

# Rhabdomyolysis revisited

## Detailed analysis of magnetic resonance imaging findings and their correlation with peripheral neuropathy

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### Abstract

The objective is to evaluate the magnetic resonance imaging (MRI) findings in rhabdomyolysis in detail and determine their correlation with the development of peripheral neuropathy.

Magnetic resonance images for 23 patients with confirmed rhabdomyolysis with (n = 11) or without (n = 12) peripheral neuropathy were retrospectively reviewed for the signal intensity on T1- and T2-weighted images, intramuscular hemorrhage, enhancement pattern, shape and margin in the longitudinal plane, edema in the deep fascia and overlying subcutaneous layer, multiplicity, and bilateral limb involvement. The collected data were statistically analyzed and the relationship between the imaging findings and the development of peripheral neuropathy was determined.

Abnormal signal intensities on T1- or T2-weighted images were observed for all patients except one. Fourteen patients (60.9%) showed intramuscular hemorrhage. Stippled enhancement (11/23; 47.8%) was the most common enhancement pattern. Nineteen patients (86.4%) showed a well-defined rectangular shape with a ragged margin in the longitudinal plane. The affected muscle volume usually increased (17/23; 73.9%), with edema in the deep fascia and the overlying subcutaneous layer (13/23; 56.5%). Multiplicity within a muscle, compartment, and limb was observed in 7 (31.8%), 18 (81.8%), and 16 (72.7%) patients, respectively. Bilateral involvement was observed in 7 patients (30.4%). Only multiplicity within a compartment showed a statistically significant correlation with peripheral neuropathy development.

Common MRI findings in rhabdomyolysis include intramuscular hemorrhage, stippled enhancement, a well-defined rectangular shape with a ragged margin in the longitudinal plane, and multiplicity. Multiplicity within a compartment may be a predictor of the development of peripheral neuropathy.

**Abbreviations:** CK = creatine kinase, DTI = diffusion tensor imaging, DWI = diffusion-weighted imaging, EMG = electromyography, FOV = field of view, MRI = magnetic resonance imaging, T1WI = T1-weighted imaging, T2WI = T2-weighted imaging, TE = echo time, TR = repetition time.

**Keywords:** MR, neuropathy, rhabdomyolysis

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### 1. Introduction

Rhabdomyolysis is a potentially life-threatening condition characterized by the breakdown of skeletal muscle with the subsequent release of intracellular contents into the circulatory system.<sup>[1]</sup> It is caused by various factors such as drug and alcohol abuse, the use of neuroleptic agents, direct trauma, compression, immobilization, ischemia, excessive muscular activity, infection, metabolic disease, and genetic disorders.<sup>[1]</sup> The most sensitive indicator of myocyte injury in rhabdomyolysis is a markedly elevated serum creatine kinase (CK) level, which peaks at 1 to 3 days and subsequently declines by 39% each day.<sup>[1]</sup> The serum CK level is not always significantly elevated in rhabdomyolysis, particularly in the early stages and in patients admitted relatively late.<sup>[1]</sup> Although the presence of rhabdomyolysis is clinically evident in most cases, it is not clinically diagnosed in 27% patients.<sup>[1]</sup> However, if treatment is delayed, rhabdomyolysis can lead to disability, renal failure, and even death.<sup>[1]</sup> Peripheral neuropathy, while rare, is one of the significant complications of rhabdomyolysis and can result in irreversible limb paralysis.<sup>[2,3]</sup> It has been known to develop in cases of acute compartment syndrome, which may lead to compressive or ischemic nerve injury.<sup>[2,3]</sup> Although magnetic resonance imaging (MRI) is an excellent imaging modality for soft tissue conditions, it is not

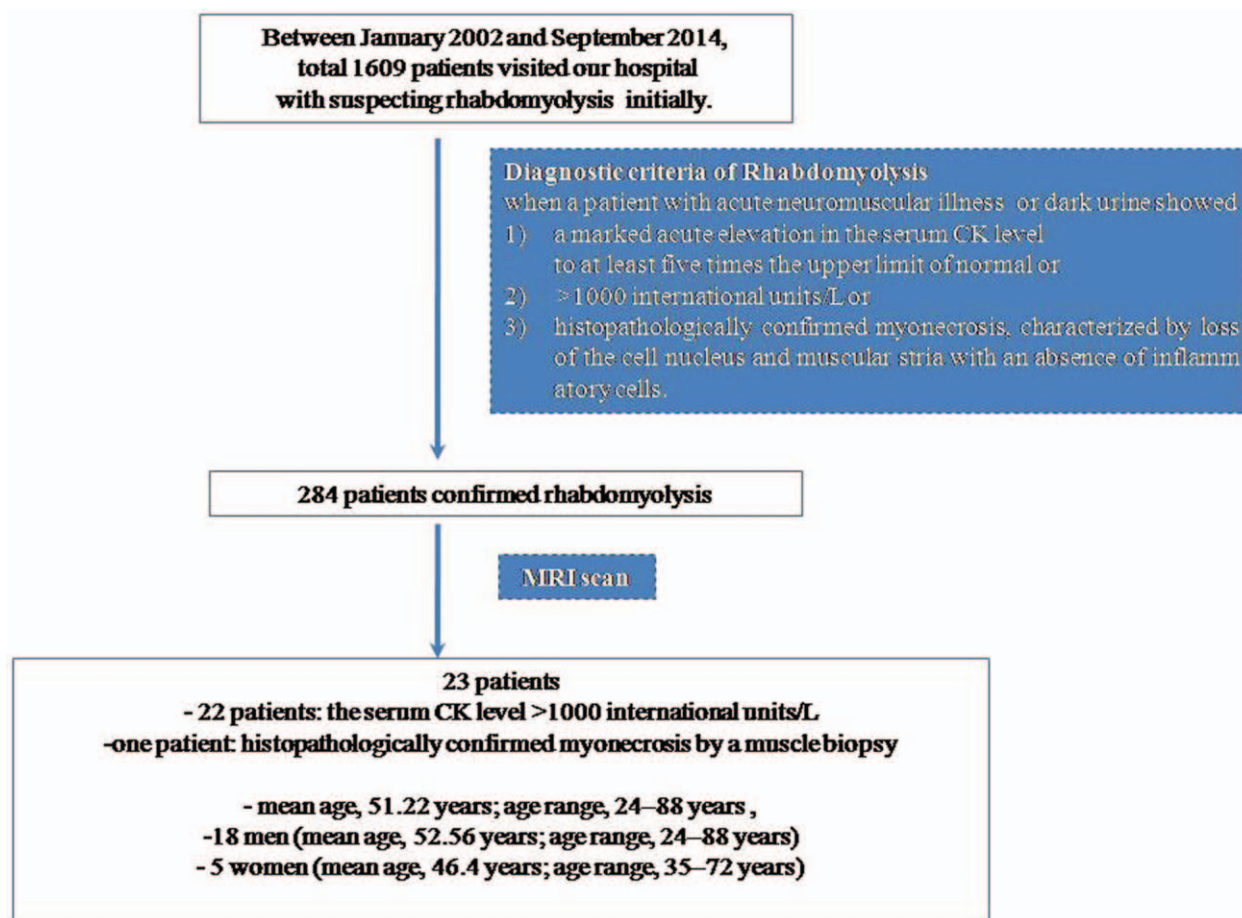


Figure 1. Flowchart showing the study selection procedure.

considered crucial for the diagnosis of rhabdomyolysis because the findings are thought to be nonspecific.<sup>[4]</sup> Till date, only case reports and a few original articles with small sample sizes have described the imaging findings in rhabdomyolysis.<sup>[4–8]</sup> These reports have documented muscle swelling, intramuscular hemorrhage, and diffuse or stippled enhancement of the affected muscle; however, other findings such as the shape and margin of the lesion, muscle volume changes, adjacent fascial changes, multiplicity, and the extent of the lesion have not been described in detail.<sup>[4–8]</sup>

Accordingly, we conducted the present retrospective study to evaluate the MRI findings in rhabdomyolysis in more detail and in a large patient sample. We also determined the correlation of the MRI findings with the development of peripheral neuropathy in these patients.

