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Whole Body MRI in the Diagnosis of Paediatric CNO/CRMO

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Whole Body MRI in the Diagnosis of Paediatric CNO/CRMO

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ABSTRACT

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3 Chronic recurrent multifocal osteomyelitis (CRMO) is an auto-inflammatory disorder affecting the
4 skeleton of children and adolescents. Whole body MRI (WBMRI) is key in diagnosis and follow-up of
5 CRMO. Imaging protocols should include sagittal STIR of the spine, imaging of the hands and feet
6 and T1 images for distinguishing normal bone marrow. CRMO lesions can be metaphyseal,
7 epiphyseal and physeal – potentially causing growth disturbance and deformity. Spinal lesions are
8 common, important and can cause vertebral collapse. Lesion patterns include multifocal tibial and
9 pauci-focal patterns which follow a predictable presentation and course of disease. Common pitfalls
10 of WBMRI include hematopoietic marrow signal, metaphyseal signal early on in bisphosphonate
11 therapy and normal high T2 signal in the hands and feet. Pictorial reporting assists in recording
12 lesions and follow-up over time. The purpose of this paper is to review the different WBMRI
13 protocols, imaging findings, lesion patterns and common pitfalls in children with CRMO
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28 **KEYWORDS:** Chronic recurrent multifocal osteomyelitis, children, whole-body magnetic resonance
29 imaging, osteomyelitis, autoinflammatory
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33 **KEY MESSAGE**

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36 Whole-body MRI protocols for CRMO must include the spine, the hands and feet.
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39 CRMO patterns on WBMRI include multifocal predominantly tibial or clavicular-spinal distribution.
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42 Radiologists need to be aware of the mimickers pitfalls of Whole-body MRI in CRMO.
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58 **INTRODUCTION**

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Chronic recurrent multifocal osteomyelitis, (CRMO) also known as chronic non-bacterial osteomyelitis (CNO), is an auto-inflammatory disorder affecting the skeleton of children and adolescents (1-4). CNO can affect all bones, but it is characterized by inflammatory lesions usually affecting the metaphyses of long bones of the lower extremities, clavicles and spine with spontaneous remissions and exacerbations (1, 3-5). An important aspect of CRMO, is the presence of multifocal bone lesions and the possibility for complications such as vertebral fractures (2). The diagnosis of CRMO is traditionally one of exclusion of other diseases but current practice suggests that when CRMO is suspected on clinical grounds, bone biopsy should not be routine. Instead, whole-body imaging is indicated to determine multi-focality, for narrowing the diagnosis (3, 6).

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The diagnosis of CRMO can be challenging as it shares many imaging features with other conditions. Bacterial osteomyelitis can mimic CRMO in patients with multiple lesions; however, soft-tissue involvement – such as abscesses – are more often seen in bacterial osteomyelitis (7). Scurvy, a metabolic disorder, manifest with diffuse lesions that can be metaphyseal initially but later spread to the diaphysis and is associated with subperiosteal hematomas (8). Malignant aetiologies, such as leukaemia or osteosarcoma, can be confused with CRMO as they can display abnormal marrow signal. However, these aetiologies present with focal or diffuse marrow replacement instead of oedema (9, 10).

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In the management of suspected CRMO, Magnetic Resonance Imaging (MRI) is useful in that it is highly sensitive for detecting inflammatory lesions without radiation exposure; it helps to exclude some of the alternative diagnoses; it can reveal features and patterns of bone involvement characteristic of CRMO; it provides an accurate site of involvement and provides a roadmap for possible biopsy; it is useful for determining response to and complications of treatment and it can identify complications of CRMO such as bone deformities due to early physal closure.

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Whole-Body Magnetic Resonance Imaging (WBMRI) is used in CRMO but there are questions regarding whether it should be a diagnostic tool, a quantitative/qualitative scoring tool, a treatment monitoring tool, or all of the above. Furthermore, to be able to generalise clinical findings

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3 and research results, radiologists should be performing similar WBMRI exams regarding sequences
4 and planes of imaging while also keeping scan times appropriate for children. Beyond performing the
5 examination in the same way, radiologists should be aware which signs are most diagnostic, what a
6 typical CRMO lesion looks like and report it in a comparable manner. In order to predict outcome,
7 scoring systems should not only incorporate lesion burden but also reflect susceptibility for growth
8 disturbance and deformity.
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16 WBMRI is already established for use in CRMO because it has further advantages over
17 localised imaging, in that it can reveal multifocal disease (increasing the likelihood of CRMO),
18 including silent (non-painful) lesions that may have characteristic features of CRMO when the
19 sentinel lesion has non-specific features. Furthermore, having images of the whole skeleton helps to
20 demonstrate patterns of skeletal involvement characteristic of CRMO, e.g. ‘bilateral, symmetric
21 pattern’ (2), ‘tibia multi-appendicular pattern’ or ‘clavicle pauci-axial pattern’ (11), and helps quantify
22 the disease in terms of lesion load (number of lesions in a patient) and lesion severity (e.g. vertebral
23 collapse, proportion of physis involved) for prognosis.
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34 Having established the role of WBMRI in CRMO, technical considerations must be optimised
35 both for minimising the time spent on the scanner and for improving sensitivity of detecting lesions
36 and relevant complications. Despite reports of 40-minute scan times, the addition of sagittal imaging
37 of the spine and diffusion weighted imaging (DWI) can extend scan times by up to and beyond 90
38 minutes. The radiologist’s role in imaging interpretation must also be optimised, by validating
39 characteristic MRI features and patterns of CRMO, highlighting pitfalls and mimickers (such as
40 carpal and tarsal high signal foci), improving prognostication from MRI through determination of
41 lesion ‘activity’ (signal intensities), lesion load (lesions per patient, scoring systems), lesion extent
42 (proportional metaphyseal, epiphyseal and paraphyseal involvement) and lastly through standardised
43 reporting for improved data collection and diagnosis.
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55 This review summarises current knowledge with regard to important technical aspects and
56 image interpretation of WBMRI for paediatric CRMO, previously presented in abstract format (12)
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TECHNICAL CONSIDERATIONS

Imaging parameters and Number of Stations / Scan Ranges

Imaging parameters reported for WBMRI in CRMO vary widely with respect to field of view, matrix and number of stations for achieving head-to-toe imaging and these are summarised in **Supplementary Table S1**, available at *Rheumatology* online. The number of stations scanned are reported to range from 4 to 8 for the coronal plane (depending on patient height) and an additional 2 stations for imaging the spine in the sagittal plane. There are no paper reports of single station / long Z-axis use.

