Muscle Magnetic Resonance Imaging in Congenital Myopathies Due to Ryanodine Receptor Type 1 Gene Mutations

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Objectives: To establish the consistency of the previously reported pattern of muscle involvement in a large cohort of patients with molecularly defined ryanodine receptor type 1 (*RYR1*)–related myopathies, to identify possible additional patterns, and to compare magnetic resonance imaging (MRI) findings with clinical and genetic findings.

Design: Blinded analysis of muscle MRI patterns of patients with congenital myopathies with dominant or recessive *RYR1* mutations and control patients without *RYR1* mutations. We compared MRI findings with the previously reported pattern of muscle involvement.

Setting: Data from 3 tertiary referral centers.

Patients: Thirty-seven patients with dominant or recessive *RYR1* mutations and 23 controls with other myopathies.

Main Outcome Measures: Each MRI was classified as typical if it was identical to the reported pattern, consistent if it was similar to the reported one but with some additional features, or different. Images with no or few changes were classified as uninformative.

Results: Twenty-one of 37 patients with *RYR1* mutations had a typical pattern; 13 had a consistent pattern. Two patients had uninformative MRIs and only 1 had a different pattern. Compared with patients with dominant mutations, patients with recessive mutations and ophthalmoparesis had a more diffuse pattern, classified as consistent in 6 of 8. In contrast, 10 of 11 with recessive mutations but without ophthalmoparesis had a typical pattern. All MRIs of 23 control patients were classified as different.

Conclusions: Our results suggest that muscle MRI is a powerful predictor of *RYR1* involvement in patients with a congenital myopathy, especially if they carry a dominant mutation or recessive mutations without ophthalmoparesis.

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CONGENITAL MYOPATHIES due to mutations in the ryanodine receptor type 1 gene, *RYR1* (OMIM *180901), are the most frequent forms of congenital myopathy. Traditionally, *RYR1* mutations were associated with central core disease and malignant hyperthermia, but in recent years, they have been found in patients with other forms of myopathies, including multiminicore disease, centronuclear myopathy, congenital fiber type disproportion, and type I fiber uniformity.[1-8] They are usually dominantly inherited, but recessive mutations are increasingly recognized.[9-11] Clinically, there is a wide spectrum of severity ranging from patients never achieving independent ambulation to individuals with malignant hyperthermia susceptibility but little or no muscle weakness.[1,12]

Considering the clinical similarities of *RYR1*-related core myopathies to other congenital myopathies and the often nonspecific pathological changes, their diagnosis is often not straightforward, and the investigation of the underlying molecular genetic defect is expensive and time-consuming owing to the large size of *RYR1*. It has been recently suggested[13] that muscle magnetic resonance imaging (MRI) may help to direct genetic testing in muscular dystrophies. The pattern of selective muscle involvement on MRI in *RYR1*-related core myopathies has already been reported in a relatively small series of patients who mainly carried dominant *RYR1* mutations.[14,15] So far, no systematic attempt has been made to correlate MRI findings to clinical and genetic findings in a larger cohort of these patients.

The aim of the present study was to review the muscle MRI findings in 37 patients with *RYR1* mutations, including

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cases with both recessive and dominant mutations. Specifically, we aimed (1) to establish the consistency of previously reported MRI patterns in a larger cohort and (2) to correlate MRI findings with clinical and genetic findings.

METHODS

We included all patients referred to the participating centers in whom a molecular genetic diagnosis of an *RYR1*-related myopathy, muscle MRI, and clinical details were available. We identified 37 patients. Seventeen of these have been described in previous reports[3,14]; in 12 patients, muscle imaging had been specifically commented on, but they were included in the present study to assess the spectrum of MRI changes and their association with genetic and clinical findings in a larger cohort. All other patients have been molecularly characterized or imaged subsequent to the previous reports.

Magnetic resonance imaging had been performed according to a previously reported protocol.[16,17] Non–contrast-enhanced T1-weighted transverse images were obtained from the legs, selecting the axial plane with respect to the long axis of the body. This procedure involved 2 sequential scans. The sections were 5 mm thick, and the gap between sections was 50 mm. All patients were fully cooperative, and no sedation or general anesthesia was required. All patients were older than 4 years. Ethical permission had been obtained by the institutions participating in the study; written informed consent was obtained for the MRI and genetic testing.

