European Journal of Radiology 129 (2020) 109044

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

MRI of complex regional pain syndrome in the foot

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ARTICLE INFO

Keywords:
Magnetic resonance imaging
Complex regional pain syndrome
Foot

ABSTRACT

Purpose: To evaluate the diagnostic potential of MRI in patients with suspected CRPS (complex regional pain syndrome).

Method: A retrospective health-record search was conducted for patients with suspected CRPS (foot). Fifty patients with initially suspected CRPS were included (37 females (51 ± 13 years) and 13 males (44 ± 15 years)). All patients underwent MRI. Two radiologists assessed skin, bone, and soft tissue parameters on MRI. The final diagnosis was CRPS (Gold standard: Budapest criteria) or non-CRPS. MRI parameters were compared between CRPS patients and non-CRPS patients.

Results: CRPS was diagnosed in 22/50(44 %) patients. Skin thickness (1.9 ± 0.5 mm vs. 1.7 ± 0.3 mm, p = 0.399), enhancement, and subcutaneous edema showed no differences between CRPS and non-CRPS patients. Bone marrow edema presence and pattern were not different between groups. Up to 50 % of CRPS patients showed no bone marrow edema. Subcortical enhancement and periosteal enhancement were not different between groups. For reader 1, muscle edema score was higher in the non-CRPS group compared to the CRPS group (0.1 ± 0.2 vs. 0.6 ± 1.0, p = 0.008), but not different for reader 2 (0.1 ± 0.5 vs. 0.2 ± 0.8, p = 0.819). Perfusion pattern was more extensive in non-CRPS patients for reader 1 (p = 0.048), but not for reader 2 (p = 0.157). Joint effusions showed no difference between groups.

Conclusions: MRI cannot distinguish between CRPS and non-CRPS patients. The role of MR imaging in patients with suspected CRPS is to exclude alternative diagnoses that would better explain patients' symptoms.

1. Introduction

Complex regional pain syndrome (CRPS) is a chronic pain syndrome with substantial morbidity [1]. Typically, CRPS may develop in hand or foot after an initiating event such as trauma or surgery (without nerve damage = CRPS type I, with nerve damage = CRPS type II). CRPS type I (referred to only as CRPS for the rest of the text) is known in the older literature as reflex sympathetic dystrophy. Patients with CRPS present with hyperalgesia, color changes to the skin, altered skin temperature, sweating, increased hair growth, and edema of the affected limb. The estimated incidence is ranging between 4–8 % after trauma or surgery [2–4]. The multifactorial etiology of CRPS is still not fully understood, and a variety of potential mechanisms have been discussed in the literature, including aberrant inflammation, vasomotor dysfunction, and maladaptive neuroplasticity [5]. CRPS is a clinical diagnosis and is based on the modified Budapest criteria, which were implemented in 2012 by the International Association of the Study of Pain [6]. By definition, the experienced pain is disproportional to the initial event and its healing stage, and there is no alternative explanation for the symptoms such as insufficiency fractures. Also, patients must fulfill some specific criteria from a list of categories, both subjective and objective, in order to be diagnosed with CRPS (see Methods).

To date, imaging is not part of the diagnostic criteria. Early studies in the 1990s and early 2000s highlighted the potential value of MRI in the diagnosis of CRPS. As time went on, the literature became less in favor of MRI. In 2012, in a meta-analysis, triple-phase bone scintigraphy was favored over MRI for ruling out CRPS, based on higher sensitivity and specificity [7]. Since the diagnostic criteria for CRPS changed in 2012 and MR imaging quality and protocols continued to improve, we opted to revisit the diagnostic potential of MR imaging in

Abbreviations: CRPS, Complex regional pain syndrome

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https://doi.org/10.1016/j.ejrad.2020.109044
Received 16 January 2020; Received in revised form 24 February 2020; Accepted 29 April 2020

the diagnosis of CRPS. Hence, the purpose of our study was to apply a set of MR imaging criteria to patients with suspected CRPS. We hypothesized that MR imaging allows differentiating between patients with CRPS and patients without CRPS, using the clinical Budapest criteria as the reference standard.

2. Material and methods

2.1. Patients

This study was approved by the local ethics committee. We retrospectively searched our medical records for all patients that were referred to the specialized CRPS clinic in our university hospital between May 2014 and December 2017 with suspected CPRS of the foot, as this has been the most frequent location of CRPS at our institution. Written informed consent was available for all patients. We adopted the final diagnosis of patients based on medical records. We excluded patients with ambiguous or unclear diagnoses at the last available follow-up visit. The same expert physician with extensive experience in CRPS made the diagnosis of CRPS or ruled it out in all patients.