## 2. Materials and methods

### 2.1. Patient selection

This study was approved by the institutional review board at Inha University Hospital. Informed consent was not required for this retrospective study. Patients were selected via a retrospective review of medical records and laboratory findings. Patient approval was not required because anonymity was preserved.

Between January 2002 and September 2014, total 1609 patients visited our hospital and clinically suspected rhabdomyolysis initially. Rhabdomyolysis was diagnosed when a patient

with acute neuromuscular illness or dark urine showed a marked acute elevation in the serum CK level to at least 5 times the upper limit of normal or > 1000 international units/L or histopathologically confirmed myonecrosis, characterized by loss of the cell nucleus and muscular stria with an absence of inflammatory cells. Accordingly, 285 patients were confirmed to have rhabdomyolysis. From these, 23 patients (mean age, 51.22 years; age range, 24–88 years), including 18 men (mean age, 52.56 years; age range, 24–88 years), and 5 women (mean age, 46.4 years; age range, 35–72 years) who underwent MRI of the affected areas were enrolled in our study. All patients except 1 showed an elevated serum CK level of > 1000 U/L. The remaining patient showed a serum CK level of approximately 977 U/L 5 days after the onset of symptoms and was confirmed to have rhabdomyolysis after histopathological analysis of a muscle biopsy specimen (Fig. 1).

### 2.2. Review of medical records

The medical records of enrolled patients were reviewed by a radiologist for the following findings: the duration from the onset of symptoms to the measurement of serum CK levels and MRI, involvement site, assumed etiology, underlying chronic disease, peak serum CK level, presence of compartment syndrome, treatment, and development of peripheral neuropathy within 2 weeks to 6 months and its treatment. Peripheral neuropathy was diagnosed by electromyography (EMG) or clinically on the basis of decreased sensory or motor function.

### 2.3. MRI technique

Patients underwent MR examinations using 1 of 2, 1.5-T MR scanners (SignaHDx, Signa Excite; GE Medical Systems, Milwaukee, WI). T1-weighted fast spin echo, T2-weighted fast spin echo with or without chemical fat suppression, and fat-suppressed T1-weighted fast spin echo images with enhancement were obtained in the axial plane, while T1-weighted fast spin echo, T2-weighted fast spin echo, and fat-suppressed T1-weighted fast spin echo images with enhancement were obtained in the sagittal or coronal plane. T1-weighted imaging (T1WI) was performed with a repetition time (TR) of 400 to 600 milliseconds and an echo time (TE) of 10 to 20 milliseconds, while T2-weighted imaging (T2WI) with or without fat suppression was performed with TR of 2200 to 4600 milliseconds and TE of 90 to 110 milliseconds. For thigh evaluation, a body coil was used, and the field of view (FOV) was 220 × 220 mm for axial images and 460 × 460 mm for sagittal or coronal images. For evaluation of the lower leg, a body coil was used, and FOV was 160 × 160 mm for axial images and 420 × 420 mm for sagittal or coronal images. For the upper arm and forearm, a cardiac coil was used, and FOV was 160 × 160 mm for axial images and 240 × 240 mm for sagittal or coronal images. The section thickness and intersection gap varied among the sites of involvement. Specifically, the section thickness/intersection gap was 9 mm/2 mm for the thigh and lower leg and 4 mm/0.5 mm for the upper arm and forearm. The matrix size was 192 × 256 or 256 × 256. Contrast-enhanced MRI was commenced within 30 seconds after injection of gadodiamide (Omniscan, 0.2 mmol/kg; GE Healthcare, Princeton, NJ). After contrast infusion, axial images were obtained followed by sagittal or coronal images.

### 2.4. Review of MRI findings

Two musculoskeletal radiologists independently reviewed the MR images for following findings: the signal intensity of the involved muscles on T1- and T2- or fat-suppressed T2-weighted images, intramuscular hemorrhage, major enhancement pattern on axial images, margin and shape of the area showing abnormal signal intensity in the longitudinal plane (coronal or sagittal images), muscle volume changes, edema in the adjacent deep fascia, edema in the overlying subcutaneous layer, multiplicity, and bilateral involvement. On T1-weighted images, the signal intensity was classified as follows: homogeneous iso-signal intensity relative to the adjacent normal muscle and heterogeneous signal intensity including iso-signal and high signal intensity. On T2- or fat-suppressed T2-weighted images, the signal intensity was classified as follows: homogeneous iso-signal intensity relative to the adjacent normal muscle; homogeneous high signal intensity; and heterogeneous signal intensity including high signal, iso-signal, and low signal intensities. Intramuscular hemorrhage was defined as an area of high signal intensity on T1-weighted sequences without fat suppression or heterogeneous signal intensity, including dark signal intensity, on T2-weighted images, with loss of the normal fibrillar pattern in the involved muscle. The major enhancement patterns were analyzed for the largest involved area on axial images and classified as follows: iso-enhancement relative to the adjacent normal muscle, diffuse increased enhancement relative to the adjacent normal muscle, peripheral enhancement with a central dot-like or linear streaky enhancement (so-called stippled enhancement), and a central nonenhancing portion with peripheral enhancement (Fig. 2). Multiple foci showing different enhancement patterns were also

recorded, although the major enhancement pattern was analyzed for the largest involved area. The margin and shape of the lesion in the longitudinal plane were evaluated on fat-suppressed, contrast-enhanced coronal, and sagittal T1-weighted images and were divided into 3 patterns: ill-defined patchy shape, well-defined round shape, and well-defined rectangular shape with a ragged margin (Fig. 3). Multiplicity was defined as multiple lesions within a muscle, multiple muscle involvement within a compartment, and multiple compartment involvement within a limb.

After separate review, the 2 musculoskeletal radiologists conducted a review in consensus for statistical analysis of the correlation between the MRI findings and the development of peripheral neuropathy.