Muscle MRIs were reviewed blindly and independently by 3 investigators (A.K., H.J., and E.M.). Selective involvement of muscles in the upper and lower leg was evaluated. The images were classified after comparing each one with the pattern previously reported in *RYR1*-related myopathies.[14,15] The images were classified as typical if they were similar or identical to the pattern described in the literature, compatible or compatible with some differences (listing additional features) or showing an overlap with another known pattern, different, and uninformative if the changes were very mild and nonspecific. The aim of this approach was not to provide scores for individual muscles but to have a cumulative pattern of muscle involvement. More specifically, we evaluated the criteria of severity of involvement of adjacent muscle groups as proposed in the first description of *RYR1*-related myopathies, and the individual muscles were graded as previously reported.[16]

To establish the specificity and sensitivity of our findings, the examiners, blinded to the genetic diagnosis, also assessed 23 MRIs of patients with overlapping clinical and muscle biopsy findings. These images were graded using the same criteria. The control MRIs included 12 from patients with nemaline myopathy (including 3 with nebulin [*NEB*] mutations, 6 with skeletal muscle α-actin [*ACTA1*] mutations, and 3 without genetic confirmation but unlinked to *RYR1*), 6 from patients with rigid spine syndrome and mutations in the selenoprotein N (*SEPN1)* gene, 3 from genetically unresolved patients with centronuclear myopathies unlinked to *RYR1*, and 2 from patients with multiminicores but without *SEPN1* or *RYR1* involvement.

To establish whether the presence of specific patterns was related to clinical findings, we also correlated muscle MRI findings with overall clinical severity and with different phenotypes, in particular, the presence or absence of extraocular eye involvement (partial or nearly complete ophthalmoplegia, collectively referred to herein as *ophthalmoparesis*), which can be observed in patients with recessive *RYR1* mutations. Clinically, we classified cases as mild (patients who did not experience any difficulties in everyday life), moderate (patients who could walk independently but were unable to climb stairs without a rail, or to run), or severe (patients who were unable to walk independently or could only take a few steps [<10]).

The molecular genetic results, biopsy findings, and patients' clinical findings were taken from the patients' records.

RESULTS

Of the 37 patients identified, including 17 previously described and 20 new patients, 29 had a typical phenotype[1] with proximal, predominantly hip girdle weakness and varying degrees of axial and facial weakness, and 8 had additional ophthalmoparesis. Details of our cohort are given in **Table 1** (imaging) and **Table 2** (clinical). Eighteen patients had dominant and 19 patients had recessive *RYR1* mutations. Sixteen patients were related. The entire *RYR1* gene was sequenced in 24 patients, whereas only C-terminal hotspots had been screened in 13 patients (indicated in **Table 3**).

IMAGING FINDINGS

RYR1 Group

In 21 of the 37 MRIs in the study group (57%), the pattern observed was classified as typical; 11 of these have been previously reported.[3,14] The rectus femoris was always relatively spared compared with the adjacent muscles, although it was not always entirely normal.

In another 13 patients (including 5 previously reported[3,14]), the changes were consistent with the previously reported pattern, although there were additional changes that did not allow defining it as typical. In particular, the rectus femoris showed markedly increased signaling in 4 cases (with patchy changes in 2 of 4) that had not previously been reported. In 4 of the consistent cases, the previously reported difference between adductor longus, typically spared or only very mildly involved, and the adductor magnus, which had been reported to be always more markedly involved, was less striking. In some patients, the involvement of the adductor magnus was more marked centrally, particularly in the early stages. In 3 of the consistent cases, the pattern was more typical in the images of the proximal portion of the leg.

In 4 cases, changes were consistent, with sparing and hypertrophy of the rectus and adductor longus muscles, but these changes overlapped with the pattern reported in *SEPN1*-related myopathies because of the additional marked involvement of the sartorius. These 4 cases were classified as consistent but with overlap with another known pattern.

The involvement or relative sparing of semimembranosus and semitendinosus muscles was equally distributed.

In the lower legs, the soleus muscle was clearly more affected than the gastrocnemius in all but 3 cases, in which the differences were not as marked. The peroneal group was more affected than the tibialis anterior muscle in 28 patients; in 6 of 35, it was similarly affected; in 1 patient only, it was less affected than the tibialis anterior muscle. In 2 patients, the images of the lower legs were not available.

Table 1. Magnetic Resonance Imaging Details[a]