2.2. Clinical data

We noted the dates and categories (contusion, surgery, fracture, distortion) of suspected CRPS initiating events in all patients. The duration of symptoms (first symptoms until MR scan) was calculated. The diagnosis of CRPS based on the modified Budapest criteria by the International Association for the Study of Pain [6]: In addition to disproportional pain to the initial event and lack of an alternative diagnosis, the following criteria applied: There are four categories in which patients must report a minimum of one symptom in at least three categories, and at least one objective clinical sign must be present in at least two categories at the time of clinical evaluation: i) sensory: hyperalgesia, allodynia; ii) vasomotor: temperature asymmetry, skin color changes, color asymmetry; iii) sudomotor/edema: edema, asymmetric sweating, sweating changes; iv) motor/trophic: reduced range of motion, weakness, tremor, dystonia, trophic changes (hair, nails, skin) [6].

We calculated a CRPS severity score in CRPS patients using the binary variables (present or not present) in two different categories (subjective symptoms and objective signs). Each variable counted as 1 point, and the total score was calculated (0–17). In patients without CRPS diagnosis, the alternative diagnosis was noted. The above score was not calculated for non-CRPS patients.

2.3. MR imaging

All patients with suspected CRPS had MRI of the affected foot during diagnostic work-up. We used the same MR protocol in all patients. Thirty-five patients were examined on a 1.5-T MR scanner (Avanto, Siemens Healthineers, Erlangen, Germany) and 15 patients on a 3.0-T MR scanner (Skyra, Siemens Healthineers, Erlangen, Germany). The MR parameters are shown in Table 1. The set of imaging criteria was gathered based on conventional teaching and literature if available (see discussion). A MR scoring system was self-developed for these parameters. Two musculoskeletal fellows (initials blinded for review) assessed the anonymized MR images in a randomized order (random number generator, Excel 2010, Microsoft), blinded to the clinical information. The foot was divided into six subregions, as shown in Fig. 1.

The following MR imaging features were assessed:

2.3.1. Skin features

2.3.1.1. Maximum skin thickness. The readers measured the skin thickness (in mm) at the thickest location in any subregion on any sequences and noted the anatomic location.

2.3.1.2. Skin enhancement. Skin enhancement was assessed regarding the presence and extent in all six subregions separately on either the sagittal T1-weighted fat-saturated gadolinium-enhanced images of the whole foot or the transverse T1-weighted fat-saturated gadolinium-enhanced images of the forefoot. Fat saturation artifacts and equivocal signal changes were considered no enhancement. A skin enhancement score was calculated (no enhancement = 0 points, mild enhancement = 1 point, moderate enhancement = 2 points, severe enhancement = 3 points) and summing all score together (range 0–18 points).

2.3.1.3. Subcutaneous edema. All six subregions were assessed regarding the presence and extent of subcutaneous edema (no edema, mild edema, moderate edema, severe edema) based on the readers' impression. A subcutaneous edema score was calculated (no edema = 0 points, mild edema = 1 point, moderate edema = 2 points, severe edema = 3 points) and summing all score together (range 0–18 points).

2.3.2. Bone features

2.3.2.1. Number of bones with bone marrow edema. Both readers counted the number of single bones presenting with bone marrow edema on the sagittal Turbo-Inversion-Recovery-Magnitude (TIRM) images of the foot. The sesamoids of the greater toe were not counted.

2.3.2.2. Bone marrow edema pattern. On sagittal TIRM images, both readers provided a judgment of the overall bone marrow edema pattern, choosing from the following options: no bone marrow edema, primarily subcortical or patchy bone marrow edema, larger focal areas of bone marrow edema (defined as > 10 mm), or diffuse, extensive bone marrow edema.

2.3.2.3. Subcortical enhancement. Subcortical enhancement was assessed on the sagittal T1-weighted fat-saturated images and the transverse T1-weighted fat-saturated images in three regions (forefoot (toes up to the metatarsophalangeal joint line), midfoot (metatarsal bones up to the Chopart joint line, and hindfoot (calcaneus, talus, tibia, fibula). Each subregion was attributed 1 point, and a total subcortical enhancement score was calculated (range 0–3).

2.3.2.4. Periosteal enhancement. Using the T1-weighted fat-saturated contrast-enhanced images (sagittal and transverse), both readers noted the presence or absence of periosteal enhancement. If present, the readers provided the exact location using a free text box.

2.3.3. Soft tissue features

2.3.3.1. Muscle edema. The muscles were divided into four groups: intrinsic and plantar muscle in the forefoot, M. quadratus plantae, M. flexor digitorum brevis, and M. abductor digiti minimi. The presence or absence of muscle edema was noted on the sagittal TIRM images, cross-referencing the specific muscle with the available coronal sequences. We calculated a total score, adding 1 point for each muscle with edema (range 0–4).

2.3.3.2. Perfusion pattern. Each reader rated soft tissue enhancement on the dynamic MR angiography series using one of the following subjective descriptions: no enhancement, mild enhancement, moderate enhancement, and severe enhancement.

2.3.3.3. Joint effusion. The following joint groups or joints were assessed for the presence or absence of joint effusion, defined as the subjective impression of too much fluid in that joint capsule: metatarsal joints (as one group), lisfranc joints (one group), naviculocuneiform joint line, talonavicular joint, calcaneocuboid joint, tibiotalar joint, subtalar joint. A total score was calculated for each patient, with 1 point for each joint or joint group with joint effusion (range 0–7).

