26 (12)	F	48	58	MYOT	S55F	F > E	Ab = Ad	F = E	E > F	D > P	−	−
27 (12)	M	50	52	MYOT	S55F	F > E	Ab > Ad	F = E	E > F	D > P	−	−
28	M	49	56	MYOT	S55F (32)	−	−	F > E	E > F	D > P	−	−
29 (12)	F	58	69	MYOT	S55C	F > E	Ab > Ad	F > E	E > F	D > P	+	−
30	F	58	68	MYOT	S60C (13)	F > E	Ab > Ad	F > E	E > F	D > P	−	−
31 (25)	M	50	62	MYOT	S55F	F > E	Ab > Ad	F > E	E > F	D > P	−	−
32 (12)	F	47	69	MYOT	S55F	F > E	Ab = Ad	F > E	E > F	P = D	−	−
33 (19)	F	†	25	FLNC	W2710X	−	−	−	−	−	−	−
34 (19)	M	40	48	FLNC	W2710X	NA	NA	NA	NA	NA	−	−
35 (19)	M	45	49	FLNC	W2710X	E = F	Ab > Ad	E > F	E > F	P > D	−	−
36 (19)	F	49	56	FLNC	W2710X	E > F	+	E = F	E > F	P > D	+	−
37 (19)	M	57	60	FLNC	W2710X	+	+	+	+	P > D	+	−
38 (19)	F	42	45	FLNC	W2710X	E = F	Ab = Ad	E = F	E > F	P > D	−	−
39 (19)	F	44	52	FLNC	W2710X	E = F	Ab > Ad	E = F	E > F	P > D	+	−
40 (19)	F	49	54	FLNC	W2710X	+	+	−	−	P	−	−
41 (19)	M	45	58	FLNC	W2710X	+	+	+	+	P > D	−	−
42 (19)	M	37	64	FLNC	W2710X	+	+	+	+	P > D	−	−
43 (19)	F	40	56	FLNC	W2710X	NA	NA	NA	NA	NA	+	−
44 (17)	F	†	54	ZASP	A165V	−	−	F = E	E > F	D	−	−
45 (17)	F	50	70	ZASP	A165V	E = F	Ab = Ad	−	F = E	D > P	−	−
46	M	27	66	ZASP	A147T (14)	+	+	−	E	D > P	−	−

*In parentheses is the reference number where more detailed clinical findings of the patient can be obtained or where the mutation was first described.

†No complaints.

F = flexion; Ab = abduction; E = extension; D = distal; P = proximal; Ad = adduction; NA = not available; + = present; − = absent.

Figure 1 Patients with desminopathy
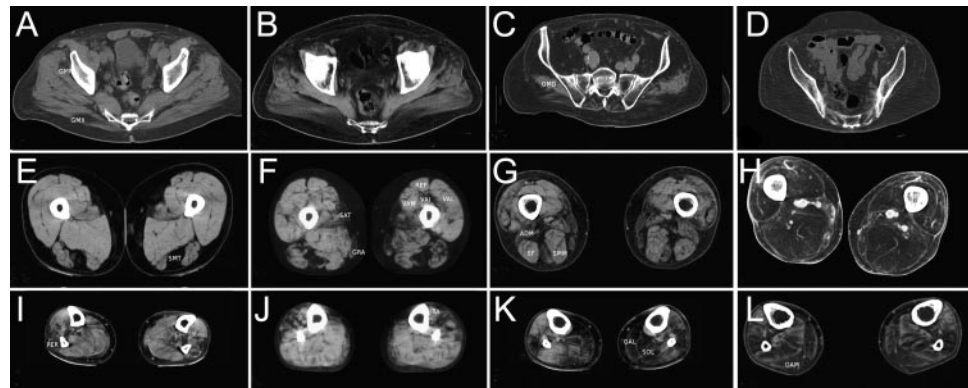
Muscular CT imaging ranging from clinically mild to more severe involvement of the pelvis (A–D), thigh (E-H), and lower legs (I–L) muscles with a characteristic temporal pattern of muscle atrophy. In the pelvis, mild changes first appeared in the gluteus maximus (A), later in gluteus minimus muscles (B,C), while the gluteus medius muscles is also involved in very advanced patients (D). In the thigh, the earliest and always most severely affected muscle is the semitendinosus (E), followed by sartorius, gracilis (F, G), and to a milder degree adductor magnus and quadriceps muscles, while semimembranosus and biceps femoris are relatively preserved for a long time (F, G), before in severely affected patients marked degeneration is observed in all muscles (H). In the lower legs, first changes appeared in the peroneal muscles (I), followed by involvement of the tibial anterior (J), and later gastrocnemius and soleus muscles in more severely affected patients (K, L).