### 2.5. Statistical analysis

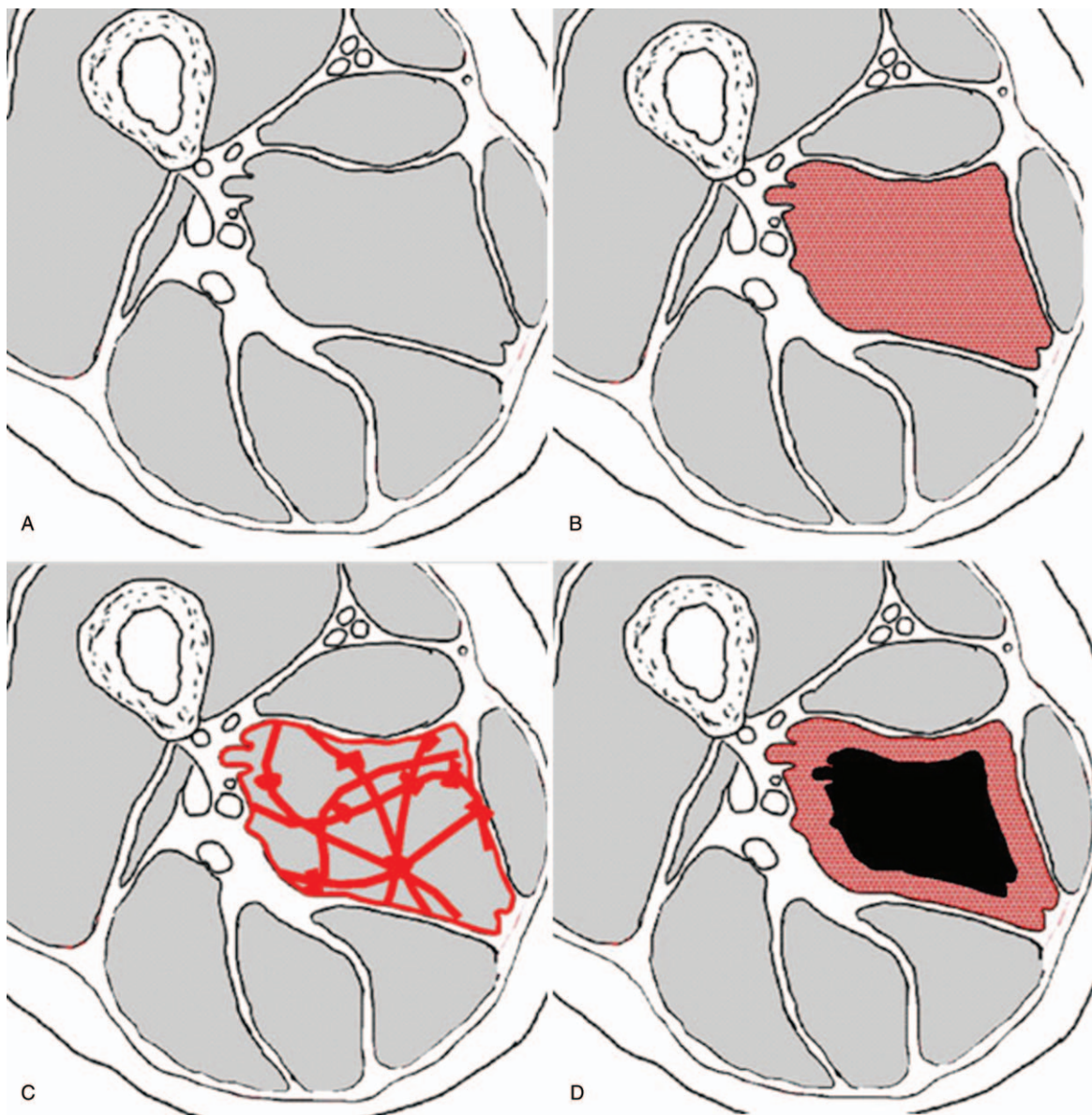
The data collected from medical records were descriptively analyzed. The interobserver agreement for each MRI finding was tested by Cohen kappa statistics<sup>[9]</sup> and considered poor when the kappa value was  $\leq 0.200$ , fair when the kappa value was 0.201 to 0.400, moderate when the kappa value was 0.401 to 0.600, substantial when the kappa value was 0.601 to 0.800, and almost perfect when the kappa value was 0.801 to 1.000.<sup>[9]</sup> The data collected from medical records and the MRI findings were compared between patients with peripheral neuropathy and those without. The patient age, duration from the onset of symptoms to the measurement of the serum CK level/MRI, and the peak serum CK level were compared and analyzed using the Mann-Whitney test. The patient sex, involvement site, assumed etiology, underlying chronic disease, and all MRI findings were compared and tested using Fisher exact test and Pearson  $\chi^2$  test. The SPSS 19.0.1 software package (SPSS, Chicago, IL) was used for all statistical analyses. A *P* value of  $< .05$  was considered statistically significant.

## 3. Results

### 3.1. Results of the medical record review

The data collected from medical records are enlisted in Table 1. The patients presented with local pain and swelling, weakness and sensory changes, or stupor mentality for a duration ranging from 1 to 40 days (mean, 3.37 days) between the onset of symptoms and the time of serum CK level measurement. The most common involvement site was the upper arm, followed by the lower leg. The most common assumed etiology was toxic and drug-related causes, followed by trauma with compression. Chronic alcoholism was the most common underlying chronic disease. The peak serum CK level ranged from 977 to 186,300 U/L (mean, 29,450.39 U/L). Eleven patients with suspected peripheral neuropathy were initially diagnosed by EMG within 2 weeks after symptom onset, although 1 patient did not undergo follow-up EMG because of emergency fasciotomy. Among these 11 patients, 3 underwent intracompartment pressure measurements, and 2 of them were diagnosed with compartment syndrome because the compartment pressures were  $> 30$  mm Hg. Of these 2 patients, 1 underwent fasciotomy immediately after symptom onset and recovered fully. The other patient underwent fasciotomy 3 days after symptom onset and exhibited residual peripheral neuropathy and contracture at the 6-month follow-up visit. The patient who was not diagnosed with compartment syndrome after pressure measurements also





**Figure 2.** Drawings illustrating the enhancement patterns for major muscles affected by rhabdomyolysis. A, The enhancement pattern appears to be the same for the affected and unaffected muscle (iso-enhancement). B, Diffuse increased enhancement of the affected muscle relative to the adjacent normal muscle. C, Peripheral enhancement with central dot-like or linear streaky enhancement (so-called stippled enhancement). D, Central nonenhancing portion with peripheral enhancement.