Damasio et al, reported in a general paper on WBMRI, that acquiring images in stations with aligned slices and gradients allows stitching together of images, reduces scan time and makes repositioning unnecessary (13). Several papers of CRMO have published images that were stitched (**Figure 1**) to demonstrate the whole body of the patient (1, 2, 4, 14-16) but none provide information as to the usefulness of stitching for diagnosis or how to best review the images. In practice, as many fields as necessary should be used for maximum resolution but it is important to use the same fields in follow-up studies, for adequate comparison. Practical tips include scanning the abdomen and pelvis separately and demonstrating the clavicles in full in at least one field [either with the head-neck or the chest range].

Additional imaging planes and balancing time constraints

In principle WBMRI aims for ‘maximum body coverage in the shortest possible time’ (17). By this definition WBMRI should involve few sequences (at best only one) and few planes (at best only one) (17) but the addition of “a dedicated scan of the whole spine in the sagittal plane for improved visualization” during WBMRI has been proposed (17). Falip et al noted that the lack of agreement on frequency of spinal lesions might be due to diagnostic underestimation (3) and Von Kalle et al noted that spinal (as well as sacral, scapular, sternal or patellar lesions) may be difficult to assess on the standard coronal images (2) (**Figure 2a**). The latter group suggested that in cases of known or suspected vertebral or sacral lesions, that sagittal imaging be performed to improve

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3 visualisation (2). Arnoldi et al go further in recommending routine sagittal plane scanning with T1WI
4 and STIR, resulting in an additional scanning time of 11 minutes (14). The whole spine can usually be
5 covered with 2 overlapping sagittal sections (1).
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10 Routine additional imaging of the spine in the sagittal plane is important because spinal
11 involvement should be considered a classic feature of CRMO (3). Damasio reported the spine as ‘the
12 most frequent radiologically involved skeletal segment’ (13). Arnoldi et al reported “regular spine
13 involvement of nearly a fifth” of their cohort and highlighted the role that WBMRI findings can have
14 in management of CRMO (14). Numerous publications report spinal involvement: 8.4% (18), 19%
15 (11) 20% (19), 26% (20), 29% (3), 33 % (13). CRMO involves the thoracic spine predominantly,
16 followed by lumbar, cervical and sacral portions of the spine (5, 11, 21).
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25 Furthermore, identification of spinal involvement is important because vertebral height loss is
26 reported as the most common location of pathologic fracture in CRMO (21, 22) (**Figure 2b**). Falip et
27 al reported vertebra plana in 22% of their patients (3) while Wipff et al reported the risk of vertebral
28 fracture from CRMO lesions as 17.5% (23). Detecting spinal involvement early, is therefore
29 important for preventing vertebral body fracture and resultant vertebra plana (1, 3, 5, 21) (16, 22)
30 because vertebral height is not regained after treatment in CRMO (3, 21, 24). It follows that adequate
31 imaging of the spine should therefore occur at the subclinical stage so that aggressive treatment (e.g.
32 bisphosphonates) can be initiated to prevent deformity (kyphosis and scoliosis) (5, 20, 25).
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43 ***Sequences for WBMRI in CRMO***

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45 WBMRI is intended to serve as a screening examination for revealing bone marrow oedema
46 and therefore uses STIR as the default imaging sequence (17). There is also currently strong support
47 for the use of T1 weighted images and recent papers reported using additional DWI in CRMO (11,
48 13). Few authors use additional T2 sequences and only occasionally are regional post contrast images
49 performed. A summary of the sequences reported for use in WBMRI of CRMO is provided in
50 **Supplementary Table S2**, available at *Rheumatology* online. Damasio et al report that T1-weighted
51 sequences are essential in imaging CRMO (13). This is because T1 hyperintensity on unenhanced
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3 sequences may suggest an alternate diagnosis including fat, blood products and proteinaceous
4 material (22). T1 is most useful in CRMO for differentiating true lesions from normal bone marrow
5 conversion (13). Differentiation of red (haematopoietic) marrow from a CRMO lesion may not be
6 possible with STIR imaging alone as both can have a moderately high signal. T1 assists the
7 radiologist because **red marrow is of intermediate signal on T1** while **CRMO lesions have a low**
8 **T1 signal** (26). Considering the extended scan times, especially with the routine addition of sagittal
9 imaging, T1 could be added for problem solving on a lesion by lesion basis, until sequence times are
10 improved all around.

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There is limited published material on DWI use in CRMO. Although WB-DWI can be
reliably performed in children at 3T (16), interpretation may be difficult due to inhomogeneous bone
marrow signal. There is no systematic data on physiological DWI signal distribution in the bone
marrow of children differentiated by age and anatomical location (27) but Merlini et al noted in their
paper that DWI did **not** improve lesion conspicuity compared to STIR (28). DWI may be useful to
distinguish malignancy from CRMO in the spine but this is not universally accepted. **Supplementary**
Table S3, available at *Rheumatology* online, in lists the papers that report on the use of DWI in
CRMO. In summary, it is likely that there will be continued use of STIR as the default sequence until
more sensitive or specific sequences are tested and become mainstream (already being tested by some
research groups).

Positioning of Hands and Feet

Frequency of **hand** involvement reported ranges from 2–11% (**Supplementary Table S4**,
available at *Rheumatology* online) (2, 11, 15, 23, 29). Hands are the most difficult portion of the
skeleton to image during a WBMRI study (13, 14). There is no agreed technique for imaging the
hands and suggestions include placing the arms and hands beside the body (which makes evaluation
of arms and hands difficult due to artefact) (13); placing the hands on the pelvis with an additional
body coil (1, 14); placing the hands under the buttocks for inclusion in the pelvic scanning range (11);
or imaging the hands separately above the head (17, 30) (**Figure 3a**) which adds to study time
because of the additional scan station required. The recommendation is to place the hands on the