Desminopathy. Muscle imaging findings of patients with desminopathy ranging from mild to severe involvement are shown in figure 1. Pelvic muscles: the gluteus maximus muscle was significantly more involved than the gluteus medius and minimus muscles. Thigh: semitendinosus, sartorius, and gracilis were the most affected muscles exceeding the involvement of the adductor magnus, biceps femoris, and semimembranosus. The anterior compartment (rectus femoris, vastus lateralis, intermedius, and medialis) was relatively spared in most patients. Lower legs: the peroneal muscles displayed significantly more lipomatous changes than the tibialis anterior and muscles of the posterior compartment (soleus, medial, and lateral gastrocnemius). Mean involvement of distal muscles slightly, but significantly, exceeded proximal muscles (thigh and pelvis).

αB-crystallinopathy. Muscle imaging findings in a patient with a R120G αBC mutation are given in figure e-1 and were very similar to patients with desminopathy. The most involved muscles were the gluteus maximus, sartorius, semitendinosus, gracilis, and the peroneal muscles.

Myotilinopathy. Muscle imaging in patients with myotilinopathy is illustrated in figure 2. Pelvic muscles: the available data were not sufficient for statistical analysis. However, the gluteus maximus was less involved than the gluteus medius and minimus muscles in two out of three patients examined. Thigh: adductor magnus, biceps femoris, vastus medialis, semimembranosus, and vastus intermedius were the most involved muscles. Vastus lateralis, semitendinosus, gracilis, and rectus femoris were least affected. Lower legs: soleus and medial gastrocnemius showed

Figure 2 Patients with myotilinopathy
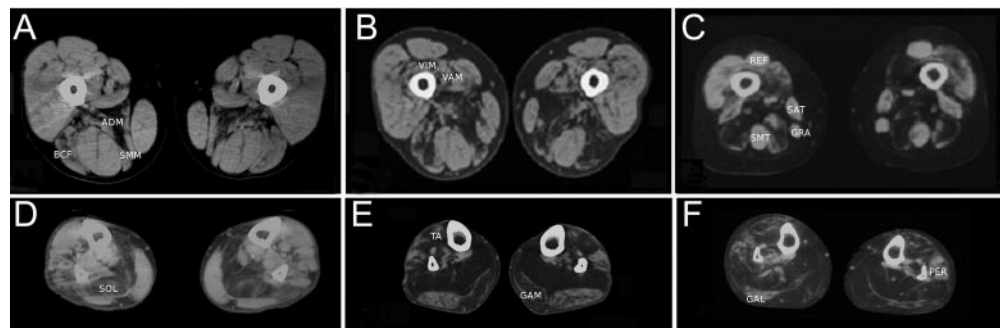
Muscle CT imaging ranging from mild to severe involvement of the thigh (A–C) and lower legs (D–F). Semimembranosus, biceps femoris, and adductor magnus of the thigh show early changes (A, B), followed by the vastus intermedius and vastus medialis muscles (B, C). Semitendinosus, rectus femoris, sartorius, and gracilis are relatively spared (C). In the lower legs, the soleus (D) and later tibial anterior and medial gastrocnemius muscles are the earliest and most affected muscles (E). Peroneal muscles and lateral gastrocnemius are relatively spared even in more severely affected patients (F).

