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Radiological diagnosis of chronic recurrent multifocal osteomyelitis using whole-body MRI-based lesion distribution patterns

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AIM: To explore the distribution patterns and extent of chronic recurrent multifocal osteomyelitis (CRMO) using whole-body magnetic resonance imaging (WBMRI).

MATERIALS AND METHODS: Children with established diagnoses of CRMO, who had undergone WBMRI, had their images reviewed by three radiologists using a novel pictorial mapping system for determining lesion load and distribution patterns.

RESULTS: Thirty-seven children (mean 12 years; range 2–18 years) had 317 lesions (8.6 lesions per patient [LPP]; range 2–27). Multifocal involvement was noted in 33 (89%) and unifocal in four (11%). The tibia was most frequently involved (68% of patients; 29% of lesions). Clavicular involvement was noted in 38% and spinal lesions in 19% of patients. Bilateral disease involved the fibulas (80%), tibias (68%), and foot phalanges (67%) most frequently. In 93% of bilateral disease, there was also symmetry. A "tibio-appendicular multi-focal pattern" (tibial but no clavicular involvement) was present in 54% whereas a "claviculo-spinal pauci-focal pattern" (clavicular lesions, no tibial involvement; few additional lesions mainly of the spine) was present in 24%. Only 14% had synchronous involvement of the clavicle and tibia. In the long bones, 65% of lesions were metaphyseal (distal metaphysis 42%) and 35% epiphyseal (173 peri-physeal lesions). Epiphyseal lesions were minimal in 60% whereas metaphyseal lesions were extensive in 75%. Sixty-six percent of tibial symmetric lesions and 100% of symmetric lesions of the radius, humerus, and ulna were of equal severity.

CONCLUSION: CRMO lesions are often multifocal and can have typical long bone distal metaphyseal locations. Two main phenotypic patterns have emerged: multifocal predominantly tibial involvement or pauci-focal clavicular and spinal disease.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) or chronic non-bacterial osteomyelitis (CNO) is an auto-inflammatory disorder affecting the skeleton of children and adolescents.[1–4] CNO can affect all bones and is characterised by inflammatory lesions affecting metaphyses of long bones of the lower extremities, clavicles and spine with spontaneous remissions and exacerbations.[1,3–5] CRMO presents with multifocal bone lesions and a possibility for complications e.g. vertebral fractures.[2] Diagnosis is one of exclusion of other diseases; however, current practice suggests that bone biopsy can be held back in favour of whole-

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body imaging to determine multi-focality.[3,6] Whole-body magnetic resonance imaging (WBMRI) CRMO pattern identification would allow for a more confident imaging diagnosis and in future aid in prognosis and treatment decisions by predicting the likelihood of permanent deformity. The aim of the present study was to explore the number and distribution patterns of CRMO lesions using WBMRI.

Materials and methods

The patient database of all children (age <18 years) with a diagnosis of CRMO (using "Bristol criteria")[7] at one paediatric referral centre was interrogated. Cases were cross-matched with an MRI database to determine if WBMRI had been performed for inclusion. Patients with irretrievable and incomplete WBMRI were excluded. Initial WBMRI images were reviewed.

Studies underwent blinded (from the original WBMRI report) panel review with instructions to identify and characterise any CRMO lesions. The panel comprised a paediatric radiologist (20 years of experience), a musculoskeletal radiologist, and a specialist radiology trainee with orthopaedic experience. The panel members reviewed the images together and each reviewer had equal power to nominate any identified site. Lesions were recorded only when two or more members agreed to the presence of high signal intensity within the skeleton on short tau inversion recovery (STIR) imaging. Lesions were recorded on a pictorial pro-forma (Fig 1) so that distribution patterns would emerge on a collated anatomical map.

Lesions in long bones were recorded as diaphyseal, metaphyseal, or epiphyseal, and the extent of peri-physeal involvement was classified by measuring the involved width as a proportion of the width of the adjacent physis: minimal, less than one-third; more than minimal, one-third to two-thirds inclusive; extensive, over two-thirds. Clavicular lesions were recorded in thirds as lateral, middle, and medial. Spinal involvement was recorded as present or not and recorded as spondylitis with or without discitis, and by lesion according to location. When assessing symmetry, lesions within the sternum and vertebrae were not considered as they are midline structures. The tarsal bones, with the exception of the cuneiforms, were deemed too small for determining if involvement was symmetric or merely bilateral. The cuneiforms were considered as there are three sites of possible involvement and symmetry could be assessed.

Patients were scanned using a Siemens Aera 1.5T unit (Siemens, Erlangen, Germany) using a 20-channel head/neck coil, 32-channel spine coil, 1 or 2 18-channel body array coils (height dependent). The STIR sequence was used in the coronal plane in 5–7 sections depending on patient height with the following imaging parameters: 5,000 ms repetition time (TR); 54–75 ms echo time (TE); 160 ms inversion time (TI); 450×310 mm field of view (FOV); 20–40 sections of 5 mm thick with a 0.5 mm gap. Diffusion sequences were used in some patients (echo planar imaging [EPI] diffusion) scanning in the axial plane in 7–10 sections depending on height with the following parameters: head: 7,400 ms TR, 89 ms TE, b-values of 0 and 800, 230×230 mm FOV, 25 section of 4 mm thick with a 1.2 mm gap; rest of body: 5,320 ms TR, 64 ms TE, b-values of 0 and 800, 300×420 mm FOV, 40 sections of 4 mm thick with a 0.4 mm gap.