Table 1
(A) MRI protocol 1.5-T. (B) MRI protocol 3.0-T.

MR Parameter	TIRM whole foot	Sag T1 whole foot	T1 forefoot	T2 ankle	Dynamic Angiography	T1 + Gd whole foot	Tra T1 + Gd forefoot
(A)							
Orientation	Sagittal	Sagittal	Transverse	Coronal	Sagittal	Sagittal	Transverse
TR (ms)	4000	475	461	4360	–	604	618
TE (ms)	30	12	13	96	–	12	13
Slice thickness (mm)	3	3	4	3	MIP	3	4
Matrix	448 × 448	640 × 640	512 × 512	512 × 512	256 × 256	448 × 364	512 × 512
FOV (mm)	280 × 280	280 × 280	160 × 160	160 × 160	250 × 250	227 × 280	160 × 160
Number of slices	27	27	26	26	5	27	26
Acquisition time (min:sec)	2:34	2:54	2:42	3:05	2:42	3:17	3:29
(B)							
Orientation	Sagittal	Sagittal	Transverse	Coronal	Sagittal	Sagittal	Transverse
TR (ms)	5040	464	759	4760	–	600	600
TE (ms)	40	9.8	12	82	–	12	12
Slice thickness (mm)	3	3	3	3	MIP	3	2
Matrix	512 × 352	640 × 440	448 × 448	512 × 512	256 × 256	512 × 352	448 × 448
FOV (mm)	192 × 280	192 × 280	119 × 119	410 × 512	250 × 250	192 × 280	119 × 119
Number of slices	27	27	23	23	5	27	23
Acquisition time (min:sec)	3:18	1:55	2:14	2:10	3:03	3:57	3:33

TR = repetition time, TE = echo time, FOV = field of view, TIRM = Turbo-Inversion-Recovery-Magnitude, Gd = Gadolinium, MIP = Maximum intensity projection.

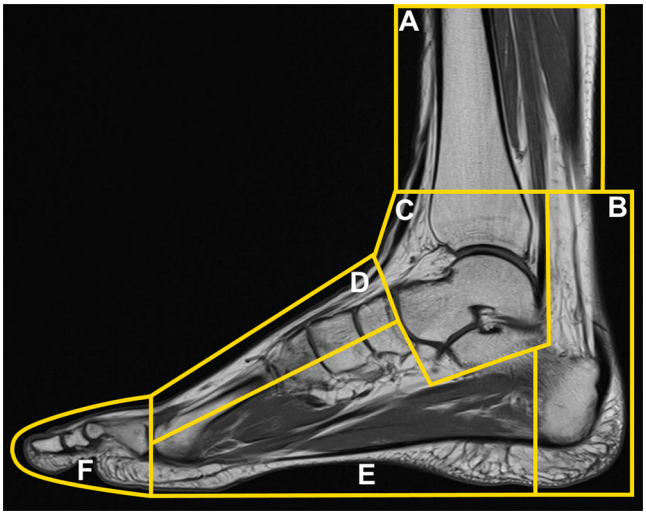

Fig. 1. Anatomic subregions for analysis: A = distal lower extremity, B = calcaneus, C = ankle, D = dorsum of the foot, E = plantar region of the foot, F = forefoot.

2.4. Statistics

We compared patient demographics between CRPS patients and non-CRPS patients. We compared all skin features, bone features and soft tissue features between CRPS patients and non-CRPS patients using chi-square tests (or Fisher's exact test where appropriate) on categorical data and Mann-Whitney *U* test to compare continues data, including the scores. Next, we checked for imaging feature differences between acute CRPS (symptoms < 3 months) and chronic CRPS (symptoms ≥ three months). Finally, interreader agreement was calculated using kappa statistics or intraclass correlation coefficients (ICC) where appropriate. Agreement for Kappa and ICC values were interpreted as fair (0.21 − 0.40), moderate (0.41 − 0.60), substantial (0.61 − 0.80), and almost perfect (0.81–1.00). The level of statistical significance was defined as $P < 0.05$. We used IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY) for the analyses.

3. Results

3.1. Patients

In total, 50 patients were included (37 females (age < at the time of MRI 51 ± 13 years old (mean ± standard deviation (SD)) and 13 males (44 ± 15 years)). There were no unclear or ambiguous diagnosis, and therefore, no patients were excluded.

3.2. Clinical data

CRPS was diagnosed in 22/50 (44 %) patients and non-CRPS in 28/50 (56 %) patients. Five out of the 22 (22.7 %) CRPS patients presented with acute CRPS. The other 17/22 (77.3 %) patients suffered from chronic CRPS. Detailed clinical characteristics of CRPS patients are shown in Table 2.

In the non-CRPS groups, the final diagnosis groups were as follows: Postoperative pain n = 12/28 (42.9 %), posttraumatic n = 5/28 (17.9

Table 2
Clinical characteristics of CRPS patients (n = 22).