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3 abdomen and to include them in the abdominal or pelvic portion of the WBMRI or to place the hands
4 under buttocks during the pelvic portion of the WBMRI (**Figure 3b**) as described by Andronikou et al
5 (11) thereby splaying the hands and avoiding air-skin interface artefact. Note should be made that
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7 according to Avenarius et al, joint fluid, bone marrow oedema-like changes, and ganglion cysts may
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9 mimic pathologic abnormalities in the paediatric wrist (31).
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14 CRMO is more common in the small bones of the feet than in the hands (21) occurring in
15 around 40% of CRMO cases (**Supplementary Table S5**, available at *Rheumatology* online). The
16 calcaneus and talus, which are metaphyseal equivalents, are reported to be involved most often (21)
17 and while most papers report that the metatarsals are only rarely involved in CRMO, Andronikou et al
18 reported abnormality involving the metatarsals in 22% of patients (11). A poor anatomical match in
19 the feet can justify targeted MRI (14) which includes an optional sagittal scan of each foot (17).
20 Purposefully positioning both feet in the lateral view (**Figure 3c**) is an optional solution for the last
21 station of a WBMRI (11) or adding a sagittal scan of the feet to improve visualisation of the talus and
22 calcaneus. Most important is to note that MR signal abnormalities of the talus and calcaneus may not
23 be pathological (**Figure 3d**) and need to be considered alongside other lesion identified and clinical
24 findings (6, 32). Our own experience with WBMRI protocols and technical considerations is
25 discussed in a prior publication (11).
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40 IMAGING INTERPRETATION

41 *Classic MRI CRMO lesions*

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43 Two main imaging features of CRMO are multi-focality and the involvement of specific
44 skeletal sites. These characteristic sites include the juxtaphyseal/periphyseal portions of the tibia and
45 femur, the clavicle and thoracolumbar spine (5, 14)(1, 6, 25, 33)(3, 4). *Clavicular* involvement is
46 expected to comprise 30% of all CRMO lesions (21) and is reported as the most common non-
47 neoplastic cause of a clavicular lesion in children and adolescents (21). These lesions typically
48 involve the medial third of the clavicle with marked periosteal reaction, soft-tissue signal abnormality
49 and hyperostosis (3, 21) (**Figure 4 a-c**). The clavicle is an atypical location for bacterial osteomyelitis,
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3 and as such, an inflammatory lesion in this location on MRI is highly suggestive of CRMO (3, 5, 14).
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5 Hence, even when unifocal, clavicular lesions in children and adolescents are sufficient to meet the
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7 Bristol criteria for CRMO (19, 25, 33).
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10 *Tibial* involvement occurs in up to 71% and femoral involvement in up to 47% of patients
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12 (**Figure 5a**) (1). Von Kalle et al suggested that because individual lesions are non-specific in CRMO,
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14 particular combinations of multi-focal skeletal sites may offer ‘diagnostic patterns’ (2). They reported
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16 that ‘*three quarters of the diagnoses in their patients could have been made through identification of*
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18 *multifocal, hyperintense geographic metaphyseal lesions adjacent to growth plates of the long bones*
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20 *of the lower extremities, combined with either bilateral symmetric involvement, or additional lesions*
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22 *in the spine, pelvis, clavicle and/or sternum*’ (2). This typical phenotypic pattern of distribution was
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24 also noted by Fritz et al who reported that multifocal symmetric lesions in the lower extremities were
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26 important (6). Khanna et al also reported bilateral tibial disease as being common (21) (**Figure 5b**).
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28 Andronikou and colleagues identified two distinct patterns of involvement in CRMO using WBMRI:
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30 a more common *tibio-appendicular multi-focal pattern seen in more than half of children with*
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32 *CRMO, presenting with tibial lesions, multifocal involvement and no clavicular involvement; and a*
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34 *claviculo-spinal pauci-focal pattern, seen in a third of children with CRMO and presenting with*
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36 *clavicular lesions and few other, mainly spinal, lesions with no tibial involvement* (11).
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40 *Spinal* involvement has more recently been recognised as a classic CRMO feature, and in
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42 contrast to older studies it is currently considered one of the most common sites of involvement (3)
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44 with a reported prevalence of up to 30% (5, 23). The thoracic spine is reported to be involved most
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46 often (5, 21) (Hospach 60%; Falip et al 75%) (3, 20) (**Figure 2a and b**).
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49 Spinal lesions show altered MR signal intensity of the vertebral marrow and endplate
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51 irregularity (3, 21, 22). Spinal involvement is also reported to be multifocal in two thirds of cases
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53 which is further support for using WBMRI (2, 3). An important aspect of spinal CRMO, is the
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55 possibility for complications such as vertebral fractures (2). When multifocal, CRMO of the spine
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57 typically involves non-contiguous vertebrae without crossing the disc - this is considered the
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59 distinguishing feature of CRMO from an infectious spondylodiscitis (3, 21, 22). However,
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3 involvement of the disc in some patients has prompted a description of spinal CRMO as a
4 spondylodiscitis (22). Falip et al reported disc involvement in 2 of 9 patients with spinal involvement
5 (22%) and recorded contiguous vertebral involvement in 1 patient (11%) (3) while Andronikou et al
6 (22%) and recorded contiguous vertebral involvement in 1 patient (11%) (3) while Andronikou et al
7 reported disc involvement in 14% of patients (5 of their 7 patients with vertebral involvement) (11).
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12 According to the Bristol criteria, CRMO lesions are diagnosed irrespective of their location,
13 preferably by STIR MRI and typically show bone marrow oedema, bone expansion, lytic areas and
14 periosteal reaction (33). Lesions are also described as ranging from 'ill-defined' to 'confluent' bone
15 marrow oedema (6, 14). **More subjective descriptions of peri-physeal CRMO lesions** include 'veld-
16 fire' appearance with 'flames' projecting into the metaphyses (**Figure 5c**) (11). Periosteal reaction is
17 part of the spectrum of the disease (6, 11, 14, 21) with 11% of patients demonstrating periosteal
18 reaction in the study by Andronikou et al (11), as is soft-tissue inflammation (reported in up to 52% of
19 children) which can be marked, mimicking a soft-tissue mass (3, 21).
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30 ***Epiphyseal and Physeal Involvement***