Figure 3   Patients with filaminopathy
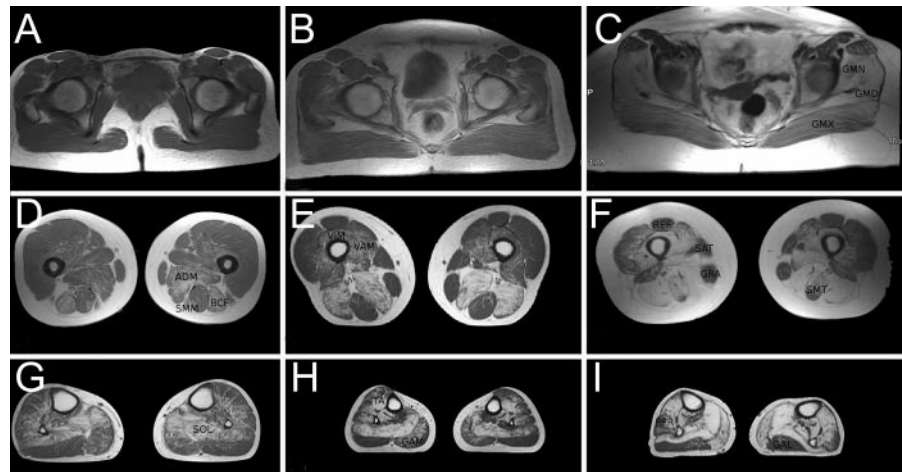
Muscle MR imaging ranging from mild to severe involvement of the pelvis (A–C), thigh (D–F), and lower legs (G–I). In the pelvis, initial changes are relatively mild (A, B), later in the course of illness the extent of degeneration in the gluteus minimus and medius muscles becomes greater than in the gluteus maximus (C). In the thigh, the vastus intermedius and medialis, adductor magnus, semimembranosus, and biceps femoris muscles show early and most severe changes (D, E). Semitendinosus, rectus femoris, sartorius, and gracilis are relatively spared (F). In the lower legs, the earliest affected muscles are soleus (G), and later tibial anterior and medial gastrocnemius muscles (H). Even in more advanced disease peroneal muscles and lateral gastrocnemius are relatively spared (I).

more alterations than the lateral gastrocnemius. The soleus was also more affected than the peroneal muscles and tibialis anterior muscle. In general, distal muscle involvement was significantly greater than proximal muscle affection.

Filaminopathy. Muscle images are provided in figure 3. Pelvic muscles: the available data were not sufficient for statistical analysis. One patient had less involvement of the gluteus maximus compared to gluteus minimus and medius muscles. Thigh: the semimembranosus, biceps femoris, adductor magnus, vastus intermedius, and medialis were most affected, whereas sartorius, gracilis, and rectus femoris were relatively spared. Lower legs: soleus and medial gastrocnemius were significantly more affected than lateral gastrocnemius and peroneal muscles.

ZASPopathy. Muscle imaging findings in a patient with an A147T ZASP mutation are shown in figure 4. Data were not sufficient for statistical analysis. In the pelvis, gluteus minimus was most affected in all three patients. At the thigh level, the posterior compartment (biceps femoris and semimembranosus) was mostly involved whereas adductor magnus and gracilis were relatively spared. In the lower legs, one patient presented only with alterations in the soleus and medial gastrocnemius muscle at onset of the disease. In one case, the soleus was most affected and in the third one, all lower leg muscles showed distinct changes.

Clinical data and correlation of manual muscle testing to muscle imaging findings. The mean age at onset was in desminopathy 33.4 ± 10.3 years (range, 14 to

53 years), myotiliopathy 54.4 ± 7.2 years (range, 47 to 69 years), in filaminopathy 44.3 ± 5.6 years (range, 37 to 54 years), and in ZASPopathy 43 years. Cardiomyopathy was present in 8 and a pacemaker in 5 of 18 patients with desminopathy. In contrast, cardiomyopathy was much less common in filaminopathy and myotilinopathy and none of the patients without desminopathy had a pacemaker.