Category	Parameters	N(%)
Initiating event (%)	Bruise	1 (4.5)
	Sprain	7 (31.8)
	Fracture	3 (13.6)
	Surgery	11 (50.0)
Subjective Symptoms (%)	Allodynia, hyperalgesia, Hypoesthesia	19 (86.4)
	Edema	20 (90.9)
	Asymmetric sweating	12 (54.5)
	Discoloration	20 (90.9)
	Asymmetric temperature	19 (86.4)
	Trophic changes	9 (40.9)
	Motor changes	11 (50.0)
	Decreased ROM	21 (95.5)
Objective Signs (%)	Hyperpathia	16 (72.7)
	Allodynia	14 (63.6)
	Asymmetric temperature	14 (63.6)
	Discoloration	17 (77.3)
	Asymmetric sweating	7 (31.8)
	Edema	17 (81.8)
	Trophic changes	6 (27.3)
	Motor changes	6 (27.3)
	Decreased ROM	22 (100.0)
CSS (mean, ± SD, range)	10.8 ± 2.7, 6 − 15	

ROM = range of motion, CSS = CRPS severity score.

%), neuropathic pain syndrome n = 4/28 (14.3 %), bone marrow edema (stress reaction) n = 3/28 (10.7 %), osteoarthritis n = 2/28 (7.1 %), stress fracture n = 1/28 (3.6 %) and plantar fasciitis n = 1/28 (3.6 %).

3.3. MR imaging

3.3.1. Skin features

3.3.1.1. Maximal skin thickness. The mean maximum skin thickness in CRPS patients showed no difference compared to non-CRPS patients (1.9 ± 0.5 mm vs. 1.7 ± 0.3 mm, $P = 0.399$). We found no difference in maximum skin thickness between acute and chronic CRPS (1.7 ± 0.3 mm vs. 1.9 ± 0.6 mm, $P = 0.345$). In all groups, the maximum skin thickness was most often measured in the hindfoot plantar at the calcaneus (acute CRPS n = 3, chronic CRPS n = 14, non-CRPS n = 23). The other locations were dorsum of the midfoot (0/2/3), anterior of the ankle joint (1/1/1), and forefoot plantar 1/0/1), respectively ($P = 0.377$) by reader 1. The respective values for reader 2 were hindfoot plantar under the calcaneus (acute CRPS n = 2, chronic CRPS n = 12, non-CRPS n = 11), dorsum of midfoot (3/5/14), anterior of the ankle joint (0/0/1), and forefoot plantar (0/0/2) ($P = 0.417$)).

3.3.1.2. Skin enhancement. Skin enhancement scores were not different between CRPS patients and non-CRPS patients (Table 3). Comparing acute vs. chronic CRPS, reader 2 detected slightly more skin enhancement in the acute form of CRPS (1.0 ± 1.2 vs. 0.1 ± 0.5, $P = 0.009$). Reader 1 rated skin enhancement higher as well on average; however, this was not statistically significant (1.6 ± 1.8 vs. 0.5 ± 0.9, $P = 0.132$).

3.3.1.3. Subcutaneous edema. Subcutaneous edema showed no substantial difference between CRPS patients and non-CRPS patients (Table 3). Subcutaneous edema scores were slightly higher in the acute vs. chronic CRPS form, but only statistically significant for reader 2 (Table 3).

3.3.2. Bone features

3.3.2.1. Number of bones with edema. Bone marrow edema was a frequent feature in CRPS patients and non-CRPS patients (Table 4).

Table 3
MR imaging feature scores.

	CRPS		Non-CRPS	P value
	Acute	Chronic		
Reader 1				
Skin Enhancement	0.7 ± 1.2		0.9 ± 0.9	.339
	1.6 ± 1.8	0.5 ± 0.9		.132
Subcutaneous edema	5.1 ± 2.8		5.9 ± 3.1	.397
	7.2 ± 3.8	4.5 ± 2.3		.123
Subcortical score	1.0 ± 1.2		1.1 ± 1.1	.796
	1.4 ± 1.3	0.9 ± 1.2		.500
Muscle edema score	0.1 ± 0.2		0.6 ± 1.0	.008
	0	0.1 ± 0.2		.588
Joint effusion score	1.5 ± 1.6		2.1 ± 1.6	.203
	1.6 ± 2.1	1.5 ± 1.5		.903
Reader 2				
Skin Enhancement	0.3 ± 0.8		0.2 ± 0.5	.456
	1.0 ± 1.2	0.1 ± 0.5		.009
Subcutaneous edema	1.2 ± 1.7		1.9 ± 2.3	.247
	2.8 ± 2.6	0.7 ± 1.		.047
Subcortical score	1.0 ± 1.2		1.5 ± 1.1	.088
	1.2 ± 1.1	0.9 ± 1.2		.642
Muscle edema score	0.1 ± 0.5		0.2 ± 0.8	.819
	0	0.2 ± 0.5		.432
Joint effusion score	1.4 ± 1.8		1.0 ± 1.1	.781
	1.0 ± 1.0	1.5 ± 2.0		1.000

Table 4
Bone marrow edema.