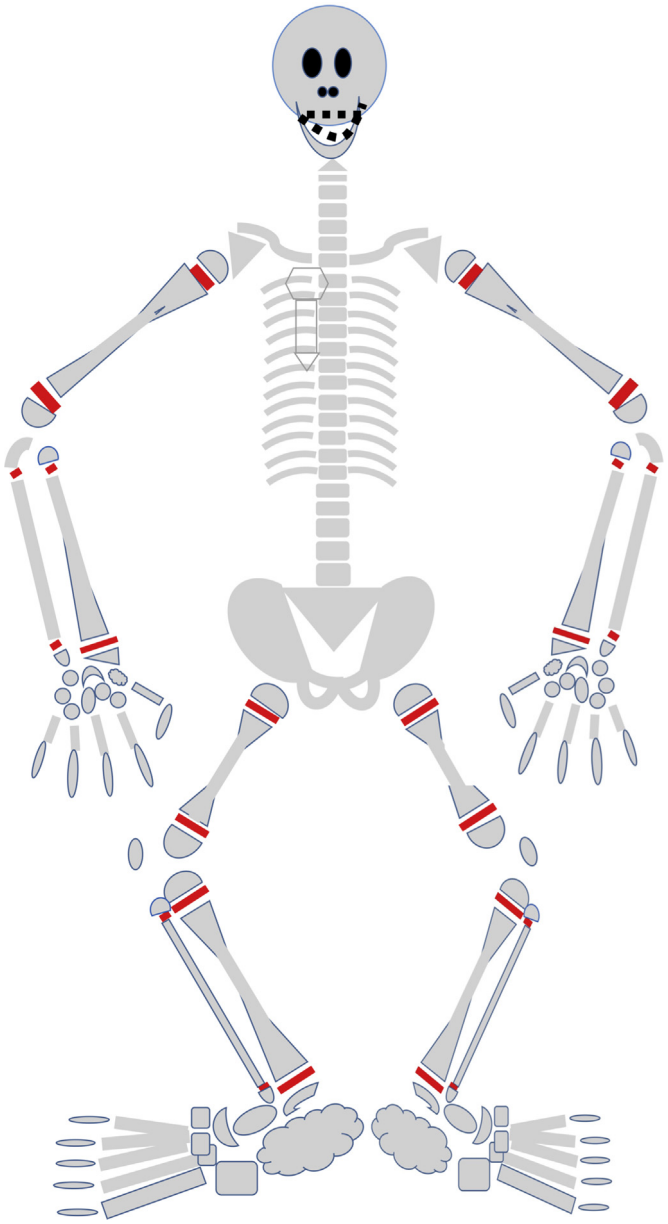

Figure 1 Pictorial pro-forma for reporting the distribution of CRMO lesions, with clear distinction of metaphyses and epiphyses of long bones to allow detailed recording of any periphyseal sites. The same pro-forma can also be used for follow-up WBMRI by indicating new (N) from existing (E) lesions, with arrow up or down for increase and decrease in size respectively, relating to persistent lesions.

The retrospective nature involving secondary review of available imaging data of this work did not mandate an ethics clearance as per current practice at this institution.

Results

From a database of 62 patients with a diagnosis of CRMO, 37 (60%; 26 female and 11 male patients; mean age 12 years, range 2–18 years) underwent WBMRI over a period of 6 years, which was available for evaluation (the remaining 25 patients had undergone only localised MRI and plain radiographs to support the clinical diagnosis). Three hundred and seventeen (317) lesions were identified in 20 different bones, with an average of 8.6 LPP (range 2–27 lesions).

There was multifocal involvement in 33 patients (89%) and unifocal disease in four (11%). The tibia was most frequently involved (68% of patients) with the greatest number of recorded lesions (29%). The femur (43% of patients) and the clavicle (38% of patients) were involved in over a third of patients. These also had the second and third highest lesion counts at 37 (14%) and 32 (10%), respectively. Frequency of involvement of each bone and lesion load per bone type, are summarised in Fig 2 and Table 1. Unifocal lesions involved the clavicle in two patients, the distal tibia in one patient, and the right distal femur in one patient. The latter two patients were diagnosed after biopsy. In the first of these, biopsy demonstrated chronic inflammation and in addition, there had been multifocal lesions on an initial localised MRI. The second of these had a trial of antibiotics for 6 weeks with no response after which a biopsy showed chronic inflammation. Both patients responded well to pamidronate therapy.

Classical locations: clavicle and spine

Thirty-two clavicular lesions were recorded (10% of lesions) in 14 patients (38%) and were evenly distributed: 12 lateral, 9 central and 11 medial (Fig 3). Six patients (16%) had unilateral total clavicular involvement. Only two of 14 affected patients had bilateral symmetric lateral lesions (one with an additional unilateral medial lesion).

Seven patients had spine (19%) involvement with 14 lesions in total (4% of lesions) (Fig 4). T6 was involved in all but one patient with vertebral lesions, and involvement of the intervertebral disc above or below T6 was present in all but one of the five patients with discitis. In four of the seven patients, the spinal disease accompanied clavicular involvement typical of CRMO whereas in the remaining three, there was multifocal disease with four lesions, 15 lesions, and 26 lesions, respectively.

Patterns: bilateral and symmetric

Fifteen bone types were assessed for bilateral and symmetric involvement: seven of these bone types had bilateral involvement in >50% of cases. The bones with the highest proportion of bilateral involvement in terms of frequency, were the fibula (bilateral in 80%), tibia (bilateral in 68%; Fig 5), and phalanges of the feet (bilateral in 67%). All patients with bilateral metatarsal lesions were noted to have as a minimum the same metatarsal affected on both sides. The same was not true for rib lesions, with only one patient having bilateral symmetric lesions.

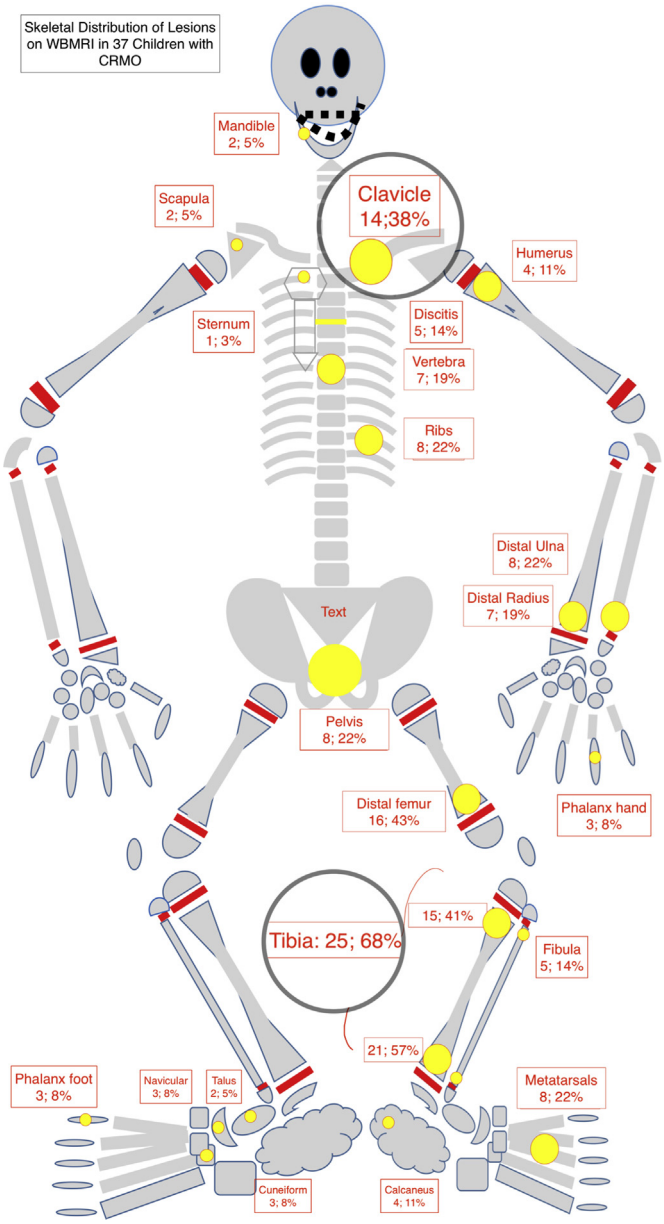

Figure 2 Summary of skeletal distribution of CRMO lesions of the whole patient group, according to frequency of patients (and percent of patients) with each type of lesion site, using the same pro-forma as for individual patient lesion recording. The frequency of patients with involvement of the tibia and clavicle is magnified.

In 50 of the 54 instances of bilateral involvement (93%), there was also symmetry. The commonest site of symmetric involvement was the fibula (80% of patients with fibular lesions were bilateral symmetric). These findings are summarised in Table 1.