Complete data of muscle weakness at time of MRI or CT examination were available for 15 patients with desminopathy, 12 patients with myotilinopathy, 4 patients with filaminopathy, and 3 patients with ZASPopathy (table). In desminopathy, myotilinopathy, and filaminopathy, manual muscle testing showed a greater impairment of knee flexion as compared to knee extension in more than half of the patients with weakness of thigh muscles. In the remaining patients, knee extension and flexion were similarly affected. Consistent with these findings muscle imaging studies revealed that posterior compartment of the thigh (mean involvement of semimembranosus, semitendinosus, and biceps femoris) was significantly more affected than the anterior compartment (mean involvement of sartorius, rectus femoris, vastus lateralis, intermedius, and medialis) in these MFM subtypes. Foot dorsiflexion was more impaired than plantarflexion in 12 out of 15 patients with desminopathy and all patients with myotilinopathy and filaminopathy with complete clinical data. In contrast, muscle imaging studies in patients with myotilinopathy and filaminopathy showed significantly more alterations in soleus muscle, one of the main plantar flexors, compared to tibialis anterior. The impairment

Figure 4   Muscle MR imaging of a patient with ZASPopathy
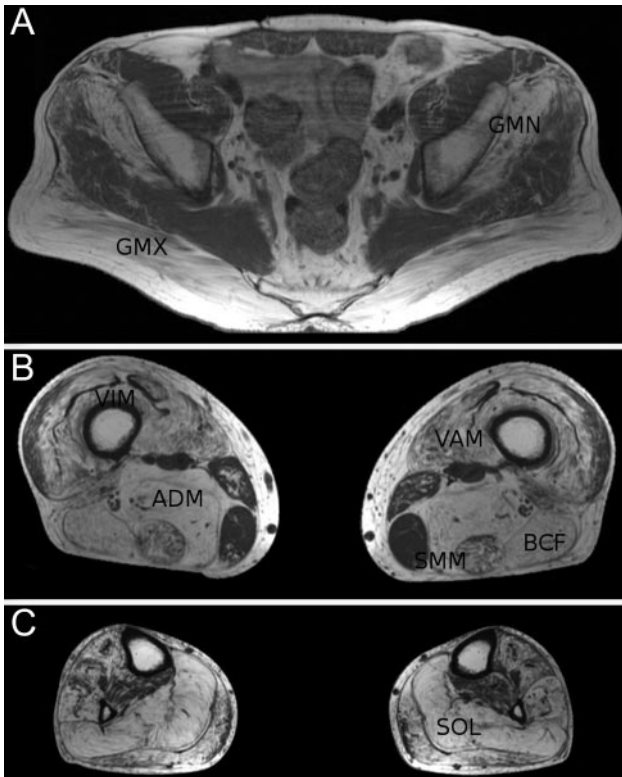
In the pelvis, the gluteus maximus and minimus muscles were the most affected (A). In the thigh, adductor magnus, vastus medialis, vastus intermedius, biceps femoris, and semimembranosus were clearly involved (B). In the lower legs, the soleus muscle was the most affected (C).

of plantarflexion due to affection of soleus may be partly compensated by significantly lesser involvement of lateral gastrocnemius (compared to tibialis anterior). In addition, distal weakness predominated in 11 patients with desminopathy, while in 5 patients proximal muscles were equally or more involved than distal muscles. In myotilinopathy, 11 patients had more distal than proximal weakness, and 1 had equal distal and proximal weakness. In 7 filaminopathy patients, proximal muscles were equally or more involved than distal muscles. All three patients with ZASP presented with predominant distal weakness.

DISCUSSION In this study we performed a systematic retrospective muscle imaging assessment in a large series of 43 patients and a prospective evaluation of 3 patients with genetically proven MFM subtypes. Different characteristic patterns of muscle involvement in desminopathy, myotilinopathy, and filaminopathy were observed which in combination with clinical data may be helpful to distinguish these subtypes from other MFM forms.