Patient No./ Age at MRI, y	Inheritance/ Ophthalmoparesis/ Final Grade	Further Observations	Clinical Severity	Gradient Comparing Adjacent Muscles/Muscle Groups				
				AM>AL	VL>RF	S>G	SO>GM	PG>TA
1/51[b]	AD/No/D		Mild	X	X	X	NA	NA
2/12[b,c]	AD/No/A		Severe	X	X	X	X	X
3/7	AD/No/B+	Mild, differences not pronounced	Mild	X	X	X	X	M
4/39[c]	AD/No/B	Proximal more typical, differences mild	Mild	X	M	N	X	X
5/	AD/No/A		Moderate	X	X	X	X	Same
6/	AD/No/A		Moderate	X	X	X	X	M
7/10	AD/No/B+	Proximal more typical	Moderate	X	X	M	Same	Same
8/9[b,d]	AD/No/B+	Mild, proximal more typical	Moderate	X	X	M	X	X
9/29[b,d]	AD/No/A		Moderate	X	X	M	X	X
10/31[b,c]	AD/No/A		Moderate	X	X	X	X	X
11/13[c]	AD/No/A		Severe	X	X	X	X	X
12/8	AD/No/A		Moderate	X	X	X	X	X
13/24[b,c]	AD/No/B+	Differences less pronounced	Moderate	X	N	X	X	X
14/14[b,c]	AD/No/A		Moderate	X	X	X	X	N
15/18[b,c,d]	AD/No/A		Moderate	X	X	X	X	X
16/13[d]	AD/No/A		Severe	X	X	X	X	X
17/5[c]	AD/No/A		Severe	X	X	M	X	X
18/12	AD/No/B		Mild	X	X	X	X	Same
19/5	AR/No/A		Mild	X	X	X	X	X
20/6[b]	AR/No/A		Moderate	M	X	N	X	X
21/9[b]	AR/No/B+	Differences less pronounced	Moderate	X	X	X	X	X
22/19[c,d]	AR/No/A		Moderate	X	X	X	X	X
23/9	AR/No/A		Moderate	X	X	X	X	X
24/17	AR/No/A		Moderate	X	X	X	Same	N
25/15[b]	AR/No/A		Mild	X	X	X	X	X
26/14[b]	AR/No/A		Moderate	X	X	X	X	X
27/6[b,d]	AR/No/A		Moderate	X	X	M	X	X
28/8[b,d]	AR/No/A		Moderate	X	X	X	X	Same
29/14	AR/No/A		Mild	X	X	X	NA	NA
30/7[b,d]	AR/Yes/B	Atrophic, diffuse	Moderate	X	X	X	X	X
31/5[b,d]	AR/Yes/D	Diffuse	Moderate	M	X	X	X	X
32/18	AR/Yes/B	Proximal more typical	Moderate	X	X	X	X	X
33/10	AR/Yes/B	Rectus not as spared	Moderate	M	N	X	X	Same
34/39[d]	AR/Yes/B	AD not spared	Moderate	N	X	X	X	X
35/30	AR/Yes/B	AD not spared	Moderate	M	X	X	X	X
36/40	AR/Yes/C		Moderate	N	N	N	M	Same
37/20	AR/Yes/B	Diffuse, atrophic except rectus	Moderate	X	N	N	X	X

Abbreviations: A, typical; AD, autosomal dominant; AL, adductor longus; AM, adductor magnus; AR, autosomal recessive; B, compatible; B+, compatible but with an overlap to other disorders such as mild cases with *SEPN1* mutations; C, different; D, uninformative; G, gracilis; GM, gastrocnemius medialis; M, mild; N, not; NA, not applicable; PG, peroneal group; RF, rectus femoris; S, sartorius; SO, soleus; TA, tibialis anterior; VL, vastus lateralis; X, observed.
[a] Empty spaces indicate no information available.
[b] Indicates siblings or relatives.
[c] Described in Jungbluth et al.[14]
[d] Described in Zhou et al.[3]

The pattern in 1 patient was classified as different with involvement of the adductor longus and rectus femoris muscles, and 2 additional patients had only minimal nonspecific muscle MRI changes.

There was agreement among the 3 observers in 33 of the cases (89%). In the remaining 4 cases (11%), 2 examiners classified the pattern as compatible and the other as typical; these cases were eventually classified as compatible.

Control Group

The 23 MRIs analyzed as disease controls all had patterns of muscle involvement different from that reported as typical of *RYR1*-related myopathies.

ASSOCIATION BETWEEN CLINICAL PHENOTYPES AND MRI FINDINGS

Of 7 patients with a mild phenotype, 3 had a typical pattern, 3 had a consistent pattern, and 1 had only mild nonspecific changes. Of 26 patients with a moderate phenotype, 14 had a typical pattern and 10 had a consistent one. In 1 patient each, findings were nonspecific or different. In all 4 patients with a severe phenotype, the pattern was classified as typical.

HISTOLOGIC AND MRI FINDINGS

In 21 patients, results of histologic studies were available. Of those, only 1 (patient 12) had type 1 predominance and

Table 2. Clinical Details[a]