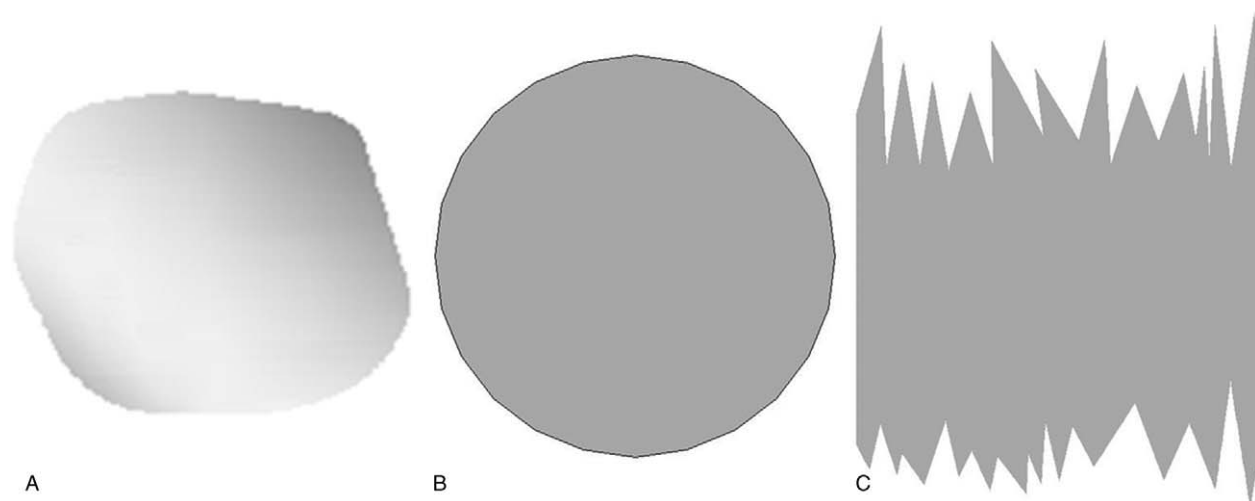
exhibited residual peripheral neuropathy and contracture at the 6-month follow-up visit. The other patients showed no clinical evidence of compartment syndrome and did not undergo compartment pressure measurements. All patients except the 2 who underwent fasciotomy received conservative treatment. Ten of the 11 patients with an initial suspicion of peripheral neuropathy (excluding the one who underwent emergency fasciotomy) exhibited the condition on EMG at the 6-month follow-up. None of the parameters collected from medical records showed a statistically significant association with the development of peripheral neuropathy.

### 3.2. Review of MRI findings

The mean duration from the onset of symptoms to MRI was 10.09 days. The site of involvement on MRI correlated with that

documented in the medical records. The results of the independent review of the MR images are shown in Table 2. Because 1 patient did not show abnormal findings on MRI, the longitudinal margin and shape of the lesion and multiplicity were evaluated only for the remaining 22 patients. The interobserver agreement was almost perfect for all analyzed MRI findings except the signal intensity on T1-weighted images and the increased muscle volume, which were associated with substantial agreement.

The results of consensus review of the MRI findings are shown in Table 3. On T1-weighted images, the affected muscles showed either homogeneous iso-signal intensity (Fig. 4) or heterogeneous signal intensity (Figs. 5 and 6). On T2-weighted images, heterogeneous signal intensity (Figs. 5 and 6) was the most common, followed by homogeneous high signal intensity (Fig. 4). Approximately 60.9% patients exhibited suspected intramuscu-



**Figure 3.** Drawings illustrating the shape and margin of rhabdomyolysis lesions in the longitudinal plane (coronal or sagittal images) of contrast-enhanced fat-suppressed T1-weighted sequences. A, Ill-defined patchy shape. B, Well-defined round shape. C, Well-defined rectangular shape with ragged margin.

lar hemorrhage (Figs. 5 and 6). The major enhancement patterns were variable, although stippled enhancement (Fig. 4) was the most common, followed by a central nonenhancing portion with peripheral enhancement (Fig. 5) and diffuse enhancement (Fig. 6). Six patients showed more than 1 type of enhancement pattern,

including stippled and peripheral enhancement (n=3), stippled and diffuse enhancement (n=2), and diffuse and peripheral enhancement (n=1). Most of the affected muscles showed a well-defined rectangular shape with a ragged margin (Figs. 4–6) in the longitudinal plane. The affected muscle volumes usually

**Table 1**

**Data collected from the medical records of patients with rhabdomyolysis with or without peripheral neuropathy.**

	Total (n=23)	Patient (n=23)		P value
		Complication – (n=12)	Complication + (n=11)	
Mean age (SD)	51.22 (16.41)	57.11 (18.1)	41.67 (11.84)	.91
Sex				.712
Men	18 (78.3)	9 (75)	9 (81.8)	
Women	5 (21.7)	3 (25)	2 (18.2)	
Mean duration from onset of symptoms to measurement of serum CK level (SD)	3.37 (8.06)	1.54 (1.2)	5.36 (11.53)	.211
Mean duration from onset of symptoms to MRI scan (SD)	10.09 (16.18)	13.33 (20.83)	6.56 (8.49)	.235
Involvement site				.0129
Upper arm	7 (30.4)	6 (50)	1 (9.1)	
Forearm	1 (4.3)	0 (0)	1 (9.1)	
Hand	2 (8.7)	0 (0)	2 (18.2)	
Gluteal region	4 (17.4)	3 (25)	1 (9.1)	
Thigh	3 (13)	1 (8.3)	2 (18.2)	
Lower leg	6 (26.1)	2 (16.7)	4 (36.4)	
Etiology				.150
Toxic and drug (including alcohol)	11 (47.8)	3 (25)	8 (72.7)	
Trauma/compression	5 (21.7)	3 (25)	2 (18.2)	
Excessive exercise	3 (13)	3 (25)	0 (0)	
CO intoxication	1 (4.3)	1 (8.3)	0 (0)	
Peripheral arterial disease	1 (4.3)	1 (8.3)	0 (0)	
Heart attack	1 (4.3)	0 (0)	1 (9.1)	
Burn	1 (4.3)	1 (8.3)	0 (0)	
Underlying chronic disease				.173
None	7 (30.4)	4 (33.3)	3 (27.3)	
Brain lesion	3 (13)	3 (25)	0 (0)	
Chronic alcoholism	10 (43.5)	3 (25)	7 (63.6)	
DM	1 (4.3)	1 (8.3)	0 (0)	
Atherosclerosis	1 (4.3)	1 (8.3)	0 (0)	
Heart disease	1 (4.3)	0 (0)	1 (9.1)	
Mean peak serum CK level (SD)	29450.39 (48227.91)	21743.33 (SD:37621.74)	37858.09 (58404.44)	.449

Data are expressed as mean (SD) or number (percentage) of patients. The percentages are based on a total of 23 patients. CK=creatinine kinase, CO=carbon monoxide, DM=diabetes Mellitus, MRI=magnetic resonance imaging, SD=standard deviation.

**Table 2**  
Findings of independent review of magnetic resonance imaging findings in rhabdomyolysis, with the kappa values for interobserver agreement.

	Reader 1	Reader 2	kappa value
SI on T1WI			0.74
Homogeneous iso-SI	12 (52.2%)	13 (56.5%)	
Heterogeneous SI	11 (47.8%)	10 (43.5%)	
SI on T2WI			0.92
Homogeneous iso-SI	1 (4.3%)	1 (4.3%)	
Homogeneous high-SI	13 (56.5%)	14 (60.9%)	
Heterogeneous SI	9 (39.1%)	8 (34.8%)	
Intramuscular haemorrhage	11 (47.8%)	11 (47.8%)	0.83
Enhancement pattern			1
IsoE	1 (4.3%)	1 (4.3%)	
Diffuse E	2 (8.7%)	2 (8.7%)	
Stipple E	11 (47.8%)	11 (47.8%)	
Central non-E with peripheral E	9 (39.1%)	9 (39.1%)	
Margin and shape*			1
Ill-defined patchy shape	3 (13%)	3 (13%)	
Well-defined round shape	1 (4.3%)	1 (4.3%)	
Well-defined rectangular shape with ragged margin	18 (78.3%)	18 (78.3%)	
Increased muscle volume	16 (69.6%)	13 (56.5%)	0.75
High SI in deep fascia in T2 WI	13 (56.5%)	13 (56.5%)	1
High SI in subcutaneous layer in T2WI	13 (56.5%)	13 (56.5%)	1
Multiplicity*			1
Within a muscle	7 (30%)	7 (30%)	
Within a compartment	18 (78.3%)	18 (78.3%)	
Within a limb	16 (69.6%)	16 (69.6%)	
Bilateral involvement	10 (43.5%)	10 (43.5%)	1

Data are expressed as number (percentage) of patients. The percentages are based on a total of 23 patients for all variables except those marked with \*. The P values of all interobserver agreement were less than 0001.