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32 There are ten reports mentioning involvement of the epiphysis in children with CRMO
33 (**Supplementary Table S6**, available at *Rheumatology* online). Andronikou et al reported 35%
34 epiphyseal involvement (11), Arnoldi et al in 46% (14) and Fritz et al in 67% of long bone sites in
35 children with CRMO (6). However, epiphyseal lesions without involvement of the metaphysis are not
36 currently considered 'classic' CRMO lesions.
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44 Two reports also specifically describe physeal involvement by CRMO on MRI in a way that
45 suggests growth arrest may occur as a complication: Falip et al described a pseudo-widening growth
46 plate of the distal fibula (3) and Khanna et al described radiological crossing of the physis in CRMO
47 (21) (**Figure 5d**). In addition to isolated reports of leg length discrepancy (34) a paper by Huber et al
48 describes a series of children with growth disturbances resulting from CRMO (35). These authors
49 reported significant bony deformities either important for cosmetic or functional reasons in 11/ 23
50 (48%) patients with CRMO, presumably due to early physeal closure, but there is no correlation with
51 imaging in this report (35). Physeal and epiphyseal lesions should be reported individually and should
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3 have additional weighting in future scoring systems because of the possibility of complicating with
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5 deformity.
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8 ***Mimickers: Carpal / Tarsal high signal***
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11 High signal in the metatarsals, tarsals and carpals should be treated with caution
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13 because of the likelihood this represents a normal variant (31, 32) (**Figure 3d**). Therefore,
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15 recording of potential lesions in the carpal and tarsal bones should continue but not be
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17 attached a full weighting towards lesion load or be considered diagnostic on their own [i.e.
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19 without the presence of one or more other classic lesions].
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23 ***Mimickers: vertebral end-plate / disc involvement***
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26 23 papers have reported data of CRMO involvement of spine in children, with incidence
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28 ranging from 2-43% (more often between 20% and 35%) (**Supplementary Table S7**, available at
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30 *Rheumatology* online, summarises 20 of those with available data). Exams should only be considered
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32 adequate when they have excluded spinal involvement (5). Lesions that may mimic CRMO of the
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34 spine range from abnormal vertebral body signal to end-plate irregularity and complications of
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36 CRMO that may cause confusion with other pathology include sub-endplate fracture, height loss and
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38 vertebra plana (5) (21) (**Figure 3**). According to Jansen et al, nearly half of the patients with vertebral
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40 fractures develop scoliosis (36).
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43 The most typical spinal manifestation resembles spondylodiscitis, describing signal
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45 abnormality in the vertebral body, endplate irregularity and extension into the disc (11, 22) with disc
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47 signal abnormality or height loss (21). Therefore, differentiating CRMO spinal lesions from bacterial
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49 spondylitis and spondylodiscitis may be difficult (2). However, only rarely in CRMO are there reports
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51 of disease crossing a disc to involve contiguous vertebrae, which differentiates CRMO from
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53 infectious discitis (5) (21, 24).
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56 Periosteal reaction is reported accompanying spinal CRMO, but identification of any
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58 paravertebral mass should suggest a different diagnosis (37) (2, 24). CRMO should therefore be
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3 included in the differential diagnosis when vertebral end-plate and discs disease are identified i.e. in
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5 the differential diagnosis of a spondylodiscitis.
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8 ***Mimickers: enchondral ossification related to cyclical bisphosphonate therapy***

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10 Bilateral, symmetric metaphyseal high signal bands after the first course of bisphosphonate
11 treatment, have been noted anecdotally (but not reported) and these may mimic disease relapse,
12 particularly after the first course of bisphosphonate therapy (**Figure 6a**). This is in contrast to reports
13 of low signal (sclerotic) lines on MRI (**Figure 6b**), equivalent to the radiographic “zebra-line”
14 appearance which affect mainly the distal femora and proximal tibiae and fibulae (**Figure 6c**) (38-40).
15 The sclerotic zebra lines vary in spacing according to the age of the patient, rate of growth, interval
16 between cycles of bisphosphonates and location of the metaphysis (41). The high signal in the
17 metaphyses related to bisphosphonate treatment, most likely represents Pamidronate-related increased
18 conspicuity of the zone of endochondral ossification, analogous to the mandibular growth zone T2
19 high signal (42).
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32 ***Scoring systems and recording of disease burden***

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34 The RINBO scoring system is the only dedicated scoring system proposed for WBMRI
35 findings of CRMO (14). It has been shown to be a significant predictor for the presence of clinically
36 active lesions, which supports the idea of RINBO offering a means to grade the intensity of disease
37 and to simplify the evaluation of progression, stability or remission during the course of the disease
38 (14). The RINBO score allocates points (to a maximum of 10) according to increasing numbers of
39 lesions (out of a 3-point scale), increasing size of lesions (out of a 3-point scale), any acute or chronic
40 inflammatory reactions of the periosteum / soft tissues (1 point for each) and for any vertebral body
41 signal and deformation (1 point for each) (14). The creators of the score, indicate that the purpose of
42 RINBO ‘is to encourage standardized reporting, improve reproducibility and ease stratification of
43 WBMRI findings’ to improve therapeutic decisions (14). However, considering that clinical activity is
44 already evident through visual analogue scaled (VAS) scores, the usefulness of correlating the
45 RINBO score with clinically active lesions is not clear (14). This is especially because patients
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3 present with pain, and management is customised to this pain. From a prognostic perspective, only
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5 spinal involvement is weighted into the score, whereas from a diagnostic perspective, no weighting is
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7 given to the likelihood of CRMO based on the distribution pattern (14).
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11 Future iterations of RINBO or an alternative scoring system should aim to correlate with
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13 outcome (i.e. deformity), for it to be used as a prognostic tool. To this end, the likelihood of future
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15 physeal fusion with growth restriction / deformity and possibility for vertebral collapse/spinal
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17 deformity should be weighted into the score. Furthermore, the scoring system should provide
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19 weighting depending on whether lesions are 'classic', 'probable' and 'possible' and downgrade
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21 carpal/tarsal bone signal abnormalities. A standardised reporting system could also reflect lesion load
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23 and spinal involvement in more detail than RINBO currently does, (e.g. actual lesion load rather than
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25 categories of lesions numbers as recorded in RINBO).
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29 To achieve this one of the several anatomic maps have been published to demonstrate
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31 proportional lesion distribution in CRMO, which may also be used to record individual findings and
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33 may assist in revealing diagnostic and prognostic distributional patterns of disease (2, 6, 11, 23, 29,
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35 43). Such a pictorial tick-sheet could assist in revealing WBRMI distribution patterns and inform
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37 modifications of scoring systems to indicate the likelihood of CRMO as the diagnosis. Phenotypic
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39 groupings (e.g. by Wipff et al and Andronikou et al) have not only correlated with severity of
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41 inflammatory disease but were also linked to outcome, likelihood of response to treatment and relapse
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43 rates, and include details of peri-physeal lesions which should in turn influence scoring (11, 23). Most
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45 clinicians who have expertise in CRMO currently use WBMRI to prognosticate on need for
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47 immunomodulatory therapies (e.g., pamidronate or anti-TNF) and depending on sites involved
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49 potential long-term outcomes at least after 6 -12 months of treatment to assess response. WBMRI
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51 remains for clinicians, in the absence of other clinical or laboratory markers, the most important tool
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53 to help in management of children and adolescents with CRMO.
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57 Finally, work is in progress for developing artificial intelligence platforms for automated lesion
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59 detection from MRI, scoring and decision making, but the numbers of children with CRMO and
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3 issues with ground truth especially when trying to differentiate lesions from normal marrow without
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5 biopsy, are proving to be obstacles at the initial stages.
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8 **CONCLUSION**