Patterns: phenotypes

Lower limb lesions frequently occurred together: all five patients with fibula lesions and 16 of 17 patients with femoral lesions had a lesion in a tibia. Radial and ulna lesions occurred together in all but one case. Despite a

Table 1
Skeletal distribution of chronic recurrent multifocal osteomyelitis (CRMO) lesions by frequency of patients and lesions

Bone involved	Patients affected (%) $n = 37$	Lesion number $n = 317$	No. of patients	No. of patients with bilateral lesions (% of total patients with lesions at this site)	No. of patients with bilateral symmetric lesions (% of total patients with lesions at this site)	Proximal metaphysis lesions	Distal metaphysis lesions	Proximal epiphysis lesions	Distal epiphysis lesions
Tibia	25 (68%)	93 (29%)	25	17 (68%)	16 (64%)	24	26	17	26
Femur	16 (43%)	37 (14%)	16	8 (50%)	8 (50%)	7	19	0	11
Clavicle	14 (38%)	32 (10%)	14	2 (14%)	2 (14%)				
Metatarsal	8 (22%)	18 (6%)	8	5 (63%)	5 (63%)				
Ribs	8 (22%)	18 (6%)	8	3 (38%)	1 (13%)				
Pelvis	8 (22%)	18 (6%)	8	3 (38%)	2 (25%)				
Ulna	8 (22%)	11 (3%)	8	3 (38%)	3 (38%)	0	11	0	0
Spinal	7 (19%)	14 (4%)							
Radius	7 (19%)	12 (4%)	7	4 (57%)	4 (57%)	0	11	0	1
Fibula	5 (14%)	13 (4%)	5	4 (80%)	4 (80%)	4	5	0	4
Humerus	4 (11%)	7 (2%)	4	2 (50%)	2 (50%)	6	0	1	0
Calcaneum	4 (11%)	4 (1%)							
Phalanx (Foot)	3 (8%)	16 (5%)	3	2 (67%)	2 (67%)				
Phalanx (Hand)	3 (8%)	8 (2%)							
Cuneiform	3 (8%)	5 (2%)	3	1 (33%)	1 (33%)				
Navicular	3 (8%)	4 (1%)							
Talus	2 (5%)	2 (<1%)							
Mandible	2 (5%)	2 (<1%)							
Scapula	2 (5%)	2 (<1%)							
Sternum	1 (3%)	1 (<1%)							
Totals	37	317		54 instances of bilateral disease	50 instances of bilateral symmetric disease	113 (65%) Metaphyseal		60 (35%) Epiphyseal	

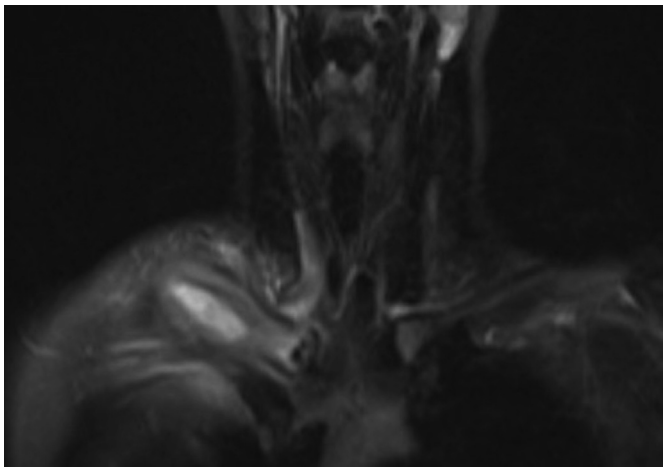

Figure 3 STIR image from a WBMRI in a 12-year-old boy, demonstrates abnormal high-signal in the right clavicle with expansion of the bone, which is considered typical for CRMO. This is the one imaging finding that, according to the Bristol criteria, does not require multifocal disease for diagnosis of CRMO.

frequency of tibial (25 patients, 68%) and clavicular lesions (14 patients, 38%) only five patients (14%) had tibial and clavicular lesions together. Based on the above separation of tibial or clavicular involvement, three phenotypic WBMRI patterns of CRMO/CNO emerged: a group with primarily

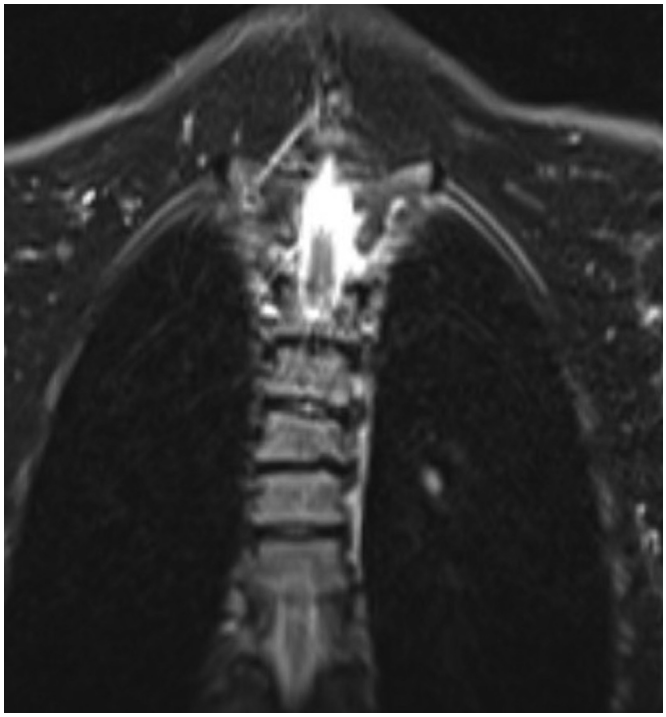

Figure 4 Coronal STIR image from a WBMRI in a 17-year-old boy with diagnosed CRMO demonstrates left-sided height loss of the vertebral body of T5 with loss of disc signal between T5 and T6. The coronal imaging is not ideal for demonstrating either the signal abnormality of the vertebral bodies or abnormalities of the disc spaces, and therefore, additional sagittal MRI of the spine is recommended.

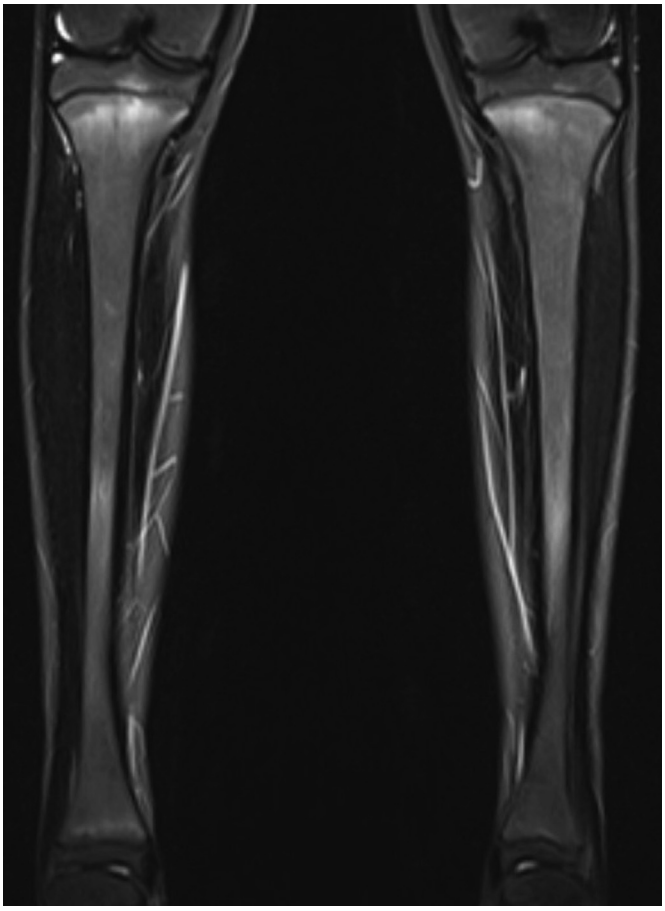

Figure 5 Coronal STIR WBMRI in a 6-year-old girl demonstrates typical bilateral symmetric abnormal high signal of the proximal tibial metaphyses. There are also unilateral/asymmetric lesions of the right proximal tibial ephysis and right distal tibial metaphysis, in keeping with the multi-focal nature of CRMO affecting the tibia.