E = enhancement, SI = signal intensity, T1WI = T1-weighted imaging, T2WI = T2-weighted imaging. \* One patient showed no particular abnormal findings on magnetic resonance imaging, so the margin and shape and multiplicity were analyzed for 22 patients.

increased (Figs. 5 and 6). Thirteen patients (56.5%) showed edema in the deep fascia and the overlying subcutaneous fat layers. Multiplicity, including multiple muscle involvement within a compartment (Figs. 4–6) and multiple compartment involvement within a limb (Figs. 4 and 6), was common. Bilateral limb involvement was seen in 7 patients (30.4%).

Among the MRI findings, only multiple muscle involvement within a compartment showed a statistically significant association with the development of peripheral neuropathy ( $P = .04$ ). The other analyzed factors showed no significant association with the development of peripheral neuropathy. Although there were no statistically significant differences, rhabdomyolysis with peripheral neuropathy was more likely to involve multiple compartments within a limb than was rhabdomyolysis without peripheral neuropathy. Decreased enhancement was more frequently observed as the major enhancement pattern in patients with peripheral neuropathy than in those without, although the difference was not statistically significant. Specifically, all patients with peripheral neuropathy showed decreased enhancement of the affected muscle relative to the adjacent normal muscle, such as stippled enhancement and a central nonenhancing portion with peripheral enhancement. In contrast, 3 patients without peripheral neuropathy showed iso-enhancement or diffuse increased enhancement of the affected muscle.

**Table 3**  
Results of consensus review of magnetic resonance imaging findings in rhabdomyolysis with or without peripheral neuropathy.

	Patient (n = 23)			P value
	Total	PPN – (n = 12)	PPN + (n = 11)	
SI on T1WI				.568
Homogeneous iso-SI	14 (60.9)	7 (58.3)	7 (63.6)	
Heterogeneous SI	9 (39.1)	5 (41.7)	4 (36.4)	
SI on T2WI				.265
Homogeneous iso-SI	1 (4.3)	1 (8.3)	0 (0)	
Homogeneous high-SI	9 (39.1)	3 (25)	6 (54.5)	
Heterogeneous SI	13 (56.5)	8 (66.7)	5 (45.5)	
Intramuscular hemorrhage	14 (60.9)	8 (66.7)	6 (54.5)	.414
Enhancement pattern				.273
Iso E	1 (4.3)	1 (8.3)	0 (0)	
Diffuse E	2 (8.7)	2 (16.7)	0 (0)	
Stipple E	11 (47.8)	4 (33.3)	7 (63.6)	
Central non- E with peripheral E	9 (39.1)	5 (41.7)	4 (36.4)	
Margin and shape*				.176
Ill-defined patchy shape	2 (8.7)	2 (18.2)	0 (0)	
Well-defined round shape	1 (4.3)	1 (9.1)	0 (0)	
Well-defined rectangular shape with a ragged margin	19 (86.3)	8 (72.7)	11 (100)	
Increased muscle volume	17 (73.9)	7 (58.3)	10 (90.9)	.95
High SI in deep fascia in T2 WI	13 (56.5)	6 (50)	7 (63.6)	.407
High SI in subcutaneous layer in T2WI	13 (56.5)	5 (41.6)	8 (72.7)	.214
Multiplicity*				.5
Within a muscle	7 (31.8)	3 (27.3)	4 (36.4)	
Within a compartment	18 (81.8)	7 (63.6)	11 (100)	.045
Within a limb	16 (72.7)	6 (54.5)	10 (90.9)	.074
Bilateral involvement	7 (30.4)	4 (33.3)	3 (27.3)	.556

Data are expressed as number (percentage) of patients. The percentages are based on a total of 23 patients for all variables except those marked with \*.

E = enhancement, PPN = peripheral neuropathy, SI = signal intensity, T1WI = T1-weighted imaging, T2WI = T2-weighted imaging.

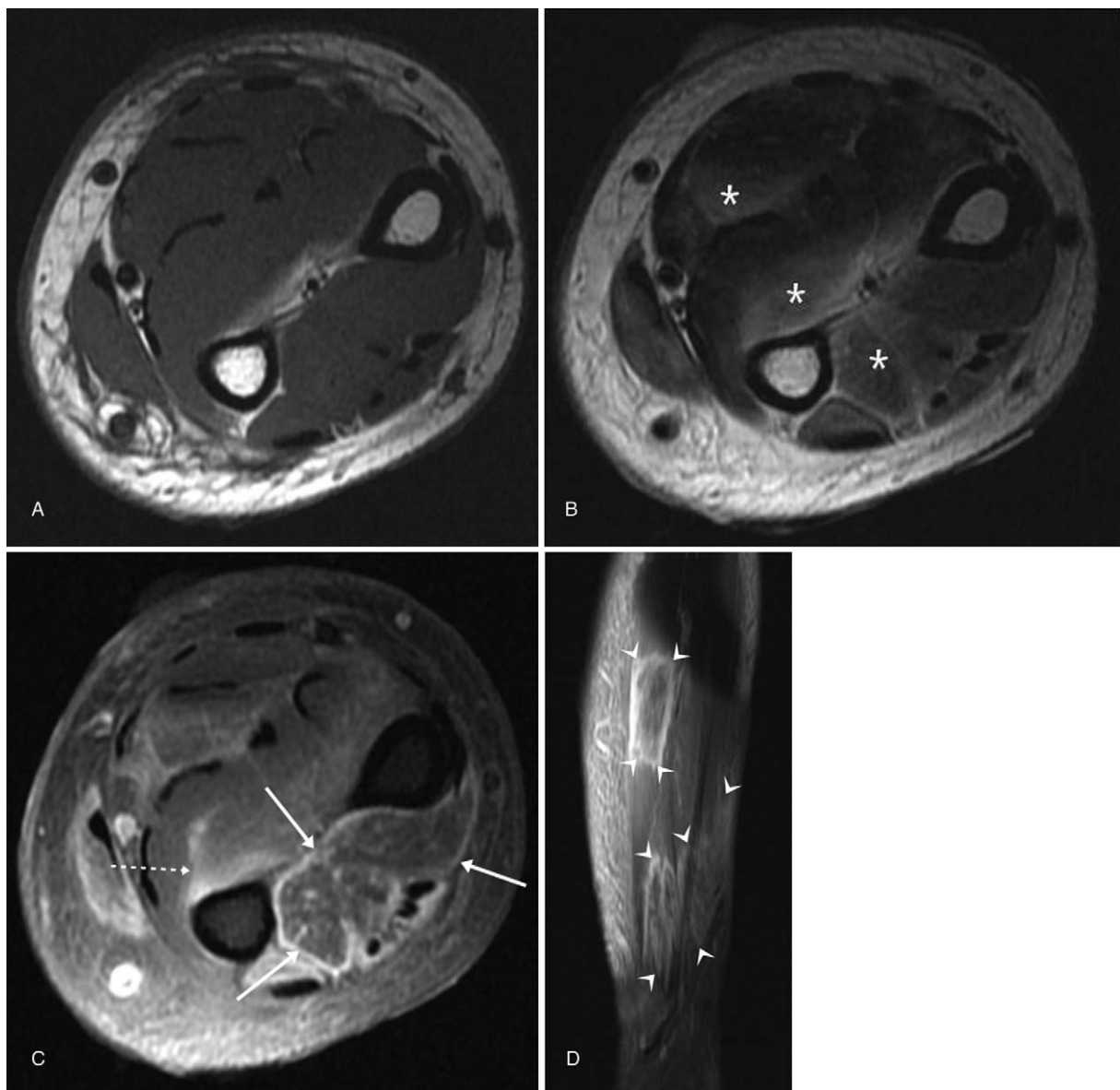
\* One patient without peripheral neuropathy showed no particular abnormal findings on magnetic resonance imaging, so the margin and shape and multiplicity were analyzed for 22 patients.