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11 WBMRI has found its role in the diagnosis and management of CRMO in children. This
12
13 review summarises technical aspects to assist diagnosis while keeping scan times practical and
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15 describes MRI features of CRMO. Sagittal STIR imaging of the spine should be routine in CRMO
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17 while improved imaging of the hands and feet can be achieved by simple positioning manoeuvres. T1
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19 can be used to differentiate pathology from normal red marrow in children. Important areas to
20
21 highlight, include that CRMO lesions are not only metaphyseal but also epiphyseal and physeal,
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23 because these can cause growth disturbance and deformity; that spinal lesions are common and
24
25 important because they cause vertebral collapse; that there are typical CRMO patterns on WBMRI
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27 including multifocal tibial pattern (bilateral, symmetric metaphyseal lesions, around the knee) and the
28
29 paucifocal pattern with few lesions involving the clavicles and spine, with predictable presentation
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31 and course of disease. The review also highlights important WBMRI pitfalls such as marrow signal,
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33 metaphyseal signal appearances early on in bisphosphonate therapy and signal in the hands and feet.
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37 Using a pictorial reporting format for recording both first-time and follow-up of CRMO lesions on
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39 WBMRI can be partnered with a scoring system that reflects not only the lesion load but also the
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41 lesion distribution and likelihood for growth disturbance / deformity.
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50

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53 have declared no conflicts of interest.
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FIGURES

Figure 1. Representative coronal image from a 'stitched' coronal STIR WBMRI in an adolescent with CRMO. This allows review of the entire body by scrolling from anterior to posterior. The patient shows bilateral symmetric periphyseal signal abnormality at the distal femora and proximal tibiae, as well as a lesion of the right distal tibia (*open circle*).

Figure 2. CRMO involving the vertebral column

- (a) Coronal STIR component of a WBRMI scan demonstrating abnormal high signal in multiple non-contiguous vertebral bodies without crossing the disc (*arrows*), in keeping with additional lesions in a child with a diagnosis of CRMO.
- (b) Sagittal STIR demonstrating multifocal thoracic vertebral CRMO lesions in a child. Over and above the signal abnormality there is endplate collapse and vertebral height loss with wedging in some. The height loss is not expected to be regained in this condition.

Figure 3. Technical aspects of imaging the hands and feet

- a) One option to achieve whole-body coverage during STIR WBMRI is an additional station for imaging the hands. This involves stretching the hands out above the head (supine or prone) but adds to the study time and results in artefact at the air-soft tissue interface (not shown here). In this patient, abnormal high signal is demonstrated in the proximal phalanx of the right ring finger (*arrow*) and possible lesions in the distal ulnar metaphyses, which provide the additional lesions required for making the diagnosis of CRMO.
- b) A proposed alternative method of imaging the hands, involves purposefully placing them under the buttocks at the start of the examination for inclusion during imaging of the abdomino-pelvic station of the WBMRI. Note that a coronal view of the hands is achieved with the fingers adequately splayed and that air-skin interface artefact is avoided, while no additional scan time is required.

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- c) Placing the feet in the externally rotated position during STIR WBMRI scanning of the last station, provides a sagittal view of the calcaneus and improved visualisation of the bones of the feet compared to direct coronal views.
 - d) Sagittal view of the foot from a WBMRI in a child with CRMO demonstrating high signal foci at multiple sites including the calcaneus which may or may not represent pathology.

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Figure 4 Coronal STIR WBMRI demonstrating clavicular involvement considered

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characteristic of CRMO

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- (a) Abnormal high signal is noted in the medial aspect of the left clavicle (arrow) compared to the right in this child with CRMO.
 - (b) Abnormal high signal is noted in the medial and middle thirds of the right clavicle (arrow) in this child with CRMO
 - (c) Abnormal high signal and marked expansion of the right clavicle (arrow) is noted in this child with CRMO

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Figure 5. Typical imaging findings of CRMO involving the peri-physeal regions and physes of the lower limbs

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- (a) Coronal STIR image extracted from a WBMRI study in a child with CRMO demonstrating abnormal high signal at the most common site of involvement in CRMO which is the metaphysis at the distal femur (in this case on the right). In this child there is also involvement of the right distal femoral epiphysis.
 - (b) Coronal STIR image extracted from a WBMRI in an adolescent with CRMO demonstrating the typical: *'hyperintense geographic metaphyseal lesions adjacent to growth plates of the long bones of the lower extremities'*
 - (c) Typical CRMO appearances on STIR WBMRI in a child with CRMO, demonstrating the 'veld-fire' appearance of abnormal signal in the peri-physeal - metaphyseal and epi-physeal (*white arrow*) - part of the right distal tibia and the 'flame-shaped' abnormal high signal

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3 lesion in the left tibial metaphysis (*black arrow*). Note that while the (physeal) aspect of the
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5 signal abnormality is well defined, the internal (diaphyseal) margin is not.
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- 7 (d) Coronal STIR providing a distal tibial view of a CRMO lesion involving the metaphysis and
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9 epiphysis of the right distal tibia with destructive changes involving the physis itself,
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11 concerning for a future growth disturbance or deformity.
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14 **Figure 6 Metaphyseal bands associated with pamidronate therapy**