tibial involvement and multifocal appendicular lesions (femoral, tarsal, fibular, radial, ulna, and pelvic); a primarily clavicular group with paucity of other lesions predominating in the spine; a small crossover group involving the tibia and clavicle together (Table 2):

(1) Tibio-appendicular multi-focal pattern: tibial lesions, multifocal involvement, and no clavicular involvement (Fig 6) comprising 20 patients (54% of the total). The characteristics of this group were: all but one (19; 95%) had lesions in other, mainly long bones (e.g., distal

Table 2
Patterns of anatomical involvement in chronic recurrent multifocal osteomyelitis (CRMO): tibial and clavicular dominance in 37 patients (%)

Tibia-appendicular multi-focal pattern: tibial involvement (no clavicle involvement)	20 (54%)
Claviculo-spinal pauci-focal pattern: clavicle involvement (no tibia involvement)	9 (24%)
Tibia-claviclular cross-over pattern: combination of tibial and clavicular involvement	5 (14%)
Outliers: neither tibia nor clavicle involved	3 (8%)

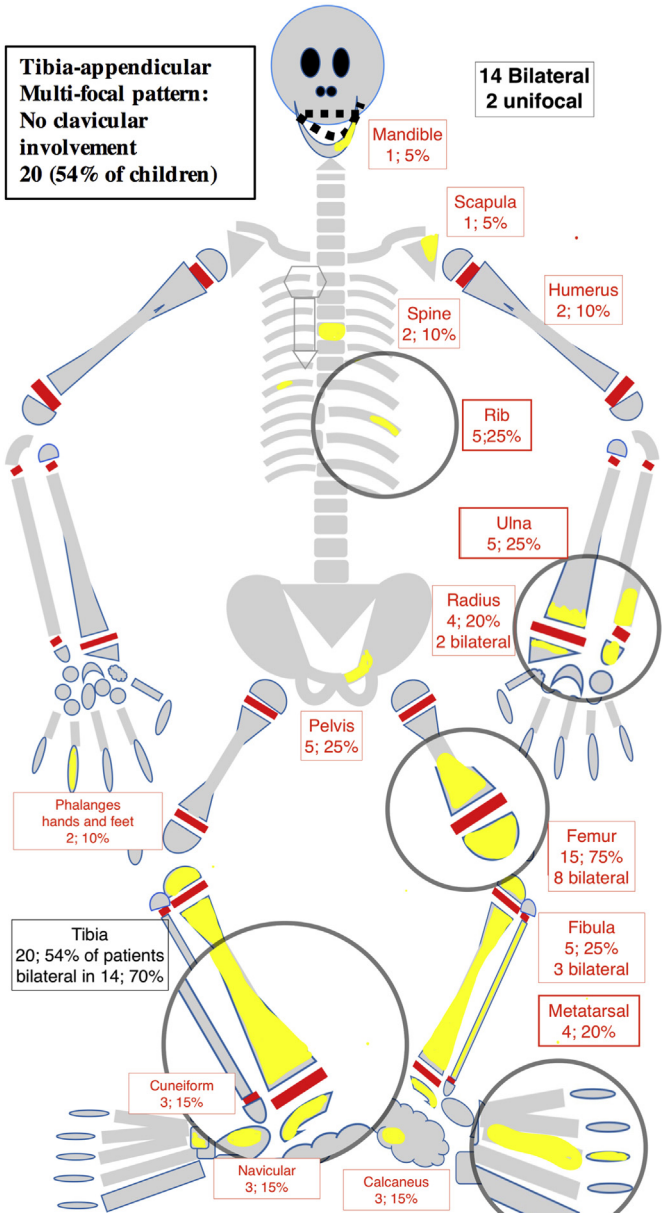

Figure 6 Summary of skeletal distribution of CRMO lesions in the "tibio-appendicular multi-focal" phenotype group, according to frequency of patients (and percent of patients) with involvement of each lesion site, on the same pro-forma that was used for individual patient lesion recording. The multifocal nature and involvement of the tibia with other appendicular sites is highlighted.

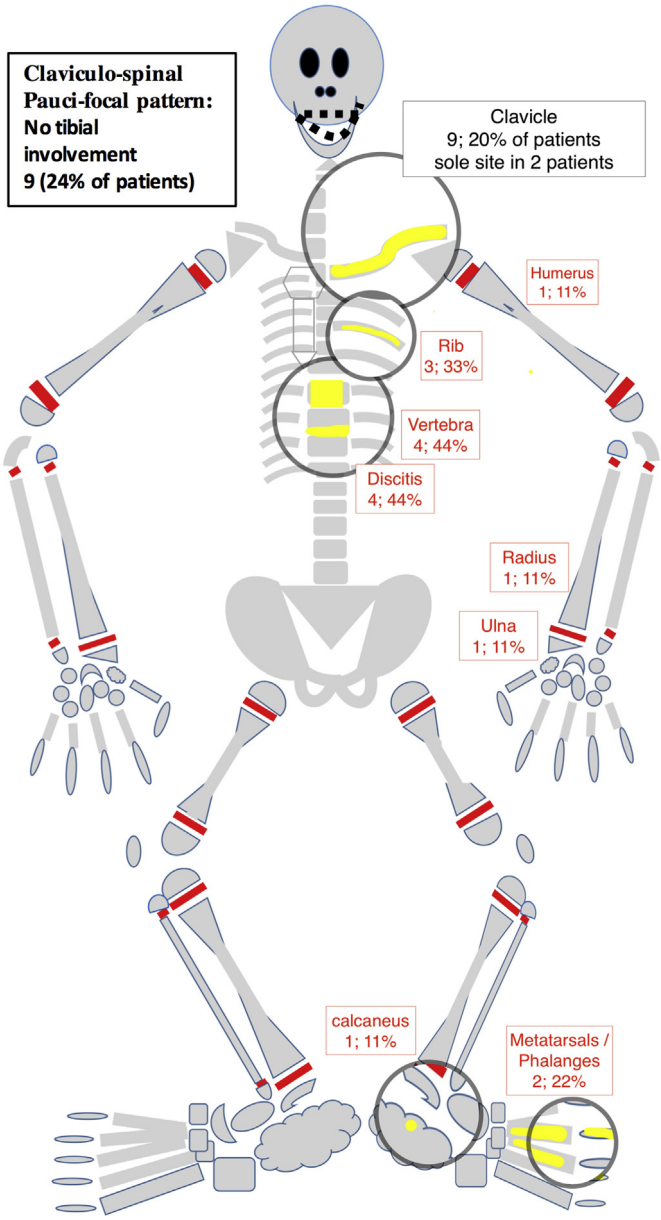

Figure 7 Summary of skeletal distribution of CRMO lesions in the "claviculo-spinal pacui-focal" phenotype group, according to frequency of patients (and percent of patients) with involvement of each lesion site, on the same pro-forma that was used for individual patient lesion recording. The limited range of locations (especially spinal lesions) that accompany clavicular lesions is highlighted in this imaging phenotype.

femur, metatarsals, ribs, and distal ulna); 14 of the 20 (70%) had bilateral tibial lesions; patients were three times more likely to have tarsal involvement than the "claviculo-spinal" group (8:1); five patients had ulnar and four had radial involvement; five of the eight pelvic lesions; and only two patients with spinal involvement.