Patient No.	Patient Age at First Concerns	Maximal Functional Ability			Ophthalmoparesis	Facial Weakness	Scoliosis	Feeding Difficulty
		Stairs	Run	Walk				
1	Years	Yes	Yes	Yes	No	No	No	
2	Birth	No	No	Steps	No	Mild	Surgery	Yes
3	2 y	Yes	Yes	Yes	No	No	No	No
4	Years	Yes	Yes	Yes	No	No	No	
5		Use rail		Yes	No	Yes	No	
6			Slow	Yes	No	Mild	No	
7	2 y	Slow	Slow	Yes	No	No	No	No
8	Months	Yes	Slow	Yes	No	Yes	No	No
9	5 y	Yes	Slow	Yes	No	Yes	Mild, 16 y	No
10	Years	Yes	Slow	Yes	No	No	No	
11	Birth	No	No	No	No	Yes	Surgery	
12	2 y	Use rail	No	No	No	No	No	No
13	5 y	Yes	Slow	Yes	No	Mild	No	No
14				Yes	No		No	
15		Use rail	Slow	Yes	No	Yes	Mild, 14 y	
16	Birth	No	No	No	No	Yes	Surgery	Yes
17	Birth	No	No	No	No	Mild	Surgery	Yes
18	3 y	Yes	Slow	Yes	No	No	No	No
19	Months	Use rail	Slow	Yes	No	Mild	No	No
20	Birth	Yes	Slow	Yes	No	Yes	No	Yes
21	Birth	Slow	Slow	Yes	No	No	No	Yes
22	4 y	Use rail	No	Yes	No	Yes	Brace	
23	1 y	Use rail	No	Yes	No		No	No
24		Use rail	No	Yes	No		No	No
25	7 y	Use rail	Yes	Yes	No	Yes	No	No
26	2 y	Use rail	Slow	Yes	No	Yes	No	No
27		Use rail		Yes	No	No	No	
28		Use rail	No	Yes	No	Yes	No	No
29	2 y	Yes	Yes	Yes	No	No	No	No
30	Birth	Use rail	No	Yes	Abduction	Yes	Kyphosis	PEG
31	Birth	Use rail	No	Yes	Yes	Yes	No	PEG
32	Birth	Use rail	No	Yes	Yes, with ptosis	Yes	Mild	PEG
33	4 y	Use rail	No	Yes	Upgaze	Mild	Mild, 17 y	Yes
34	6 y	Use rail	Slow	Yes	Yes			
35	Birth	Use rail	No	Yes	Upgaze, abduction	Mild	No	Yes
36	1 y	Yes	Slow	Yes	Yes	Mild	No	No
37		Slow		Yes	Yes	Yes	No	No

Abbreviations: PEG, percutaneous endoscopic gastrostomy.
[a] Empty spaces indicate no information available.

large cores running along the fiber, previously reported to be a typical sign of central core disease, and she had typical MRI findings. Four patients had few cores, and 6 had corelike areas or unevenness of staining on oxidative enzyme staining. Of the 6, 4 had peripheral and 2 had multiple cores. Eleven patients had type 1 predominance, and all others had unspecific myopathic signs. Of the patients with cores or corelike areas, 8 of 13 had typical imaging findings. Of the 13 patients with compatible MRI findings, 3 had corelike areas and 4 did not.

MODE OF INHERITANCE AND MRI FINDINGS

Of 18 patients with dominant mutations, 11 had typical, 6 had consistent, and 1 had uninformative changes. Nineteen patients had recessive mutations; of these, 10 had typical, 7 had consistent, 1 had different, and 1 had uninformative findings. None of the recessive cases with ophthalmoparesis (n=8) had a typical pattern, whereas this was found in 10 of 11 without ophthalmoplegia. Ophthalmoparesis ranged from mild restriction of eye movements mostly in abduction and upward gaze to severe limitation in the horizontal and vertical plane. None of the patients, however, had complete ophthalmoplegia. When data from this subset of patients were analyzed separately, the difference between the adductor longus muscle (usually spared or only mildly involved) and the adductor magnus muscle (usually severely affected) in 5 of 8 patients with ophthalmoparesis was less striking. In 3 of 8 patients with ophthalmoparesis, the rectus femoris was not as strikingly spared as in the typical cases.

Imaging findings are summarized in Table 1. **Figure 1** shows a schematic diagram of the selective muscle involvement. **Figure 2** shows examples of typical moderate and severe findings of patients with dominant mutations. **Figure 3** demonstrates typical and a compatible pattern of patients with recessive mutations.

Table 3. Mutation Details[a]