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17 (a) Coronal STIR WBMRI in a child who received pamidronate treatment for the first time,
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19 demonstrating a symmetric thick band of high signal in the distal femoral metaphyses (*thin*
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21 *arrows*), separable from the thinner linear band of high signal of the physis (*thick arrows*).
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23 The non-physeal aspect of the signal has a sharp margin, which differentiates this from the
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25 ‘veld-fire’ appearance or ‘flame-shaped’ CRMO lesions. It is thought that this represents the
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27 visible expanded zone of endochondral ossification (present early on in Pamidronate therapy),
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29 which has a reported high signal on T2.
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32 (b) A coronal STIR image from a WBMRI study in a patient with CRMO who received a single
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34 dose of pamidronate demonstrates a typical Pamidronate line which is seen as a thin, low-
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36 signal linear band mirroring the metaphyseal edge (*arrow*), which (as a result of growth) has
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38 migrated some distance away from the physis (a high signal band).
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41 (c) A coronal STIR image from a WBMRI study in a patient with CRMO who received multiple,
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43 evenly-spaced, doses of pamidronate. The image demonstrates the typical zebra-line pattern
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45 (*rectangle*). Note that the last course was some time previously, as noted by the large distance
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47 between the most distal pamidronate line and the high signal physis (*arrow*).
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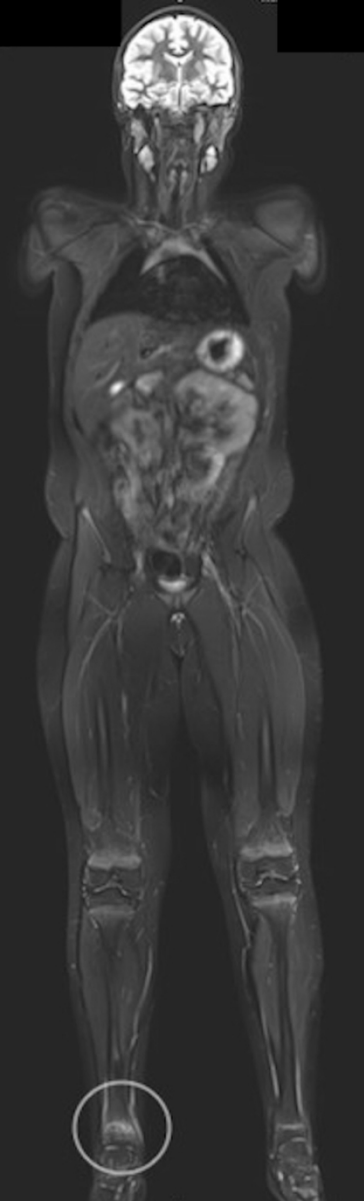
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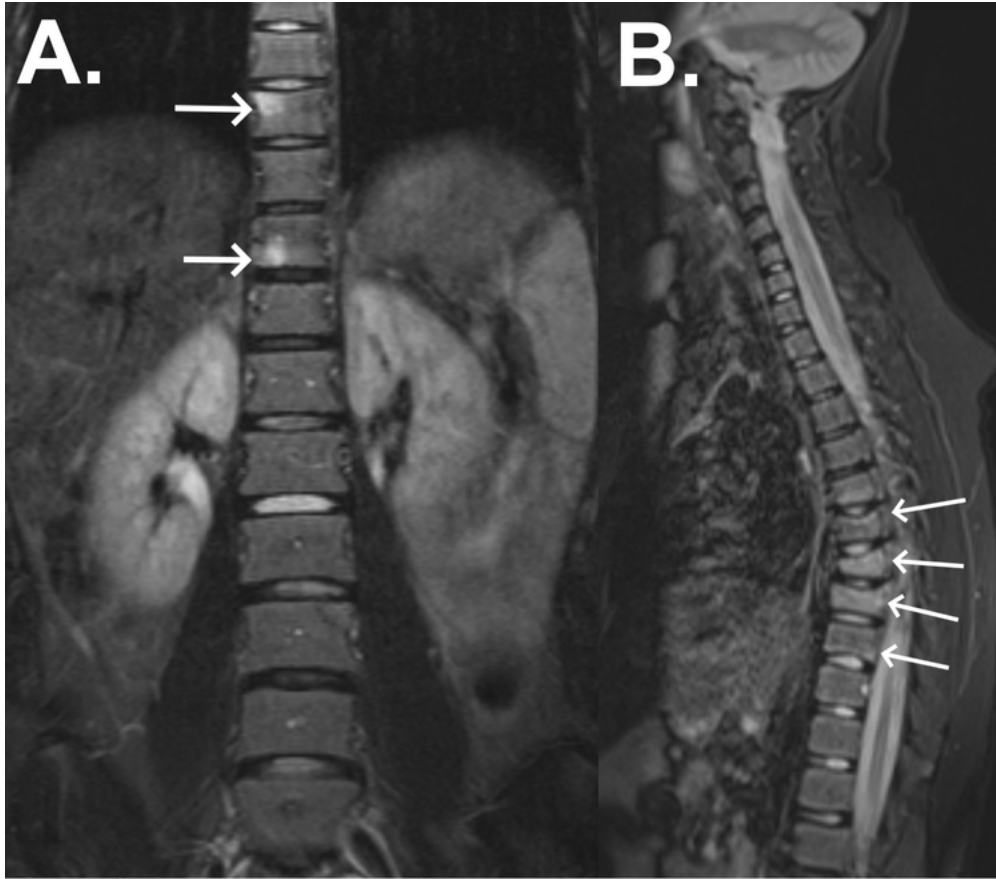
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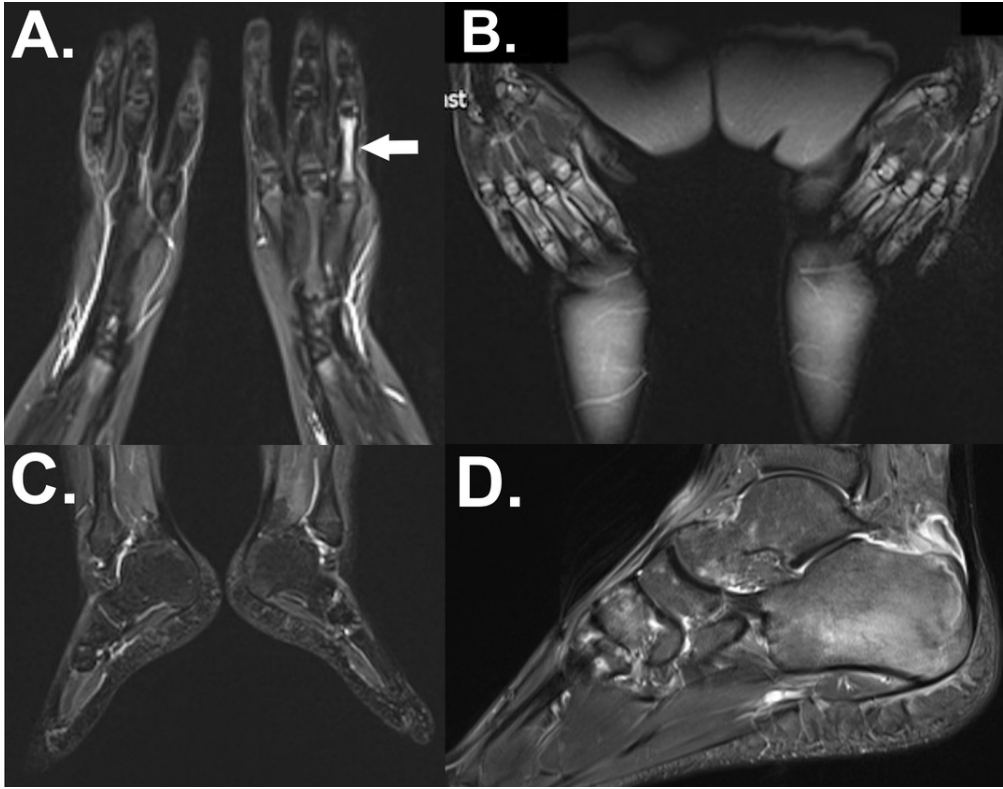
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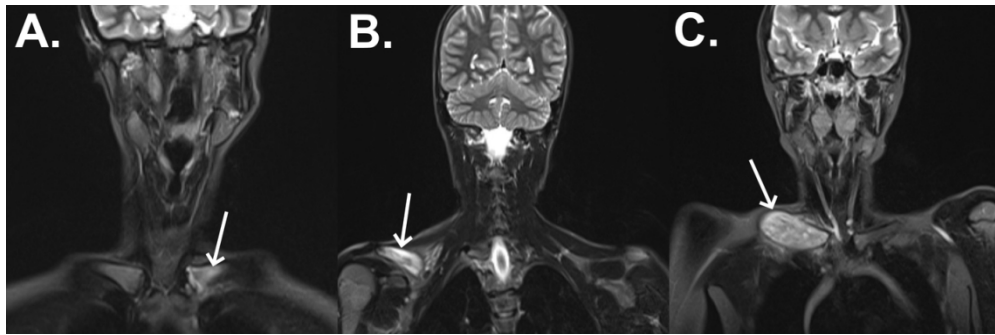