#### 4. Discussion

In the present study, we found that common MRI findings in rhabdomyolysis include intramuscular hemorrhage, stippled enhancement, a well-defined rectangular shape with a ragged margin in the longitudinal plane, and multiplicity, and that multiplicity within a compartment may be a predictor of the development of peripheral neuropathy.

Rhabdomyolysis literally means striated muscle dissolution or disintegration.<sup>[10]</sup> The dissolved sarcolemma leads to muscle necrosis with the release of toxic muscle cell components into the circulation.<sup>[4]</sup> Locally, the released products result in microvascular damage, capillary leakage and increased intracompartmental pressure, reduced tissue perfusion, and ischemia.<sup>[4]</sup> Our study reveals several MRI findings that may reflect the pathophysiological changes occurring in rhabdomyolysis, such as intramuscular hemorrhage, diffuse muscle edema, and variable enhancement of the affected muscle.



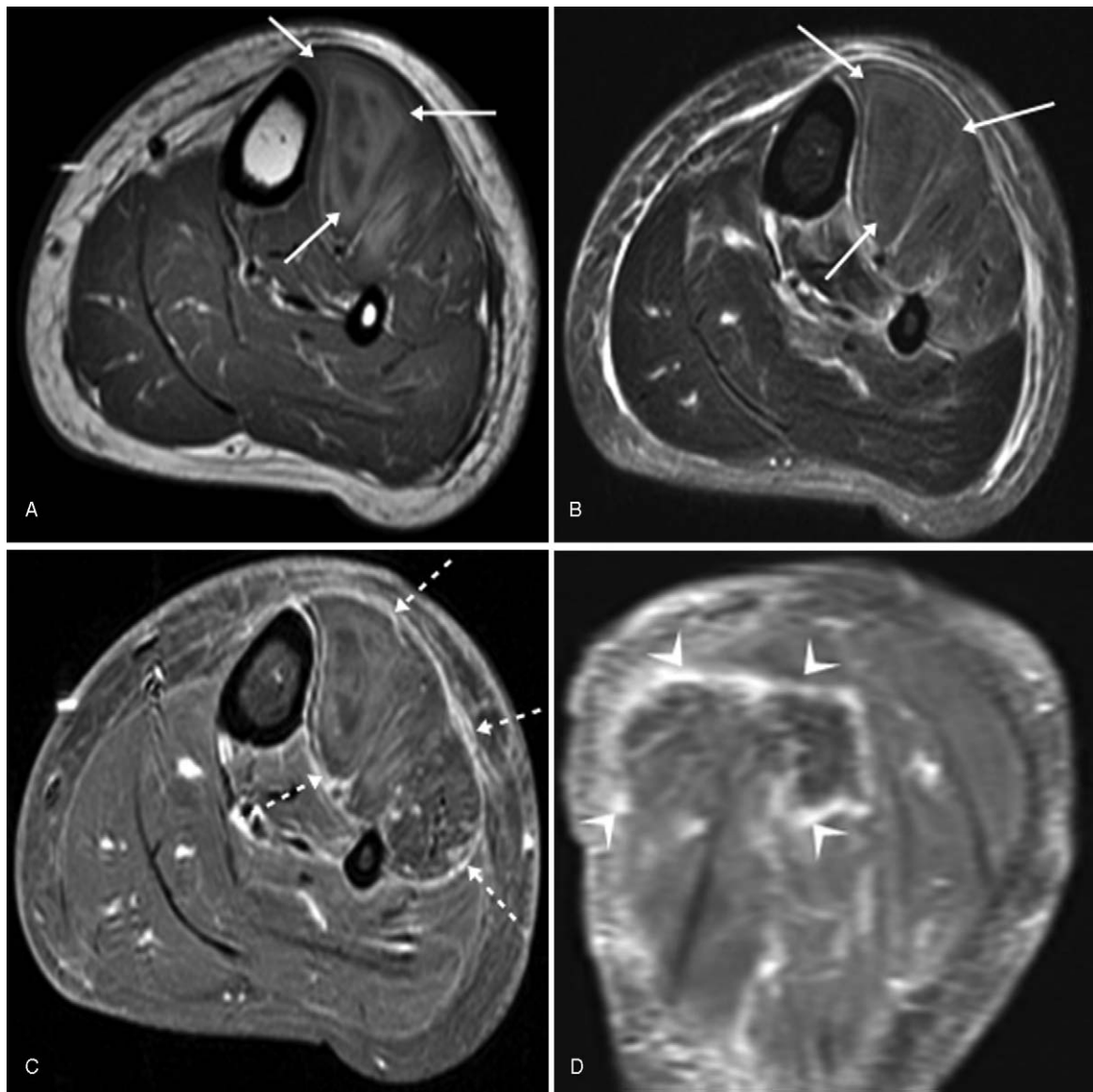


**Figure 4.** Axial T1-weighted (A), T2-weighted (B), contrast-enhanced, fat-suppressed T1-weighted (C), sagittal contrast-enhanced, fat-suppressed T1-weighted (D) images for a 41-year-old man with rhabdomyolysis due to drug intoxication. On a T1-weighted image (A), all the muscles show iso-signal intensity relative to the adjacent normal muscle (A). On a T2-weighted image (B), the affected areas of the muscles show homogeneous high signal intensity (asterisks). A contrast-enhanced, fat-suppressed T1-weighted image (C) shows peripheral enhancement with a central dot-like or linear streaky enhancement (so-called stippled enhancement) (arrows) of the muscles in the dorsal compartment, whereas some muscles in the deep volar compartment show diffuse increased enhancement (dashed arrows). On a sagittal contrast-enhanced, fat-suppressed T1-weighted image (D), the lesions show a well-defined rectangular shape with a ragged margin (arrowheads).