Patient No.	Exon	Mutation Details	Type 1 Predominance/Cores
1	101	c.14581C>T, p.Arg4861Cys[b]	No/no
2	101	c.14581C>T, p.Arg4861Cys[b]	No/yes
3	91	c.12861_12869dup, p.Thr4288_Ala4290dup	Yes/no
4	102	c.14678G>C, p.Arg4893Pro[b]	No/yes
5	101	c.14693T, p.Ile4898Thr de novo	
6	95	c.13885G>A, p.Val4629Met	
7	28	c.4024A>G; p.Ser1342Gly	Yes/no
8	102	c.14667C>G, p.Tyr4889X[b]	Yes/no
9	102	c.14667C>G, p.Tyr4889X[b]	Yes/no
10	101	c.14587_14604del, p.Phe4863_Glu4868del[b]	No/yes
11	101	c.14587_14604del, p.Phe4863_Glu4868del[b]	No/yes
12	101	c.14582G>A, p.Arg4861His[b]	Yes/yes
13	102	c.14740A>G, p.Arg4914Gly[b]	
14	102	c.14740A>G, p.Arg4914Gly[b]	
15	101	c.14581C>T, p.Arg 4861Cys[b]	
16	101	c.14582G>A, p.Arg4861His[b]	
17	101	c.14581C>T, p.Arg4861Cys[b]	No/yes
18	91	c.12861_12869dup9, p.Thr4288_Ala4290dup	
19	2, 86	c. 122T>C, p.Phe41Ser; c11798A>G, p.Tyr3933Cys	Yes/P
20	21, 25	c.2635G>A, p.Glu879Lys; c.3381 + 1	Yes/P
21	21, 25	c.2635G>A, p.Glu879Lys; c.3381 + 1	Yes/no
22	101	c.14545G>A, p.Val4849Ile homozygous	No/no
23	85	c.11813G>A, p.Gly3938Asp homozygous	Yes/P
24	15, 104	c.1609G>A, p.Ala537Thr; c.14939C>T, p.Thr4980Met	
25	95, 87	c.13892A>G, p.Tyr4631Cys; c.11798A>G, p.Tyr3933Cys	
26	95, 87	c.13892A>G, p.Tyr4631Cys; c.11798A>G, p.Tyr3933Cys	
27	79	c.11315G>A, p.Arg3772Gln homozygous	No/yes
28	79	c.11315G>A, p.Arg3772Gln homozygous	
29	44, 86	c.7215-1G>C, c.11798A>G, p.Tyr3933Cys	Yes/no
30	4, 41	c.325C>T, p.Arg109Trp; c.6721C>T, p.Arg2241X	Yes/P
31	4, 41	c.325C>T, p.Arg109Trp; c.6721C>T, p.Arg2241X	
32	13, 60	c.1250T>C, p.Leu417Pro; c.9172 + 1G>A	
33	68, 100	c.10343C>, p.Ser3448Phe; c.14365-2A>T	
34	18, 45	c.1983G>A, p.Trp661X; c.7268T>A, p.Met2423Lys	
35	57, 18, 41	c.8816G>A, p.Arg2939Lys; c.6721C>T, p.Arg2241X; c.2122 G>A, p.Asp708Asn	No/yes
36	25, 30	c.3381 + 1 G>A, c.4405C>T, p.Arg1469Trp	No/yes
37	20, 26	c.2374_2376delCTT, p.Leu792del; c.3494G>A, p.Gly1165Asp	

Abbreviation: P, peripheral cores.
[a] Empty spaces indicate no information available.
[b] Indicates C-terminal hotspot screening, no full gene sequencing.

COMMENT

The pattern of selective involvement of muscles on MRI in patients with central core disease due to *RYR1* mutations was initially reported in 2004.[14] In that small series (11 cases), patients with mainly dominant mutations had a similar pattern consisting of adductor longus, rectus, gracilis, and semitendinosus muscles being selectively or relatively spared compared with other thigh muscles. Anterior thigh muscles were more affected than the posterior compartment. In the lower legs, the peroneal group was usually more affected than the tibialis anterior, and the soleus was generally more involved than the other posterior muscles, with the lateral head of the gastrocnemius often more affected than the medial. These findings have been subsequently confirmed in a separate study[15] from another group in patients with dominant *RYR1* mutations. The aim of the present study was to establish whether these original findings could be confirmed in a considerably larger cohort that included 20 patients with different degrees of clinical severity and dif-

ferent modes of inheritance who had never previously been described, including 19 patients with clear autosomal recessive inheritance and 8 with associated ophthalmoparesis. Although we were able to confirm the pattern previously reported as the most frequent finding, we also demonstrated additional features, mainly depending on genotype and the presence of ophthalmoparesis, that were still consistent with the typical pattern but expanded the spectrum of MRI findings in *RYR1*-related myopathies.