	CRPS	No CRPS	P value
Reader 1			
Bones with BME (mean ± SD)	4.8 ± 6.2	4.8 ± 4.6	P = .571
No BME	10	6	P = .192
Primarily subcortical patchy BME	6	7	
Larger focal areas > 10 mm BME	4	7	
Diffuse, extensive BME in several bones	2	8	
Reader 2			
Bones with BME (mean ± SD)	3.8 ± 5.4	5.0 ± 4.8	P = .085
No BME	11	5	P = .020
Primarily subcortical patchy BME	10	19	
Larger focal areas > 10 mm BME	0	3	
Diffuse, extensive BME in several bones	0	1	

Note: BME = bone marrow edema, CRPS = complex regional pain syndrome, SD = standard deviation.

However, the number of affected bones was not substantially different between groups for both readers. For reader 1, 10/22 (45 %) of CRPS patients presented with no bone marrow edema (11/22 (50 %) for reader 2). Comparing acute vs. chronic CRPS, both readers found no statistically significant difference in the number of bones with bone marrow edema (7.4 ± 7.1 vs. 3.9 ± 5.9, $P = 0.543$ for reader 1 and 6.2 ± 6.6 vs. 3.0 ± 4.9, $P = 0.445$ for reader 2).

3.3.2.2. Bone marrow edema pattern. The bone marrow edema pattern is presented in Table 4. The pattern was not different between CRPS and non-CRPS patients for reader 1, while for reader 2, bone marrow edema was more pronounced in the non-CRPS group ($P = 0.020$, Table 4).

3.3.2.3. Subcortical enhancement. Subcortical contrast enhancement was not different between CRPS patients and non-CRPS patients for both readers (Table 3). Also, in acute vs. chronic CRPS, no difference in subcortical enhancement was detected (Table 3).

3.3.2.4. Periosteal enhancement. Periosteal contrast enhancement was uncommon in CRPS patients (3/22 (13.6 %)) for both readers and not statistically significantly different compared to the non-CRPS group ($P = 0.128$ and $P = 0.498$ for reader 1 and 2, respectively). In the non-CRPS group, periosteal enhancement was present in 9/28 (32.1 %) patients for reader 1 and 5/28 (17.9 %) patients for reader 2. No acute CRPS patient showed periosteal enhancement (both readers). Comparing acute vs. chronic CRPS patients, no relevant difference in periosteal enhancement was found (0/5 (0%) vs. 3/17 (17.6 %) $P = 0.442$, both readers.

3.3.3. Soft tissue features

3.3.3.1. Muscle edema. For reader 1, muscle edema score was higher in the non-CRPS group compared to the CRPS group (0.1 ± 0.2 vs. 0.6 ± 1.0, $P = 0.008$), but not different for reader 2 (0.1 ± 0.5 vs. 0.2 ± 0.8, $P = 0.819$). Also, there was no difference in muscle edema scores between acute and chronic CRPS (Table 3). None of the acute CRPS patients showed muscle edema (both readers), and it was rare in the chronic CRPS patients (n = 1 for reader 1, n = 2 for reader 2).

3.3.3.2. Perfusion pattern. The soft tissue enhancement pattern (Fig. 2) on the dynamic MR angiography images was not different between CRPS patients and non-CRPS patients for reader 2 ($P = 0.157$), while reader 1 rated stronger and more extensive enhancement in the non-CRPS group ($P = 0.048$, see Table 5). For both readers, there was no difference in perfusion patterns between acute and chronic CRPS ($P = 1.0$, both readers).