The muscles of rhabdomyolysis-affected individuals showed either homogeneous iso-signal intensity or heterogeneous iso-signal and high signal intensities on T1-weighted images. The high signal intensity on T1WI was probably caused by the presence of methemoglobin after hemorrhage, proteinaceous material, or fat.<sup>[8]</sup> On T2WI, the affected muscles showed diffuse high signal intensity or heterogeneous high signal, iso-signal, and low signal intensities in most patients. The high signal intensity on T2-weighted images may represent diffuse edema, whereas the iso-signal and low signal intensities may be caused by hemosiderin formed in association with intramuscular hemorrhage or muscle necrosis.<sup>[4]</sup> Half of our patients were considered to have intramuscular hemorrhage. These results are consistent

with the findings of previous studies reporting pathophysiological changes in rhabdomyolysis.<sup>[4,8]</sup>

With regard to enhancement, prior studies reported 2 distinct enhancement patterns, namely homogeneous enhancement and stippled enhancement. The former represents diffuse edema in the affected muscles in the initial stage of rhabdomyolysis, while the latter has been considered a characteristic finding of muscle necrosis.<sup>[8]</sup> Stippled enhancement may represent either viable muscle fibers or inflammatory cells separating the nonenhancing necrotic muscle fibers.<sup>[6,8]</sup> These 2 types of enhancement were also visualized well in the present study. We additionally found another enhancement pattern, that is, central nonenhancement with peripheral enhancement in the affected muscles. The pattern



**Figure 5.** Axial T1-weighted (A), fat-suppressed T2-weighted (B), axial contrast-enhanced fat-suppressed T1-weighted (C), coronal contrast-enhanced fat-suppressed T1-weighted (D) images for a 46-year-old woman with rhabdomyolysis in the left lower leg due to drug intoxication. Heterogeneous signal intensity in the anterior compartment of the lower leg, with increased muscle volume, can be seen on T1-weighted (A) and fat-suppressed T2-weighted (B) images. The area showing high signal intensity on the T1-weighted and fat-suppressed T2-weighted (arrows) images is interpreted to be intramuscular hemorrhage. On an axial contrast-enhanced, fat-suppressed T1-weighted image (C), peripheral enhancement with a central non-enhancing portion can be seen (dashed arrows). On a coronal contrast-enhanced, fat-suppressed T1-weighted image (D), the lesion shows a well-defined rectangular shape with a ragged margin (arrowheads).

of a central nonenhancing portion with peripheral enhancement may reflect an irreversible severe degree of myonecrosis in the central portion and an inflammatory and reparative response in the peripheral portion.<sup>[6]</sup>

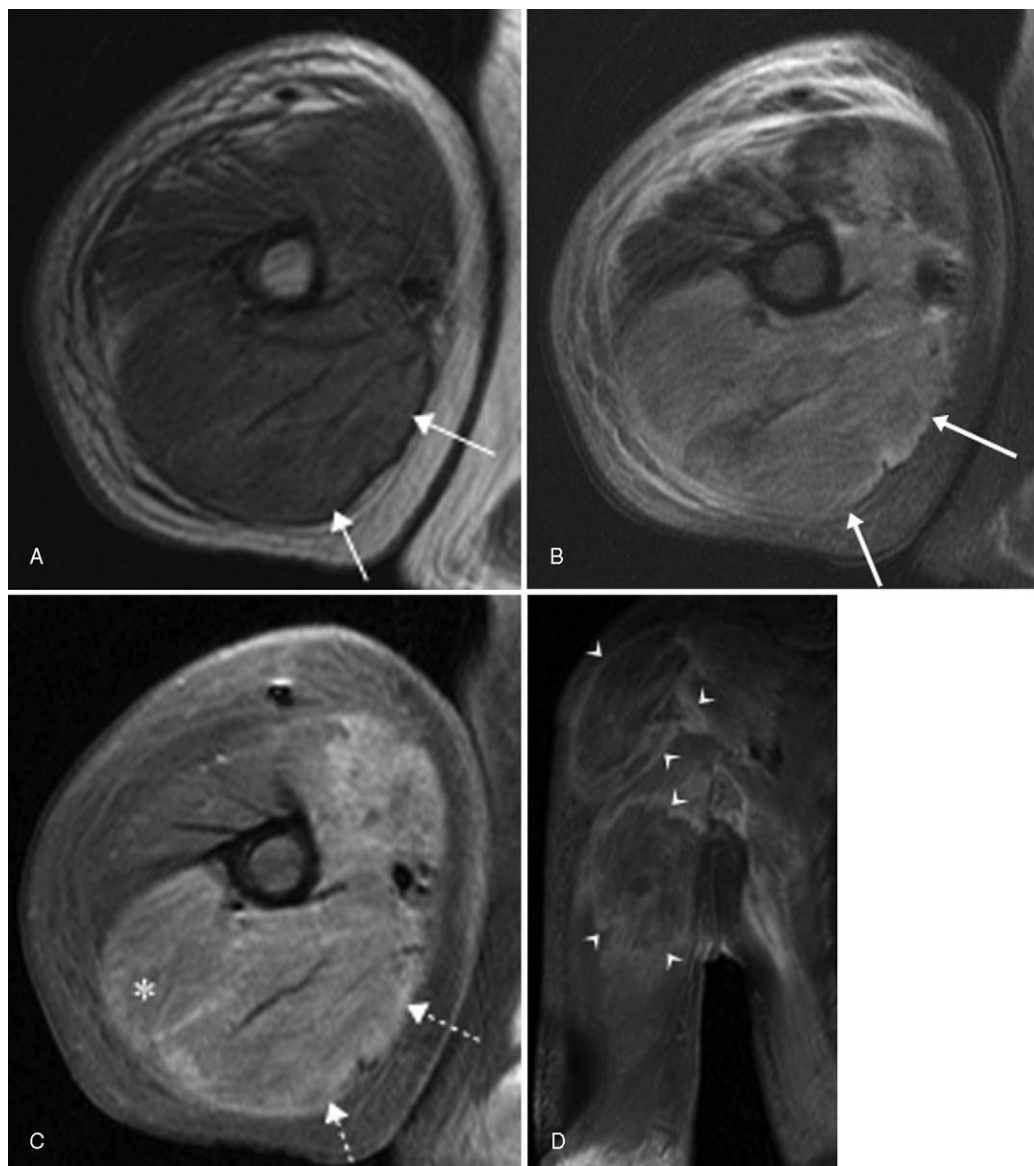
In the present study, the affected area usually showed a well-defined rectangular shape with a ragged margin on postcontrast T1-weighted sagittal or coronal images. The rectangular and ragged margin of the affected area may reflect the longitudinally oriented muscle fibers. Kattapuram et al<sup>[6]</sup> reported that the muscle fiber pattern in areas of myonecrosis was maintained by persistent necrotic myocytes. The nonviable muscle cells lost their nuclei and, occasionally, striations, whereas they frequently retained their structural architecture.<sup>[6]</sup> Therefore, the rectangular shape of the affected area observed in the present study was

probably related to the retained muscle fiber pattern,<sup>[6]</sup> while the ragged margin was probably caused by the interposed necrotic myocytes at the border between ischemic and normal muscle. In our opinion, this is a very important feature for distinguishing rhabdomyolysis from other pathologies such as necrotic tumors and abscess pockets of pyomyositis, which usually destroy or displace normal muscle fibers.