(2) Claviculo-spinal pauci-focal pattern: clavicular lesions and few other mainly spinal lesions; no tibial involvement (Fig 7) comprising nine patients (24% of the total). Characteristics of this group were: two patients had the clavicle as a sole site; fewer overall lesions (average 6.4); four patients (44% of the group) had only a single other site affected (thoracic vertebral, talus and ribs); no pelvic lesions; three of the seven cases of spondylitis; four of the five cases of discitis.

(3) Tibio-clavicular crossover pattern: synchronous clavicular and tibial involvement: comprising five patients (14% of the total). Tibial lesions in this group were all distal. Relatively few other lesions were demonstrated. No involvement of the tarsal bones or spine was seen.

Three patients (8% of total) did not fit the above patterns, i.e., neither tibial nor clavicular lesions: two had multifocal disease and the third had an isolated distal femur lesion (the same patient described for unifocal lesions above who underwent a trial of antibiotics for 6 weeks and after no response underwent biopsy, which showed chronic inflammation. The latter patient also responded well to pamidronate).

Relation to the physis, metaphysis, and epiphysis

Overall, 113 (65%) metaphyseal and 60 (35%) epiphyseal lesions were identified (total 173 peri-physeal lesions, 55%; Fig 8). The commonest site was the distal metaphysis (42% of long bone lesions), except at the humerus, where the proximal metaphysis was more common (Table 1). One patient had bilateral greater trochanter involvement (metaphyseal-equivalent; Fig 9).

Peri-physeal extent

Epiphyseal lesions were minimal in the majority (35/58; 60%), whereas metaphyseal lesions were extensive in the majority (85/114; 75%; Table 3, Fig 10). Sixty-six percent of tibial symmetric lesions and 100% of radial, humeral, and ulnar symmetric lesions were of equal severity.

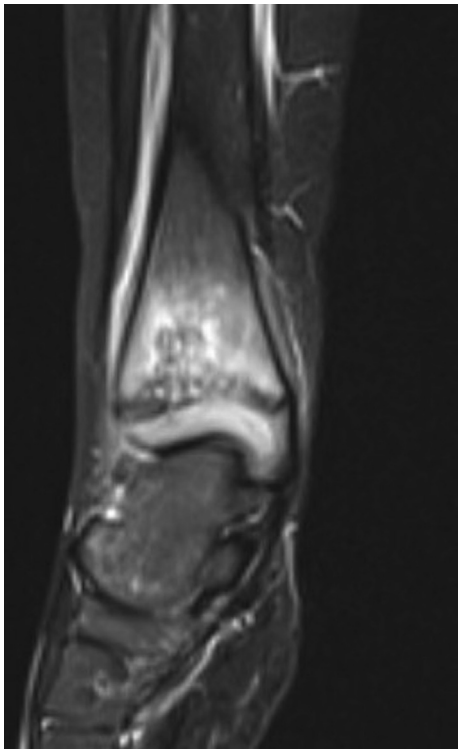

Figure 8 Coronal STIR WBMRI in a 11-year-old boy demonstrating abnormal high signal involving the distal tibial metaphysis and epiphyisis, along the full width of the growth plate. Note the "veld-fire"/"bush-fire" pattern of the abnormal signal on the metaphyseal side of the physis with a "smouldering" appearance at the physis and "flames" projecting into the diaphysis; this is considered typical for CRMO in the long-bone metaphysis. There is also involvement of the physis centrally and a suggestion of early physeal bar formation.

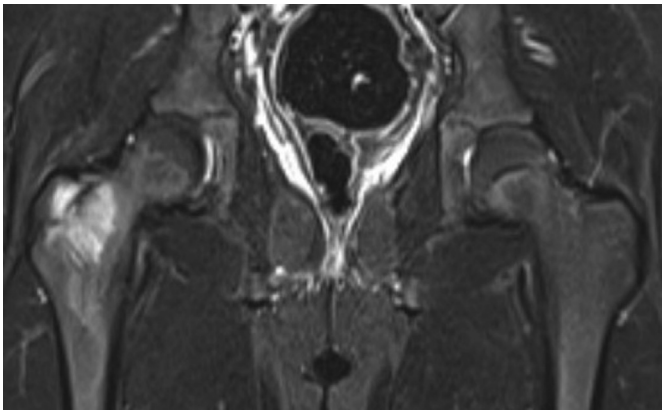

Figure 9 Coronal STIR WBMRI in an adolescent with CRMO, demonstrating abnormal high signal involving the secondary ossification centre of the greater trochanter and the metaphyseal equivalent portion of the proximal femur relating to this.

Periosteum and soft tissue

Four patients (11%) had periosteal reaction and two had knee effusion (one bilateral).

Table 3
Extent of lesions by location

Extent of physeal width involved in thirds	Metaphyseal 114 lesions	Epiphyseal 58 lesions
Minimal (<1/3)	14 (12%)	35 (60%)
More than minimal (1/3–2/3)	15 (13%)	12 (21%)
Extensive (>2/3)	85 (75%)	11 (19%)

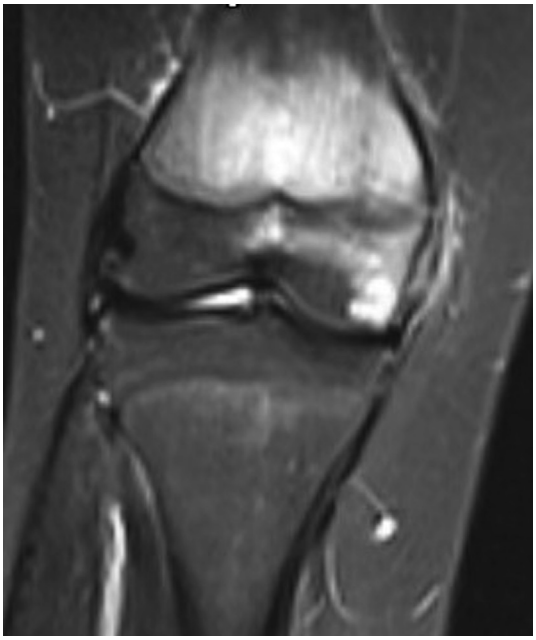

Figure 10 Coronal STIR WBMRI in a 14-year-old girl with CRMO demonstrating typical distal femoral abnormal signal of the metaphysis associated with less severe involvement of the distal epiphysis and possible involvement of the physis.