3.3.3.3. Joint effusion. Joint effusion patterns were not different

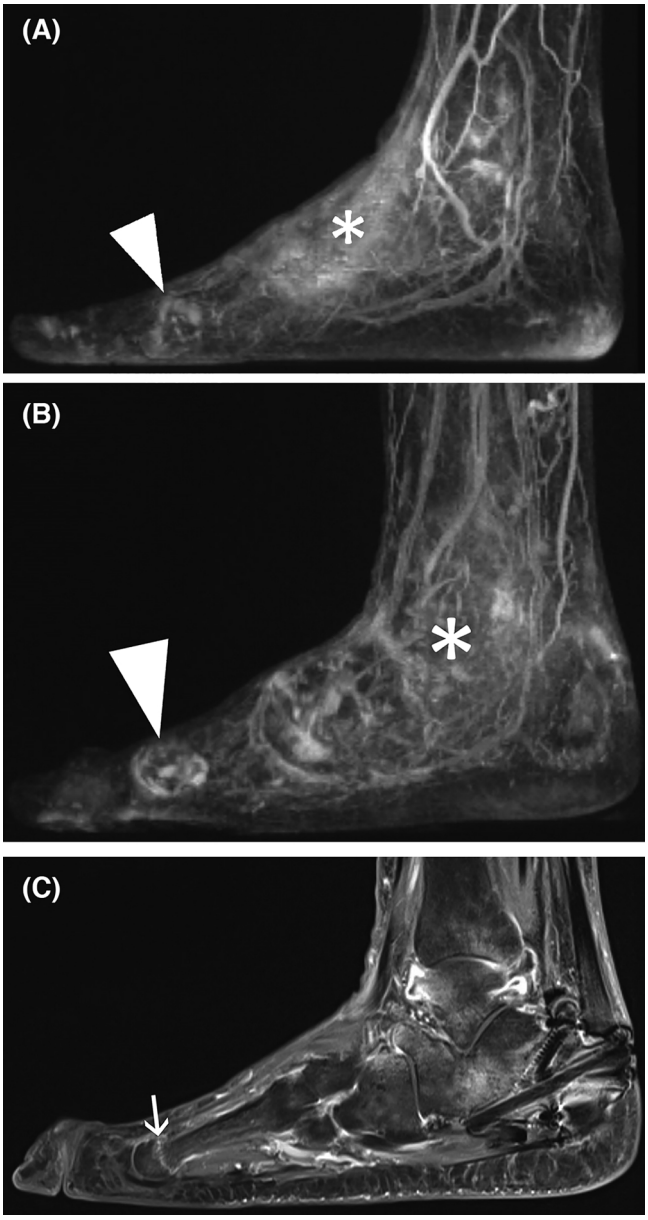

Fig. 2. A) 65-year-old woman with CRPS type 1 of her left foot after tibialis anterior tendon surgery 5 months prior to MRI. Maximum-intensity-Projection of dynamic MR angiography shows diffuse enhancement in the midfoot (*) around the operated tibialis anterior tendon and mild synovitis in the first metatarsophalangeal joint (arrowhead). B) 70-year-old woman without CRPS. Prolonged pain after open reduction and internal fixation of a calcaneus fracture 6 months before MRI. Maximum-intensity projection of the dynamic MR angiography series shows extensive synovitis of the first metatarsophalangeal joint (arrowhead) and synovitis and diffuse enhancement in the mid- and hindfoot (*). C) (Same patient as in B). Sagittal TIRM image shows insufficiency fracture of the third metatarsal neck (arrow) and extensive bone marrow edema in the hindfoot.

between CRPS patients and non-CRPS patients, nor between acute and chronic CRPS (Table 3).

Interreader agreement was substantial to almost perfect. For number of bones with bone marrow edema, the interreader agreement was almost perfect (ICC = 0.918 (95 %CI 0.851 − 0.954), $P < 0.001$). Kappa statistics for periosteal enhancement were perfect (k = 1.0, $P < 0.001$). ICC for the different scores were as follows: skin enhancement score ICC = 0.788 (95 %CI 0.626 − 0.879), $P < 0.001$, subcutaneous edema score ICC = 0.888 (95 %CI 0.803 − 0.937), $P < 0.001$, subcortical enhancement score ICC = 0.731 (95 %CI 0.526 − 0.847), $P < 0.001$, muscle edema score ICC = 0.606 (95 %CI 0.305 − 0.776), $P < 0.001$, and for joint effusion score ICC = 0.767 (95 %CI 0.589 − 0.868), $P < 0.001$.

Table 5
Perfusion Pattern.

	CRPS			No CRPS	P value
		Acute	Chronic		
Reader 1					
No	15	4	11	12	CRPS vs. non-CRPS P = 0.048[a]
Mild	5	1	4	7	
Moderate	0	0	0	7	
Severe	2	0	2	2	
Reader 2					
No	13	3	10	9	CRPS vs. non-CRPS P = 0.157[a]
Mild	7	2	5	16	
Moderate	2	0	2	2	
Severe	0	0	0	1	

[a] Contingency table fisher's exact test.

4. Discussion

No MR imaging feature that was able to differentiate between CRPS (complex regional pain syndrome) and non-CRPS patients. Neither skin parameters, bone parameters, nor soft tissue parameters showed substantial differences between groups. Interestingly, bone marrow edema was absent in up to 50 % of CRPS patients. We recognize that our non-CRPS group was heterogeneous with regards to their final diagnosis. CRPS may result from any trauma or surgery - sometimes even spontaneously without any known previous event (in around 7% of CRPS patients) [8]. When CRPS is clinically suspected, patients get referred to our specialized university clinic, and MRI is performed. Hence, a wide range of findings can be detected on MR imaging in such a setting. Of note, MRI also showed no difference between acute and chronic forms of CRPS, albeit their different clinical presentation. The reasoning behind MR imaging in suspected CRPS patients is to rule out an alternative explanation for the patients' symptoms (such as stress fracture, osteoarthritis, etc.). It is essential to realize that the diagnosis of CRPS cannot be made on MR images. Still, we occasionally get MRI requests explicitly asking for CRPS, potentially a consequence of outdated literature [9,10].