Other imaging findings such as increased muscle volume and edema in the adjacent deep fascia and subcutaneous layer also corresponded with the findings in prior studies.<sup>[4–8]</sup>

Multiplicity, including multiple muscle involvement within a compartment and multiple compartment involvement within a limb, was frequent. Bilateral involvement was also common, corresponding with the findings in prior studies.<sup>[4,8]</sup> Because





**Figure 6.** Axial T1-weighted (A), fat-suppressed T2-weighted (B), contrast-enhanced, fat-suppressed T1-weighted (C), coronal contrast-enhanced, fat-suppressed T1-weighted (D) images for a 43-year-old man with rhabdomyolysis caused by excessive exercise. Heterogeneous signal intensity in the posterior compartment and medial portion of the anterior compartment in the upper arm, with increased muscle volume (arrows), can be seen on T1-weighted (A) and fat-suppressed T2-weighted (B) images. Note the edema in the subcutaneous layer. On a contrast-enhanced, fat-suppressed T1-weighted image (C), diffuse enhancement is noted in not only the area with heterogeneous high signal intensity (dashed arrows) but also the area with iso-signal intensity on a precontrast T1-weighted image (\*). On a coronal contrast-enhanced, fat-suppressed T1-weighted image (D), the lesions show a well-defined rectangular shape with a ragged margin (arrowheads).

multiplicity and bilateral limb involvement are rare in cases of infection and primary tumors, they can be used as distinguishing features of rhabdomyolysis.<sup>[4]</sup>

Most of the clinical findings in rhabdomyolysis are related to its complications, such as metabolic acidosis, hypovolemia, and myoglobinuric renal failure.<sup>[10]</sup> When treated early and aggressively, rhabdomyolysis has an excellent prognosis, and most of these complications are reversible.<sup>[10]</sup> In contrast, peripheral neuropathy, although rare, is a significant irreversible complication<sup>[2,3]</sup> due to compression by the severe muscle edema, particularly in the setting of compartment syndrome.<sup>[2,3]</sup> In the present study, only 2 patients with peripheral neuropathy were diagnosed with compartment syndrome. In our opinion, not only compartment syndrome but also extensive ischemia may play an

important role in the development of peripheral neuropathy in patients with rhabdomyolysis. The patients with rhabdomyolysis and peripheral neuropathy in our study tended to show a greater degree of myonecrosis in the major enhancement pattern, with multiple muscle and compartment involvement reflecting the important role of the degree and extent of ischemia. Multiple muscle involvement within a compartment showed a statistically significant association with the development of peripheral neuropathy; this suggests that direct compression of edematous muscles within a compartment can also cause nerve injury. Recently, several studies reported that diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) can help in the detection of muscle ischemia and differentiation between healthy and injured nerves.<sup>[11,12]</sup> Although we did not perform

DWI and DTI in the present study, further studies should use these advanced techniques for evaluation of the predictors of peripheral neuropathy in patients with rhabdomyolysis.<sup>[11,12]</sup>

The major limitation of this study was its retrospective design. Second, the sample size was small, which could be a reason for the lack of statistically significant associations between several MRI findings and peripheral neuropathy development. Although we gathered patients diagnosed with rhabdomyolysis over a long period of time, the sample size was small because of the rarity of the disease. However, to our knowledge, the present study is the largest one evaluating the MRI findings in rhabdomyolysis. Third, there were variable gaps (several hours–20 days) between the time of symptom onset and MRI, which may have influenced the imaging findings. Fourth, we tried to include patients with all disease severities, but there is a possibility that we missed patients in the early stage, which is represented by mild symptoms that do not require imaging studies. Although peripheral neuropathy is considered a rare occurrence in patients with rhabdomyolysis, 50% of our patients exhibited this condition. Therefore, our study tended to enroll more severe, complicated cases. Fifth, we did not perform histopathological analysis for confirmation of muscle necrosis in all patients except one. Sixth, we did not perform advanced MRI techniques such as DWI and DTI for the detection of muscle and nerve abnormalities. Finally, we did not compare the imaging findings in rhabdomyolysis with those in other musculoskeletal diseases with limb swelling that can clinically mimic rhabdomyolysis.

Despite these limitations, our study may have useful clinical implications. As we mentioned earlier, rhabdomyolysis cannot be clinically diagnosed in a quarter of patients because the serum CK level peaks rather early and rapidly decreases after injury.<sup>[10]</sup> If a patient is not immediately admitted, recognition and evaluation of rhabdomyolysis may become difficult. In this situation, radiological diagnosis seems to be important. The imaging findings in rhabdomyolysis recorded in the present study may help in the prompt recognition of rhabdomyolysis, differentiation from other musculoskeletal diseases, and prevention of serious complication such as peripheral neuropathy.

In conclusion, the findings of the present study suggest that common MRI findings in rhabdomyolysis include intramuscular hemorrhage, stippled enhancement, a well-defined rectangular shape with a ragged margin in the longitudinal plane, and multiplicity. Moreover, multiplicity within a compartment may be a predictor of the development of peripheral neuropathy in these patients.

## Author contributions

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## References

- [1] Thomas MA, Ibels LS. Rhabdomyolysis and acute renal failure. *Aust N Z J Med* 1985;15:623–8.
- [2] McDonald S, Bearcroft P. Compartment syndromes. *Semin MusculoskeletRadiol* 2010;14:236–44.
- [3] Kim JY, Lee JW, Cha SO, et al. Compressive radial neuropathy developed under a fibrotic band associated with rhabdomyolysis and successfully treated with surgery. *Ann Rehabil Med* 2014;38:421–6.
- [4] Moratalla MB, Braun P, Fornas GM. Importance of MRI in the diagnosis and treatment of rhabdomyolysis. *Eur J Radiol* 2008;65:311–5.
- [5] Delaney-Sathy LO, Fessell DP, Jacobson JA, et al. Sonography of diabetic muscle infarction with MR imaging, CT, and pathologic correlation. *AJR Am J Roentgenol* 2000;174:165–9.
- [6] Kattapuram TM, Suri R, Rosol MS, et al. Idiopathic and diabetic skeletal muscle necrosis: evaluation by magnetic resonance imaging. *Skeletal Radiol* 2005;34:203–9.
- [7] Lamminen AE, Hekali PE, Tiula E, et al. Acute rhabdomyolysis: evaluation with magnetic resonance imaging compared with computed tomography and ultrasonography. *Br J Radiol* 1989;62:326–30.
- [8] Lu CH, Tsang YM, Yu CW, et al. Rhabdomyolysis: magnetic resonance imaging and computed tomography findings. *J Comput Assist Tomogr* 2007;31:368–74.
- [9] Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74.
- [10] Khan FY. Rhabdomyolysis: a review of the literature. *Neth J Med* 2009;67:272–83.
- [11] Zhang H, Wang X, Guan M, et al. Skeletal muscle evaluation by MRI in a rabbit model of acute ischaemia. *Br J Radiol* 2013;86:20120042.
- [12] Razek AAKA, Shabana AAE, El Saied TO, et al. Diffusion tensor imaging of mild-moderate carpal tunnel syndrome: correlation with nerve conduction study and clinical tests. *Clin Rheumatol* 2017;36:2319–24.