Discussion

Diagnosis of CRMO is traditionally achieved by exclusion of infective osteomyelitis, Langerhans cell histiocytosis, Ewing's sarcoma, osteosarcoma, and leukaemia/lymphoma osteoid osteoma, osteoblastoma, neuroblastoma metastasis, and fibrous dysplasia.[1–3,5,8–10] The MRI appearances of CRMO are described as "ill-defined, edema-like lesions most frequently located in the lower appendicular skeleton in a periphyseal location".[6] Bone biopsy is therefore, reserved for when imaging is inconclusive, especially when multi-focality is not revealed.[3] The Bristol criteria represent a guideline for diagnosing CRMO using clinical and radiological findings[7,10] comprising (1) the presence of typical clinical and radiological findings in more than one bone (or clavicle alone) without significantly raised inflammatory markers; and (2) typical clinical and radiological findings in one bone plus inflammatory changes (plasma cells, osteoclasts, fibrosis or sclerosis on bone biopsy with no bacterial growth). Typical radiological findings included plain radiographs showing a combination of lytic areas, sclerosis, and new bone formation or preferably STIR MRI showing bone marrow oedema, bone expansion, lytic areas, and periosteal reaction.[10]

The two main imaging features of CRMO are therefore: (a) multifocal locations and (b) specific skeletal sites of involvement, i.e., juxtaphyseal portions of the tibia and femur, clavicle, and thoracolumbar spine.[5,8,10,11] The present study demonstrated multifocal involvement in 33 of 37 patients (89%) using WBMRI with 317 lesions in total and an average of 8.6 LPP. This is amongst the highest counts of LPP reported for WBMRI comparing well with Fritz *et al.* (8 LPP),[6] Roderick *et al.* (6.8 LPP)[12] and Von Kalle *et al.* (9.7 LPP).[2] Involvement of the lower limbs most frequently was also demonstrated, with the tibia involved in 68% of patients (29% of lesions) and the femur involved in 43% of patients (14% of lesions) comparing well with Voit *et al.* (tibial 71%; femoral 47%).[1] In addition, frequent involvement of the fibula, tarsals, metatarsals, and foot phalanges was demonstrated (Table 1, Fig 1), comparing well with reports of over 10 patients, summarised in Table 4.

Periosteal reaction is also part of the disease[6,8,9] as is soft-tissue inflammation (up to 52% of children), which can be marked, mimicking a soft-tissue mass.[3,9] Periosteal reaction was demonstrated in only 11% of patients (three-quarters of whom had soft-tissue oedema).

Clavicular involvement is reported to involve 30% of all CRMO lesions,[9] and is the most common non-neoplastic cause of a clavicular lesion in children and adolescents.[9] Clavicular involvement was seen in 38% of patients in the present study, which is higher than all previous paediatric reports, bar that by Jimenez *et al.* comprising only 12 patients. Lesions typically involve the inner third of the clavicle with marked periosteal reaction, soft-tissue signal abnormality, and hyperostosis[3,9] but only one-third of the present cohort had medial clavicular involvement. The clavicle is an atypical location for bacterial osteomyelitis, therefore inflammatory clavicular lesions are almost diagnostic of CRMO[3,5,8]; hence, even unifocal clavicular lesions are considered positive Bristol criteria.[7,10,11]

Spinal lesions are recently reported as a classic and one of the most common sites for CRMO[3] (reported 30%[5,13]; 19% frequency in the present cohort). Voit *et al.* reported spinal involvement in 82%.[1] WBMRI has relevance[8] because it can demonstrate occult vertebral sites, i.e., asymptomatic and not demonstrated by plain radiographs or scintigraphy.[9] MRI shows increased signal of vertebral marrow, endplate irregularity[3,9,14] and is multifocal in two-thirds of cases.[3] When multifocal, CRMO typically involves non-contiguous vertebrae without crossing the disc, distinguishing it from infectious spondylodiscitis[3,9,14]; however, reports of disk involvement have prompted descriptions of CRMO as a spondylodiscitis.[14] Falip *et al.* reported disc involvement in two of nine patients with spinal involvement (22%) and contiguous vertebral involvement in one patient (11%). Five of the present seven patients with spinal involvement (14% of the total) demonstrated discitis. The thoracic portion of the spine is reportedly involved most often[5,9] (Hospach 60%; Falip *et al.* 75%[3,15]; T6 involved in all but one of the present cases).

Vertebral height loss is the most common pathological fracture in CRMO.[9,14] Falip *et al.* reported vertebra plana in 22%[3] while Wipff *et al.* reported the risk of vertebral fracture at 17.5%.[13] Detecting spinal involvement is important for prevention[1,5,9,16] as vertebral height is not regained with treatment.[3] Imaging should occur at the subclinical stage for initiating aggressive treatments (e.g., bisphosphonates) to prevent deformity (kyphosis and scoliosis).[11,15] Two of the eight patients with *asymptomatic* spinal lesions in the study by Hospatch, had vertebral deformities (22% had scoliosis or kyphosis).[15] Imaging should exclude vertebral involvement and differentiate CRMO from other causes of vertebra plana. STIR WBMRI can achieve the former by inclusion of a sagittal plane sequence and sometimes achieve the latter by demonstrating multifocal disease with characteristic lesions at other locations or typical patterns (such as clavicular involvement). Falip *et al.* reported poor sensitivity of WBMRI for spinal lesions,[3] probably because routine WBMRI is performed in the coronal plane. This is why dedicated sagittal MR imaging of the spine,[17] and diffusion-weighted imaging (DWI) are additional recommendations. DWI is sensitive for lesions, and even though it is believed by some that restricted diffusion can differentiate CRMO from malignancy,[3] this is not universally accepted.

MRI and WBMRI for CRMO

MRI advantages include non-invasiveness and radiation safety; sensitivity to oedema and soft-tissue lesions; ability to exclude differentials; and ability to assess activity/treatment efficacy.[1–3,5,12,18] Active lesions show high STIR signal[5,6,12] and are described as "botchy and ill-defined" or "confluent marrow oedema".[8] There is, however, lack of standardisation of the MRI protocol, scoring systems (including definitions of CRMO lesions and on

Table 4
Summary of published research papers of whole-body magnetic resonance imaging (WBMRI) in chronic recurrent multifocal osteomyelitis (CRMO) with more than 10 patients compared to the results of the current study – sites involved are recorded as a proportion of the patient sample (clear cells) and as a proportion the number of lesions (shaded cells), according to the anatomic site involved

Paper	Patients with lesions	Age Median/ mean	Lesions	Lesions Per patient (range	Tibia	Femur	Fibula	Pelvis	Calcaneus	Talus	Tarsus/Foot	Patella	Phalanx/ metatarsal Foot	Humerus	Radius	Ulna	Carpus	Phalanx/ metacarpal Hand	Clavicle	Spine	Sternum	Rib	Mandible
Arnoldi 2017 patients	33 (of 40) WB MRI				20 proximal 20 distal	13 proximal 15 distal		40			8				5				15	23 Thoracic 3 Cervical	8		5
Arnoldi lesion			95	2.9 (1–8)	13 proximal 13 distal	9 proximal 9 distal	1	22			8				3				6		3		2
Damasio					15 distal	9 proximal		4			5								4	33			
2016 lesions																							
Falip 2013 patient	15 WB MRI (of 31)	11 years			39 (% of 31)	42 (% of 31)	16 (% of 31)	32 (% of 31)	13 (% of 31)	10 (% of 31)	16 (% of 31)	3 (% of 31)	13 (% of 31)	7 (% of 31)	13 (% of 31)	13 (% of 31)	3 (% of 31)	3 (% of 31)	19 (% of 31)	29 (% of 31)		3 (% of 31)	10 (% of 31)
Falip lesion			108	3.5 (1–4)	17	17	5	11			7	2	4	2	5	4	2	1	7	17		1	3
Fritz 2009 patients	13 WB MRI	13 years																					
Fritz lesion			101	8 (3–14)	17 proximal 14 distal	21 distal	14	5	9	10										3	1	1	
Girsch ick 2005 patients	30 ? WB MRI	11 years			9	17	5	7	19					3				2	37	2	16		
Girsch ick lesion			59	2 (1–6)															24		10		