In keeping with our recent observation in other muscle disorders,[13] our results suggest that the analysis of the gradient of muscle involvement, as shown in the schematic in Figure 1, is a more valuable approach than the analysis of individual muscles, which may be misleading. For example, although in the original description of muscle MRI in patients with *RYR1* the rectus femoris muscle appeared to be strikingly spared, in our larger cohort we found a mild involvement of the rectus femoris in a significant proportion of cases (15 of 36 cases studied) and a marked signal increase in 4 patients. In all these
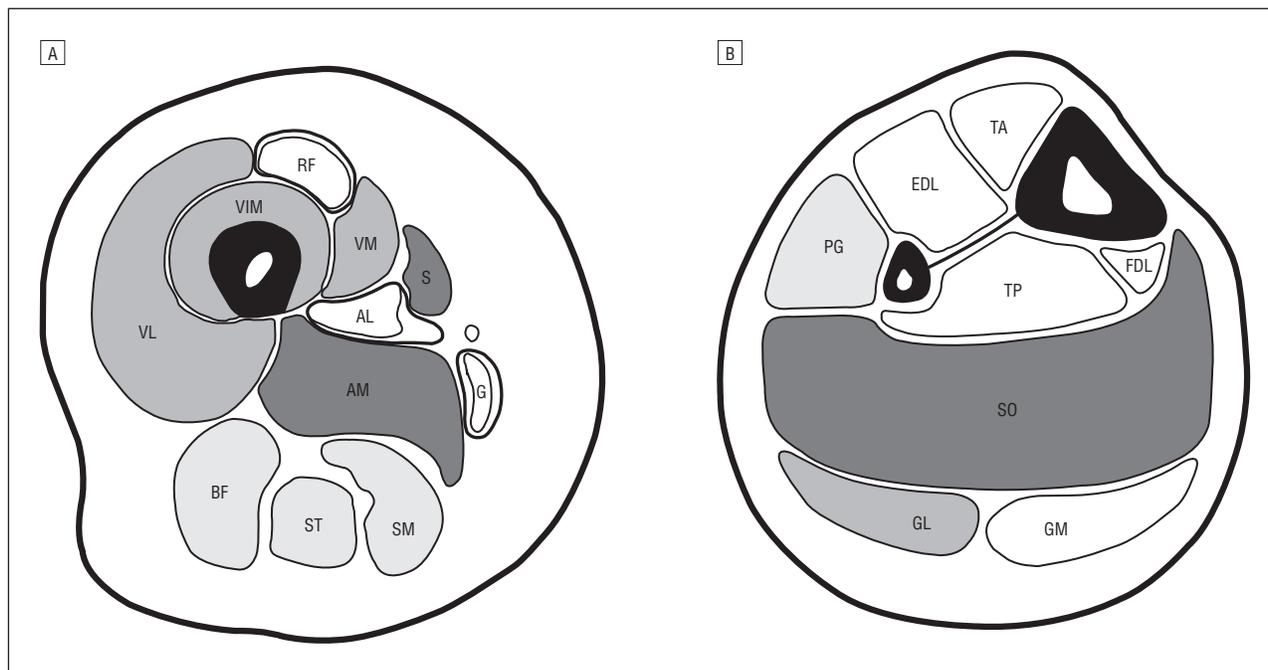
Figure 1. Schematic diagram of the typical pattern in *RYR1*-related myopathies. A, In the thighs, the rectus femoris (RF), adductor longus (AL), and gracilis (G) are spared and in some patients hypertrophied; the adductor magnus (AM), sartorius (S), vastus lateralis (VL), vastus intermedius (VIM), and vastus medialis (VM) are affected; the hamstrings are less affected; and the involvement of semimembranosus (SM) and semitendinosus (ST) is nonspecific. BF indicates biceps femoris. B, In the calf, the most affected muscle is the soleus (SO), followed by the gastrocnemius lateralis (GL) and to a lesser effect the gastrocnemius medialis (GM). In the anterior compartment, which is less affected than the posterior, the peroneal group (PG) is more affected than the tibialis anterior (TA). EDL indicates extensor digitorum longus; FDL, flexor digitorum longus; and TP, tibialis posterior.

cases, however, the rectus was always clearly less involved than the vasti, indicating that the previously reported gradient still applies, even in cases in which the rectus is affected. However, we also found 3 cases with recessive mutations and 1 mild dominant case that had a less striking difference with the adjacent muscles.

Other observations further expand the spectrum of the MRI findings associated with *RYR1* mutations. For example, the pattern of involvement of the hamstring muscles proposed in the original description,[14] in which the semitendinosus was less affected than the semimembranosus in 9 of 11 cases, was not confirmed. However, the semimembranosus or semitendinosus muscles were variably involved in the present series.

When we compared MRI findings with clinical severity, we observed that the pattern was more often typical in the severe or moderate cases, whereas, not surprisingly, mild or nonspecific changes were generally found in patients with milder clinical phenotypes. In 4 cases with mild involvement on MRI, the sartorius appeared to be involved even when other muscles, such as the vasti and the adductor magnus (usually more affected in the typical pattern), appeared to be relatively spared. In those cases, the pattern resembled the one observed in mildly affected patients with *SEPN1*-related myopathies.[13,18]

Because all patients in our *RYR1* cohort had a genetically confirmed diagnosis, we were also able to correlate MRI findings to the mode of inheritance. Typical and consistent patterns were similarly found in dominant and recessive mutations; however, we noted that, although recessive cases without ophthalmoparesis consistently showed the typical pattern, those with ophthalmoparesis showed

a consistent pattern but more diffuse changes with a lesser gradient between involved and spared muscles. In particular, we found that, in the latter group, the differential involvement between the typically spared adductor longus and the markedly affected adductor magnus was not as striking as in the typical dominant cases previously reported. This feature was observed in 5 of 8 patients with recessive *RYR1* mutations and ophthalmoparesis and in only 1 of 11 patients with recessive mutations without ophthalmoparesis. This pattern likely reflects the overall more widespread muscle involvement in recessive *RYR1*-related myopathies with ophthalmoparesis.[19]

Our results suggest that, although the spectrum of *RYR1*-related muscle MRI findings is broader than originally reported, evaluating the pattern and the gradient of involvement of the leg muscles considerably helps in the differential diagnosis.