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SUPPLEMENTAL MATERIAL

8 **Supplementary Table S1: Summary of routine sequences and imaging parameters for WBMRI in CRMO**

References	Sequences	Field of view	Matrix	Stations	Comments
Fritz 2009 (6)	Coronal STIR Coronal T1	479x479mm 480x480mm	384x384 384x384	4-5 stations	
Kennedy 2012 (44)	Coronal STIR			5 stations	Case report
Von Kalle 2013 (2)	Coronal STIR	Max 500mm	384x269	4-5 stations	
Falip 2013 (3)	Coronal T1 STIR			4-5 stations	Limited information on technique
Von Kalle 2013 (2)	Coronal STIR	Max 500mm	384x269	4-5 stations	
Voit 2015 (1)	Coronal STIR	480x336mm	320x259	5-6 stations	
	Coronal T1	480x336mm	384x307		
	Sagittal STIR	400x400mm	384x326	2 sections	
Leclair 2016 (16)	Coronal STIR	500x500mm	448x336	6-8 depending on height	Paper mainly on DWI
Merlini 2017 (28)	Coronal STIR	448x448mm	300x320	'According to size'	General paper on WBMRI in children
	Coronal T1	400x400mm	360x360		
Andronikou 2019 (11)	Coronal STIR		450X310	5-7 depending on height	

26 STIR: Short Tau inversion recovery; CRMO: Chronic Recurrent Multifocal Osteomyelitis; WBMRI: Whole-body
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Supplementary Table S2: Summary of MRI sequences and plane of imaging reported for WBMRI in children with CRMO

Reference	STIR plane	In addition to STIR	Plane of additional sequences	Comments
Miettunen 2009 (45)				Used different sequences in different patients
Fritz 2009 (6)	Coronal	T1 T1 Fat Sat post gad	Coronal Coronal	
Kennedy 2012 (44)	Coronal			
Guerin-Pfyffer 2012 (15)	Coronal Selected axial	T1 T2	Coronal Coronal	
Falip 2013 (3)	Coronal/ Sagittal	T1	Coronal / Sagittal	
Von Kalle 2013 (2)	Coronal Regional Sagittal Axial			Regional images in abnormal areas only
Roderick 2014 (46)	Coronal	T1 T2 Post gad	Coronal Coronal Selective	
Voit 2015 (1)	Coronal/ Sagittal	T1	Coronal / Sagittal	
Leclair 2016 (16)	Coronal/ Axial	DWI	Axial	
Moussa 2017 (47)	Coronal			Additional regional sequences including post gad
Merlini 2017 (28)	Coronal 3D	T1 DWI	Coronal Axial	General paper on WB-MRI in children only 8 /54 had CRMO
Arnoldi 2017 (14)	Coronal/ Sagittal	T1 DWI	Coronal / Sagittal regional	
Andronikou 2019 (11)	Coronal			

STIR: Short Tau inversion recovery; CRMO: Chronic Recurrent Multifocal Osteomyelitis; WBMRI: Whole-body Magnetic Resonance Imaging

1 **Supplementary Table S3: Summary of publications reporting on the use of DWI in children with CRMO**