Jimenez 2017 ? Lesions or patient	12	11	3.5																50		33		
Roderick 2014 patients	11	14 years	75	6.8																3			
Voit 2015 patients	17	9 years			71	47		41			18	6		6	18				35	82			
Voit lesion			55	3 (1–4)								2	18							8			
Vonkalle 2013 patients	53	11 years						77			43	13						2		36			4
Vonkalle lesion			513	9.7 (1–27)	18	15																	
Wintrich 2015 patients, not WBMRI	32 (30 MRI)	8 years			31	31	6	34	16	19	16	3		3		9			34	13		3	3
Wintrich lesions			114	3.6 (1–12)	12	13	3	14	7	11	9	1	4	2		4			13	5		2	1

which sequences they are detected), and indications for imaging, which makes comparison of different research publications more difficult. In the present study, any STIR abnormal high signal was recorded, but a typical "veld-fire" appearance of peri-physeal lesions with "flames" projecting into the metaphyses was noted (Fig 10). The wide distribution of CRMO is grounds for imaging the whole skeleton[2]: targeted imaging underestimates the number and characteristic distribution patterns[2] (hence the exclusion of patients with localised MRI). WBMRI can reveal multifocal disease including asymptomatic (occult) lesions[1–3,5,8,9,16] providing objective disease burden (load) assessment and distributional pattern detection, i.e., bilateral lesions are detected more frequently with WBMRI than targeted MRI (75% versus 22 %).[1,2,8] WBMRI STIR is routinely performed coronal.[3] Not all published studies clarify whether WBMRI was used and whether lesion frequency and distribution represent WBMRI findings. An attempt was made to compare only WBMRI data in the summary (Table 4).

Phenotypic WBMRI patterns

Diagnosing CRMO with WBMRI relies on recognising multifocal phenotypic patterns or typical single lesions.[4,5] Von Kalle *et al.* described multifocal "diagnostic patterns": *"geographic metaphyseal lesions adjacent to growth plates of the long bones of the lower extremities, combined with either bilateral symmetric involvement, or additional lesions in the spine, pelvis, clavicle and/or sternum"*.[2] Others also report multifocal symmetric lesions in the lower extremities as typical.[6,9] Bilateral *symmetric* distribution differentiates CRMO from many differentials.[6,19] In the present study, bilateral symmetric lesions were seen in 80% of fibular, 64% of tibial, and 63% of metatarsal lesions. Wipff *et al.* were first to define more distinct phenotypes relating to clinical presentation and outcome[13]: (1) a *severe phenotype* (20%) of only male patients with *multifocal* CRMO (97%) and *rare clavicular involvement (11%)* — 33% of whom had clinical inflammatory syndrome and worst prognosis (remission rate 22% despite bisphosphonates/anti-tumour necrosis

factor [TNF])[13] — corresponding to the present *"tibio-appendicular multi-focal"* group (54%), which by definition, excluded patients with clavicle involvement. Wipff *et al.* did not identify the tibia as the primary site (often bilateral, 70%) or that the other sites involved mainly long bones[13]; and (2) a *mild phenotype* (31%) comprising mainly females (73%) with predominantly *unifocal* (80%) and *clavicular* (43%) involvement — 26% of whom had inflammatory syndrome and best prognosis (despite infrequent bisphosphonates/anti-TNF use) (2%)[13] — corresponding to the present "*claviculo-spinal pauci-focal*" group (24%), which by definition, involved the clavicle. Only two of the present patients had uni-focal disease involving the clavicle whereas 44% of patients had one other site of involvement, e.g., spine, hence *"pauci-focal"*. The limited use of WBMRI in the study of Wipff *et al.* (two of 38 patients) should be noted.[13] Considering that targeted imaging underestimates the number of lesions,[2] there is a likelihood that some of their unifocal cases may have been pauci-focal. Spinal involvement featured heavily in the present cohort (3/6 cases of spondylitis and 4/5 cases of discitis). Hospach *et al.* recorded eight patients with spinal involvement who were asymptomatic/occult (despite two with vertebral deformity); therefore, the infrequent use of WBMRI by Wipff *et al.* may underestimate spinal involvement.[13,15]

An intermediate phenotype (48%) with multifocal CRMO (91%) described by Wipff *et al.*[13] had inflammatory syndrome in >50%, a remission rate of 48%, and 13% used bisphosphonates/anti-TNF[13] would probably fall within the present WBMRI tibio-appendicular multifocal group.[13]

Metaphyseal and epiphyseal involvement

Multifocal metaphyseal and metaphyseal-equivalent involvement (adjacent to cartilage in non-tubular bones; 75%) suggests CRMO,[19] i.e., "juxtaphyseal" or "peri-metaphyseal" descriptions.[3,6,9,11,14,18] Epiphyseal lesions, previously thought rare, are reported in >50%.[3,6] Metaphyseal involvement was demonstrated in two-thirds and epiphyseal involvement in one-third of long bone cases. Epiphyseal and diaphyseal lesions without metaphyseal lesions are considered rare,[3] hence Fritz *et al.*'s description of the *"peri-physeal"* pattern is more appropriate.[6] The present study identified 173 peri-physeal lesions (55% of all lesions); however, epiphyseal and transphyseal injury is of prognostic significance because of risk for growth deformities and leg-length discrepancy[3,9,11] and these must be weighted in scoring systems.

MRI scoring systems: RINBO

RINBO is a WBMRI scoring system by Arnoldi *et al.* that predicts clinically active lesions.[8] It is intended to represent intensity of disease and simplify follow-up imaging evaluation.[8] The creators claim the purpose of RINBO "is to encourage standardised reporting, improve reproducibility, and ease stratification of WB-MRI findings" to improve therapeutic decisions[8]; however, apart from using the number, size, and extra-medullary involvement of CRMO lesions[8] only spinal involvement is weighted into the score: no weighting is given to the likelihood of a CRMO diagnosis based on the distribution pattern or to physeal involvement.[8] Considering that clinical activity is already evident