In particular in desminopathy, the clinical phenotype can be very variable. However, our muscle imaging studies revealed some common findings in patients with desminopathy presenting with different muta-

tions, disease progression, and distribution of muscle weakness. In all of these patients, the semitendinosus was at least equally affected as the biceps femoris, and the peroneal muscles were never less involved than the tibialis anterior. Regarding the other MFM subtypes, only the patient with αBC mutation and one patient with myotilinopathy fulfilled these criteria. Therefore, the sensitivity and specificity for detection of desminopathy using these criteria were very high in our cohort (table e-5). This characteristic pattern was also observed in MRI images of three patients who harbored the same R350P mutation in *DES* but presented with very different clinical phenotypes.[20] In contrast, patients with mutations in the myotilin, filamin C, and ZASP genes presented with clearly distinctive patterns of muscular involvement. Most of the patients with myotilinopathy had a greater involvement of the adductor magnus compared to the gracilis muscle, and the sartorius muscle was at least equally affected as the semitendinosus. Regarding the other MFM groups, only one patient with desminopathy and one with filaminopathy showed such a combination. In filaminopathy, the biceps femoris and the semitendinosus were at least equally affected as the sartorius muscle, and the medial gastrocnemius was always more affected than the lateral gastrocnemius. In all patients with filaminopathy except one, the semimembranosus was equally or more involved than the adductor magnus. According to the other MFM subgroups, only one patient with desminopathy showed this pattern. Therefore, the sensitivity and specificity of the imaging criteria for separating myotilinopathy and filaminopathy were also high in our cohort (table e-5). After defining these differentiating criteria, we have identified three additional patients with MFM (14, 21, 36 in the table). They presented with mutations in *DES*, *MYOT*, and *FLNC*. Each of them fulfilled the imaging criteria of the respective MFM subgroup.

Muscle imaging is nowadays often used in neuromuscular centers before performing a muscle biopsy to select the most suitable muscle for analysis. Furthermore, muscle imaging in combination with clinical examination has been useful in order to characterize the phenotype of muscular disorders and may be helpful in assessing follow-up. The results of our study indicate that muscle imaging may also be a useful tool for separating genetically distinct forms of MFM. The criteria mentioned above to differ between the MFM subtypes are practically not testable by clinical examination alone. This emphasizes that assessment of individual muscles, that are part of compound muscle actions, is much more reliable by imaging.

However, there are some limitations of this study. First, the data were collected retrospectively in most cases and patients with unknown causative mutation

have not been considered. Therefore, the criteria that have been defined for separating MFM subgroups must be verified in a prospective study. In addition, it can be intricate to perform muscle imaging to schedule molecular genetic testing after a diagnosis of MFM is made by biopsy. Furthermore, the presence of a pacemaker generally prohibits MRI studies while CT scans have less contrast and involve radiation exposure. Muscle imaging can be much less useful in asymptomatic patients or in patients in very early disease stages as it might not show any involvement (e.g., patient 33 with filaminopathy) or only alterations of a single muscle (soleus in myotilinopathy[31]) not being sufficient for a correct classification. Also, patients in very advanced stages with severe muscle degeneration may not show a distinctive pattern.

Clinical findings besides muscle imaging may also be useful for the differentiation of MFM subtypes. Clinical data of our study and previous reports[12-14,17-20] indicate that patients with MFM with cardiac involvement, especially arrhythmogenic cardiomyopathy requiring pacemaker implantation, and early adult onset before the age of 40 are more likely to have desminopathy. Patients with MFM with onset in the 5th decade of life and muscle weakness more pronounced proximally than distally are more likely to have filaminopathy, while distal myopathy is more often seen in ZASPopathy and myotilinopathy. In the latter, first clinical symptoms mostly occur above the age of 50 years.

Muscle imaging in combination with clinical data may be helpful for separation of genetic distinct subforms of MFM and to schedule molecular genetic testing.

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