A strength of our study was the standardized MR protocol with advanced imaging sequences, including a dynamic MR angiography and gadolinium application in all patients. The use of the modified Budapest criteria was a plus because they are much stricter compared to the older criteria used up to 2012 on which many of the older studies relied upon. The substantial to almost perfect interreader agreement for the assessment of the MR imaging features showed that the chosen features were clearly defined and assessable by different radiologists.

The value of MR imaging in the assessment of CRPS changed over the last three decades. In 1991, MRI showed promising diagnostic potential in the diagnosis of CRPS in 20 patients [11]. In 1995, MRI was beneficial in demonstrating different soft-tissue changes in CRPS patients in a prospective study with 51 patients [9]. In 1996, a retrospective study with 22 patients "confirmed" MRI's value, especially in the warm phase of CRPS, while MRI was often considered normal in the cold phase of CRPS [12]. A report in 1998 suggested that joint effusions on MR imaging might be an early sign of CRPS [13]; the reason why we included this parameter in our study. In 1999, MRI was still considered good enough to detect the warm phase of CRPS, but it was suggested that MRI might be more helpful to exclude underlying pathology [10]. In 2003, it was described that absence of bone marrow edema did not rule out CRPS (as seen in our study as well) and that fractures were

found in one-third of patients (however, this would exclude CRPS based on the current criteria) [14].

In 2007, it was concluded that imaging (triple-bone scintigraphy and MRI) might not reliably distinguish between CRPS and post-operative changes [15]. Still, triple-phase bone scintigraphy is used and considered a diagnostic tool in the workup of CRPS in some institutions. In a meta-analysis in 2012, the pooled sensitivity and specificity of triple bone scintigraphy was 87 % and 69 %, respectively [16]. However, all these studies were not based on the modified Budapest criteria. In a recent systematic analysis and Bayesian meta-analysis when applying the Budapest criteria, the sensitivity of triple-phase bone scintigraphy decreased to 55 %, with an increased specificity of 94 % [17]. The authors of that study concluded that triple-bone scintigraphy does not add any value for the diagnosis of CRPS and also cannot confirm the diagnosis [17]. The text-book findings on triple-phase bone scintigraphy are typically hyperperfusion in the early phase scan and bone uptake on the late images. That is the reason why we hypothesized that we should be able to find even subtle changes in the bone with MRI. Hence, we assessed perfusion pattern, periosteal enhancement, subcortical enhancement, and bone marrow edema. However, none of our parameters showed any difference between CRPS patients and non-CRPS patients. Of note, many of our finale diagnoses in the non-CRPS groups potentially would have shown tracer uptake on bone scintigraphy as well (e.g., osteoarthritis, bone marrow edema, fractures).

Whether CRPS is a separate unique disease is debated [18,19]. Our findings are in line with this skepticism, as we did not find any CRPS-specific finding. To this day, CRPS remains a poorly understood and potentially overdiagnosed disease. Some argue that CRPS may just be a relatively new term given to a collection of symptoms that are ultimately shared by many common pathologies. However, there is some evidence, that CRPS I may be a small fiber neuropathy [20].

A limitation of our study was the heterogeneity in our CRPS group with only five acute CRPS patients, while the rest were patients with chronic CRPS. As a result, the comparison between acute and chronic is underpowered. The explanation for this difference is that we get these suspected CRPS patients referred to our clinic often only after a prolonged course at other institutions. No triple-phase bone scintigraphy scans were acquired in our patients. At our institution, bone scans are not available. The use of a marginal classification system (Budapest criteria) and only one clinician potentially introduced the risk of substantial bias. Another limitation is the self-developed MR scoring system. However, to develop a more refined and validated MR scoring system we should have at least an idea which imaging parameters to investigate and based on our results, there are currently none. Also, we did not correct for multiple comparisons, but with the current results would not make a difference.

5. Conclusion

MRI cannot distinguish between CRPS (complex regional pain syndrome) and non-CRPS. CRPS remains a clinical diagnosis. The role of MR imaging in patients with suspected CRPS is to exclude alternative diagnoses that would better explain patients' symptoms.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of Competing Interest

The authors have nothing to disclose.

CRediT authorship contribution statement

Christoph A. Agten: Conceptualization, Methodology, Project administration, Formal analysis, Writing - original draft. **Adrian Kobe:** Resources, Writing - review & editing. **Isabelle Barnaure:** Investigation, Writing - review & editing. **Julien Galley:** Investigation, Writing - review & editing. **Christian W. Pfirrmann:** Conceptualization, Resources, Writing - review & editing. **Florian Brunner:** Conceptualization, Resources, Writing - review & editing.