Of the 23 patients with other myopathies in the control group, none had MRIs that were compatible with the pattern observed in *RYR1*-related myopathies. Several conditions might overlap clinically and/or pathologically with core myopathies, including cases with rigid spine muscular dystrophy, Ullrich congenital muscular dystrophy, nemaline myopathy with cores, centronuclear myopathy,[20-22] and congenital fiber–type disproportion due to mutations in genes other than *RYR1*.[23] However, muscle MRI patterns observed in our series are distinct from those reported in *DNM2*-related centronuclear myopathies,[24,25] Ullrich congenital muscular dystrophy, and *NEB*- or *ACTA1*-related nemaline myopathy.[13,17,26,27] The only exception in our cohort were cases with a degree of overlap with the pattern found in early rigid spine muscular
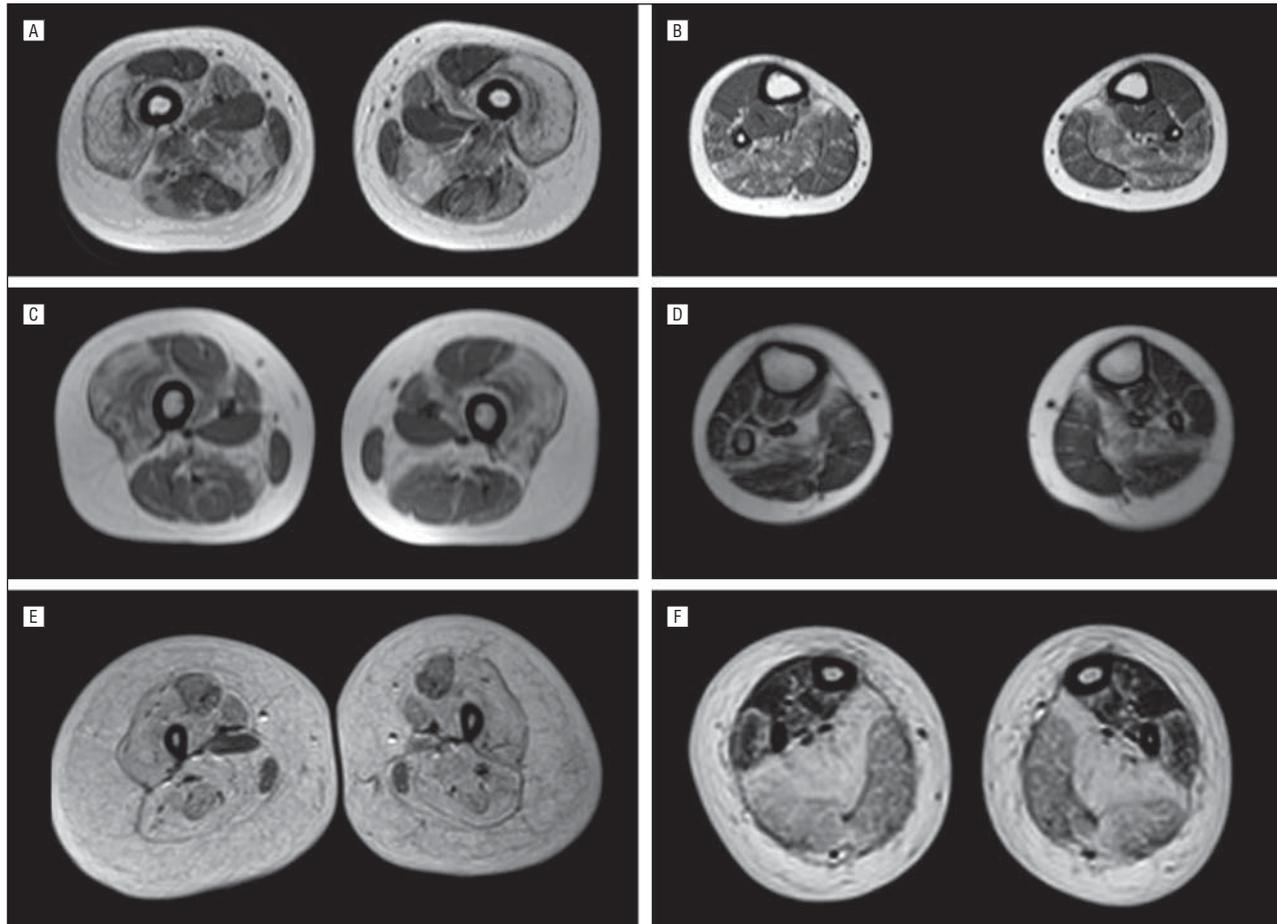
Figure 2. Typical pattern in magnetic resonance imaging of the thigh (images in the left column) and the calf (images on the right). A and B, Patient 12 is 8 years of age, with moderately severe disease. C and D, Patient 6 has a moderate phenotype. E and F, Patient 16 is 13 years of age with a severe phenotype; relatively spared rectus femoris, adductor magnus, gracilis, and to a lesser extent the sartorius; and with the soleus most affected in the calf.
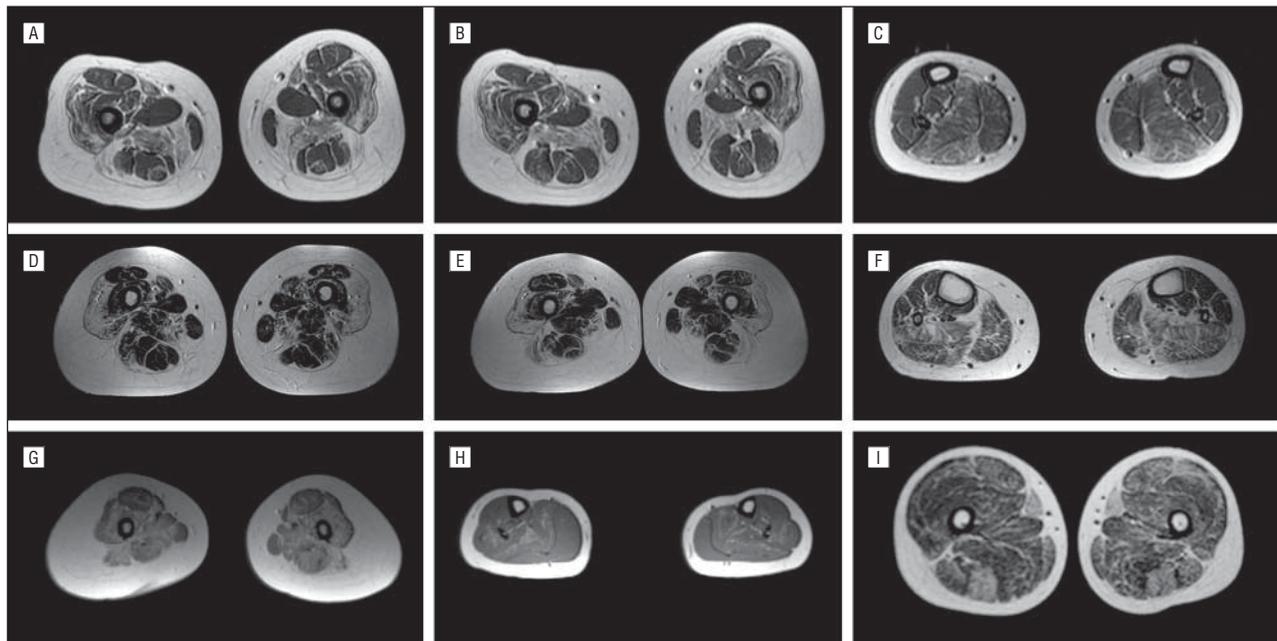
Figure 3. Magnetic resonance imaging findings in patients with recessive mutations. A, B, and C, Axial T1-weighted images with a typical pattern in patient 26, 14 years of age, with recessive disease without ophthalmoplegia. More diffuse but still recognizable relative sparing of the rectus, adductor longus, and gracilis muscles is seen. D, E, and F, Patient 19 with a mild phenotype without ophthalmoparesis in a proximal view, middle thigh, and calf, respectively. G, Axial images of the thigh of patient 32, 18 years of age, with ophthalmoplegia reveal diffuse, atrophic muscles, relative sparing of the rectus, and hypertrophied adductor longus affected on the central part. H and I, Axial images of the calf and proximal thigh, respectively, of patient 33, 10 years of age, with ophthalmoplegia. In this patient, compatible but diffuse involvement of vasti, rectus, and adductor longus only marginally less involved than the adductor magnus are seen.