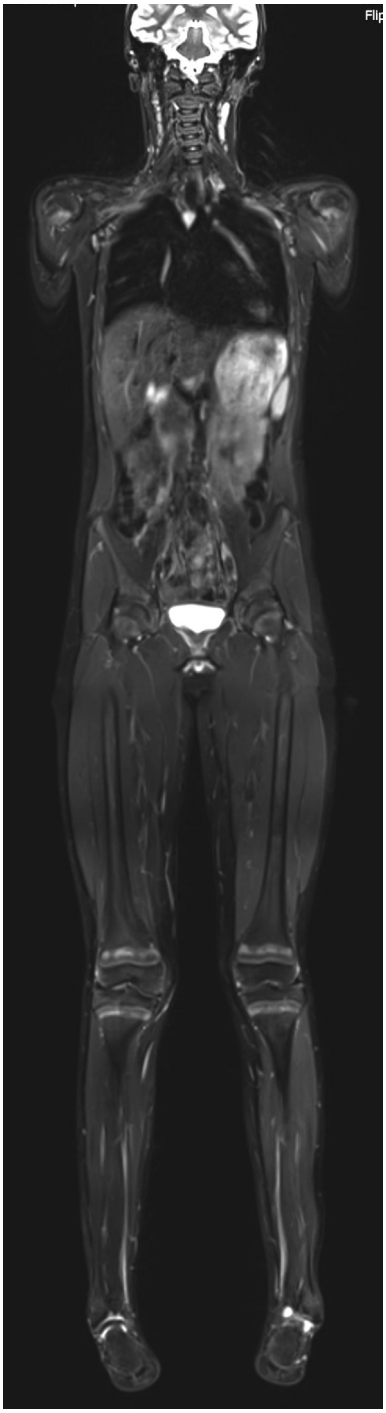

Figure 11 Coronal STIR WBMRI in a 13-year-old boy being treated for CRMO demonstrating "stitched" STIR imaging from multiple coronal stations, which can be scrolled through. This technique is especially useful for providing an overview of the multiple sites and patterns involved in CRMO; in this instance bilateral symmetric abnormal high signal involving the proximal tibial and distal femoral metaphyses as well as horizontal low-signal pamidronate lines.

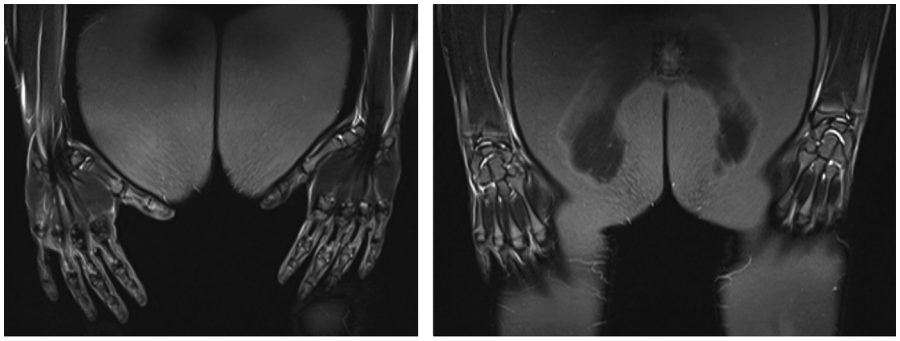

Figure 12 Coronal STIR WBMRI in a 13-year-old girl demonstrating the technique of imaging the hands placed under the buttocks to avoid having to perform additional imaging stations of the hands and wrists. This patient shows no artefactual abnormal high signal intensities that are common at air interfaces on STIR and the hands have been kept splayed out under the weight of the buttocks. There are clearly no CRMO lesions involving the phalanges, metacarpals, carpals or distal radius/ulna.

through VAS scores, the usefulness of correlating RINBO score of 0–8 with clinically active lesions is not clear.[8] Patients present with pain in the first instance and management is customised to their pain. A score should not primarily correlate with symptoms, but rather with outcome for prognostication, i.e., the likelihood of future physeal fusion with growth restriction/deformity and possibility for vertebral collapse/spinal deformity. The phenotypic groupings of Wipff *et al.* are not only correlated with severity of inflammatory disease, but are also linked to outcome, likelihood of response to treatment, and relapse rates.[13] WBRMI phenotypic patterns described in the present patients should inform modifications of current scoring systems to indicate the likelihood of CRMO as a diagnosis, and in future, they may also be shown to predict outcome, complications, response to treatment, and relapse.

Problems and solutions for WBMRI

By definition, WBMRI is a screening examination that includes few sequences and planes (at best one), intended to reveal bone marrow oedema, the principle being "maximum body coverage within the shortest possible time".[17] Coronal is the standard plane for WBMRI, performed over several scan-stations covering the "head and neck; thorax and upper arms; abdomen/pelvis and forearms; thighs and hands; calves and feet".[17] WBMRI uses STIR as a default because it is sensitive for bone oedema, but it is also susceptible to breathing artefact (ghosting).[8] Long acquisition times of WBMRI of up to 45 minutes are reported[3,5,8] and are well-tolerated by older children with adequate image quality,[3,5,8] but young children require anaesthesia.[5] The addition of other planes and sequences prolong scan times. WB DWI (performed by Leclair and routine in the authors' practice) can increase scan time by 15 minutes or more,[16] and is performed because it is sensitive for lesions and thought by some to differentiate CRMO from malignancy,[16] but this is not universally accepted. Studies can be shortened by decreasing the number of averages (with reduced quality) and using a moving table-top, which also allows for automatic image realignment and "stitching" of stations (Fig 11)[17]; however, coronal MRI can result in missed spinal, sacral, scapular, sternal, rib, patella, and skull lesions.[2,3,17,18] Arnoldi *et al.*, recommend adding two sagittal scan stations to image the spine routinely.[8] With WBMRI, there is also poor coverage of the upper extremities and feet[8]: to image the hands, an additional sequence is performed with the patient prone and arms stretched above the head, which increases the scan time.[17] The present authors avoid this by placing the hands under the buttocks during imaging of the abdomen/pelvis, a method not previously described, resulting in artefact-free imaging of the hands and wrists. The digits are widely spaced-out under the weight of the buttocks and ghosting artefact from an air–skin interface is avoided (Fig 12).

Considering the known involvement of the calcaneus and talus in CRMO and that small bones of the feet are more commonly affected than the hands, with the possibility of premature physeal closure, high-quality foot imaging remains a priority.[9] To image the feet adequately, additional sagittal scanning is recommended,[17] which is achieved through premeditated external rotation of the feet prior to starting the last station. It should be noted that MRI signal abnormalities of the talus and calcaneus may not be pathological.[6,20]

Study limitations

This was a retrospective study where WBMRI review was performed with advance knowledge of the CRMO diagnosis, but without access to MRI reports, clinical symptoms, prior imaging, or follow-up imaging. The first WBMRI examination was reported irrespective of whether this was performed at presentation or subsequently. Without a control group, it is not possible to distinguish pathological from physiological signal, such as that which occurs in the small bones of the hands and feet or that due to marrow changes. In future, the intention is to examine the WBRMI scans against follow-up studies and clinical symptoms to attempt to resolve some of these issues. Future prospective work should also include controls.

In conclusion, WBMRI for CRMO showed 89% multifocal disease, predominantly affecting the tibia and distal femur metaphyses in a bilateral symmetric pattern. Two diagnostic phenotypic patterns were identified: "tibio-appendicular multifocal" (>50%) and "calviculo-spinal paucifocal" (24%) patterns.

It would be useful to extract more prognostic value from WBMRI, hence the idea that different WBMRI patterns of the disease can predict outcome, such as the potential for leg length discrepancy and spinal deformity, will be pursued. Further exploration in a prospective study where MRI protocols are standardised and where normal variants are taken into account through the use of controls, is warranted. Future CRMO scoring should consider weighting according to phenotypes that may predict deformity.

Conflict of interest

The authors declare no conflict of interest.

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