References

[1] S. Bruehl, Complex regional pain syndrome, BMJ (Clinical Research Ed.) 351 (2015) h2730.
[2] A. Beerthuizen, D.L. Stronks, A. Van't Spijker, A. Yaksh, B.M. Hanraets, J. Klein, F.J. Huygen, Demographic and medical parameters in the development of complex regional pain syndrome type 1 (CRPS1): prospective study on 596 patients with a fracture, Pain 153 (6) (2012) 1187–1192.
[3] G.L. Moseley, R.D. Herbert, T. Parsons, S. Lucas, J.J. Van Hilten, J. Marinus, Intense pain soon after wrist fracture strongly predicts who will develop complex regional pain syndrome: prospective cohort study, J. Pain 15 (1) (2014) 16–23.
[4] V.V. da Costa, S.B. de Oliveira, C. Fernandes Mdo, R.A. Saraiva, Incidence of regional pain syndrome after carpal tunnel release. Is there a correlation with the anesthetic technique? Rev. Bras. Anestesiol. 61 (4) (2011) 425–433.
[5] J. Marinus, G.L. Moseley, F. Birklein, R. Baron, C. Maihofner, W.S. Kingery, J.J. van Hilten, Clinical features and pathophysiology of complex regional pain syndrome, Lancet Neurol. 10 (7) (2011) 637–648.
[6] R.N. Harden, S. Bruehl, R.S. Perez, F. Birklein, J. Marinus, C. Maihofner, T. Lubenow, A. Buvanendran, S. Mackey, J. Graciosa, M. Mogilevski, C. Ramsden, M. Chont, J.J. Vatine, Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome, Pain 150 (2) (2010) 268–274.
[7] Z.J. Cappello, M.L. Kasdan, D.S. Louis, Meta-analysis of imaging techniques for the diagnosis of complex regional pain syndrome type I, J. Hand Surg. 37 (2) (2012) 288–296.
[8] A.M. de Rooij, R.S. Perez, F.J. Huygen, F. van Eijs, M. van Kleef, M.C. Bauer, J.J. van Hilten, J. Marinus, Spontaneous onset of complex regional pain syndrome, Eur. J. Pain (London, England) 14 (5) (2010) 510–513.
[9] M.E. Schweitzer, S. Mandel, R.J. Schwartzman, R.L. Knobler, A.J. Tahmoush, Reflex sympathetic dystrophy revisited: MR imaging findings before and after infusion of contrast material, Radiology 195 (1) (1995) 211–214.
[10] H. Darbois, B. Boyer, P. Dubayle, D. Lechevalier, H. David, A. Ait-Ameur, MRI symptomology in reflex sympathetic dystrophy of the foot, J. Radiol. 80 (8) (1999) 849–854.
[11] S. Schimmerl, H. Schurawitzki, H. Imhof, G. Canigiani, J. Kramer, V. Fialka, Sudeck's disease–MRT as a new diagnostic procedure, Rofo 154 (6) (1991) 601–604.
[12] D. Lechevalier, P. Dubayle, P. Crozes, J. Magnin, J.F. Gaillard, B. Boyer, C. Pharaboz, F. Eulry, Magnetic resonance imaging in the warm and cold forms of algodystrophy of the foot, J. Radiol. 77 (6) (1996) 411–417.
[13] M. Graif, M.E. Schweitzer, B. Marks, T. Matteucci, S. Mandel, Synovial effusion in reflex sympathetic dystrophy: an additional sign for diagnosis and staging, Skeletal Radiol. 27 (5) (1998) 262–265.
[14] F. Crozier, P. Champsaur, T. Pham, J.M. Bartoli, M. Kasbarian, C. Chagnaud, P. Lafforgue, Magnetic resonance imaging in reflex sympathetic dystrophy syndrome of the foot, Joint Bone Spine 70 (6) (2003) 503–508.
[15] M. Schurmann, J. Zaspel, P. Lohr, I. Wizgall, M. Tutic, N. Manthey, M. Steinborn, G. Gradl, Imaging in early posttraumatic complex regional pain syndrome: a comparison of diagnostic methods, Clin. J. Pain 23 (5) (2007) 449–457.
[16] R. Ringer, M. Wertli, L.M. Bachmann, F.M. Buck, F. Brunner, Concordance of qualitative bone scintigraphy results with presence of clinical complex regional pain syndrome 1: meta-analysis of test accuracy studies, Eur. J. Pain (London, England) 16 (10) (2012) 1347–1356.
[17] M.M. Wertli, F. Brunner, J. Steurer, U. Held, Usefulness of bone scintigraphy for the diagnosis of Complex Regional Pain Syndrome 1: a systematic review and Bayesian meta-analysis, PLoS One 12 (3) (2017) e0173688.
[18] A.T. Borchers, M.E. Gershwin, The clinical relevance of complex regional pain syndrome type I: the Emperor's New Clothes, Autoimmun. Rev. 16 (1) (2017) 22–33.
[19] C. Chang, P. McDonnell, M.E. Gershwin, Complex regional pain syndrome - false hopes and miscommunications, Autoimmun. Rev. 18 (3) (2019) 270–278.
[20] V.F. Rasmussen, P. Karlsson, P.D. Drummond, E.L. Schaldemose, A.J. Terkelsen, T.S. Jensen, L.F. Knudsen, Bilaterally reduced intraepidermal nerve fiber density in unilateral CRPS-I, Pain Med. (Malden, Mass.) 19 (10) (2018) 2021–2030.