dystrophy; this is an interesting observation considering the recently suggested link between the conditions as a result of secondary RyR1 dysfunction as a result of *SEPN1* mutations.[28]

Regarding the diagnostic aspects, our findings are important for 2 reasons. First, they reinforce the importance of considering *RYR1* involvement in individuals with relatively nonspecific pathological findings; second, the finding of a typical pattern will help the interpretation of emerging genetic data. Systematic *RYR1* sequencing often reveals variants of uncertain significance, and identification of a typical muscle MRI pattern may aid the often challenging task of assigning pathogenicity to these changes. Taking into account potential overlap with *SEPN1*-related myopathies on muscle MRI imaging in a few patients, *SEPN1* involvement should be excluded in those patients first, considering the small size of the gene. However, we would proceed with *RYR1* screening in patients with suggestive muscle MRI findings because we are not aware of any other condition with normal creatine kinase levels and muscle involvement similar to *RYR1*-related myopathies.

In conclusion, our results expand the spectrum of muscle MRI findings in patients with *RYR1*-related myopathies. Although a pattern of muscle involvement consistent with that previously reported characterizes most of the patients with dominant and recessive mutations without ophthalmoparesis, additional features, particularly in patients with ophthalmoparesis, are present. In addition, this larger study suggests that muscles originally reported to be relatively spared, such as the rectus femoris, adductor longus, or semimembranosus and semitendinosus muscles, can show variable involvement. However, even in these cases, the gradient of selective muscle involvement still allows the *RYR1* pattern to be recognized. In addition to the clinical and pathological findings, this information should be used to direct genetic testing and when interpreting the significance of novel genetic variants.

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