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References	DWI plane	Whole body?	Technique used, if specified	ADC	Result	Comments
5 Neubauer 2012 (27)	6 Axial 7 (8 8 additional 9 sagittal 10 and 11 coronal)	12 Regional 13 only	14 B values: 15 0-50, 800-1000, 16 Slice 6mm 17 1.5 and 3T	18 Yes	19 DWI can reliably detect 20 and characterise lesions 21 Sagittal and coronal 22 images had marked 23 artefact 24 (distortion and ghost 25 artefact) 26 Limited in-plane 27 resolution	28 Only 13 of 52 29 with CRMO 30 Some with non- 31 specific marrow 32 oedema and 33 arthritis
34 Leclair 2016 (16)	35 Axial	36 Whole 37 body	38 B values: 39 800 40 3T, slice 4mm reconstructed 41 in coronal plane 5mm and as 42 thick 3d MIP	43 Yes 44 Used 45 ADC 46 ratio 47 to 48 normal 49 side	50 ADC values 51 substantially elevated in 52 CRMO lesions, 53 Problems with artefact 54 (2 patients DWI non- 55 diagnostic)	56 16 patients 57 Did not look at 58 sensitivity of DWI 59 compared to STIR 60 Only used to help 61 characterise 62 Useful as 63 additional scan 64 12-16min scan 65 time
66 Merlini 2017 (28)	67 Axial	68 Whole 69 body		70 No	71 DWI did not enhance 72 lesion conspicuity 73 compared to STIR	74 General paper on 75 WBMRI in 76 children only 8 77 children with 78 CRMO (n=54)
79 Arnoldi 2017 (14)	80 Axial	81 Not 82 known	83 B values: 800	84 ?	85 Not presented	86 Mention of DWI 87 in the discussion; 88 showed high 89 signal in some 90 lesions when 91 performed; 92 suggest inclusion 93 in future
94 Andronikou 2019 (11)	95 Axial	96 Whole 97 body	98 Head: 7,400 ms TR, 89 ms 99 TE, B-values of 0 and 800, 100 230x230 mm FOV, 25 101 section of 4 mm thick with a 102 1.2 mm gap 103 Body: 5,320 ms TR, 64 ms 104 TE, B-values of 0 and 800, 105 300x420mm FOV, 40 106 sections of 4 mm thick with a 107 0.4 mm gap.	108 No		109 Not used for 110 analysis

111 STIR: Short Tau Inversion Recovery; CRMO: Chronic Recurrent Multifocal Osteomyelitis; WBMRI: Whole-body Magnetic Resonance
112 Imaging; DWI: Diffusion-weighted imaging; FOV: Field of view; ADC: Apparent Diffusion Coefficient; MIP: Maximum Intensity
113 projection; TR: Repetition Time

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Supplementary Table S4: Summary of WBMRI descriptions of hand involvement in children with CRMO

References	Hands comment	Hand technique
Girschick 2004 (29)	2% Phalanges (of 30 patients)	
Darge 2008 (17)	WBMRI review Not CRMO paper	For improved depiction of the upper extremities, the arms can be placed above the head.
	Different scan stations are head and neck, thorax and upper arms, abdomen/pelvis and fore- arms, thighs and hands and the calves and feet.	This can also be done with repositioning the patient in prone position with outstretched arms above the head.
Khanna 2009 (21)	Review	Both measures entail adding an imaging stage and thus, increase the scan duration. Short tubular bones typically demonstrate lytic lesions with surrounding sclerosis, periosteal reaction, and associated soft-tissue inflammation
Guérin-Pfyffer 2012 (15)	1/9 (11%) hand	
von Kalle 2013 (2)	1/53 (2%)	
Voit 2015 (1)		Upper arms were positioned parallel to the chest, and lower arms Hands were positioned upon the pelvis covered by an additional body coil
Wipff 2015 (23)	2% (of 178)	
Damasio 2016 (13)	Review WBMRI	Arms at the sides Larger children: arms sometimes not included in the scan field - makes evaluation of arms and hands difficult due to artefacts. In some cases, additional examination of the arms, placed above the head [Ley Eur J Radiol 70(3):442–451]
Roderick 2016 (19)	30 with WBMRI	
Arnoldi 2017 (14)	Hard to adequately delineate elbows, hands or feet in some exams	Upper arms were positioned parallel to the chest, lower arms and hands were positioned upon the pelvis covered by an additional body coil.
Taddio 2017 (25)	Review	Majeed syndrome (more severe phenotype than CRMO) typically involves the small bones of the hands and feet
Andronikou 2019 (11)	3/37; 8%	8 lesions of the phalanges

STIR: Short TI inversion recovery; CRMO: Chronic Recurrent Multifocal Osteomyelitis; WBMRI: Whole-body Magnetic Resonance Imaging.

Supplementary Table S5: Summary of the involvement of the feet in children with CRMO

References	Feet Comment	Feet technique
Darge 2008 (17)	Not CRMO paper	Sagittal scan of each foot is optional.
Khanna 2009 (21)	Review	CRMO is more common in the small bones of the feet than in the hands It can involve the tarsal bones e.g. calcaneus and talus, which are metaphyseal equivalents
von Kalle 2013 (2)	23/53 (43 %) feet Metatarsal (n = 27) Cuneiform (n = 25) Navicular (n = 21) 93/513 lesion (18%)	Small punctiform areas of high signal intensities are common in the bone marrow of children, especially in the feet - considered remnants of red marrow Lesions in metatarsals, rarely in CRMO
Walsh 2015 (34)	7/34 metatarsal 4/34 talus 2/34 Calcaneum	
Wintrich 2015 (43)	12/32 (38%) foot Most frequently affected region was the foot	Talus 5 th , tarsals 6 th , calcaneus 7 th and metatarsals 9 th most common out of 15 bones with CRMO lesions
Wipff 2015 (23)	7% (of 178)	
Leclair 2016 (16)	1/16 (6%)	
Roderick 2016 (19)	10% of lesions	16 lesions small bone of foot
Moussa 2017 (47)	5/7 talar (71%)	1 x talar and calcaneal 1x foot involvement (intertarsal, meta-tarsophalangeal, talar and calcaneo-navicular joints)
Taddio 2017 (25)	Review	Majeed syndrome (more severe phenotype than CRMO) typically involves the small bones of the hands and feet
Arnoldi 2017 (14)		Hard to adequately delineate elbows, hands or feet in some exams Poor anatomical match in the feet can justify targeted MRI
Andronikou 2019 (11)	Metatarsals 8; 22% Phalanges 3; 8% Calcaneus 4; 11% Talus 2; 5% Navicular 3; 8% Cuneiforms 8%	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

CRMO: Chronic Recurrent Multifocal Osteomyelitis; WBMRI: Whole-body Magnetic Resonance Imaging.

Supplementary Table S6: Summary of papers reporting involvement of the epiphysis in children with CRMO

References	Epiphysis comment
Anderson 2003 (48)	Single case from 3 - Multiple epiphyseal and metaphyseal regions, right shoulder, left wrist, right hip, right tibia, right distal femoral condyle, left sternoclavicular joint, fourth costosternal joint, left talocalcaneal joint, T8, left T3/4 costovertebral joint, left mid-tarsus, right first metatarsal
Fritz 2009(6)	In 101 patients In tubular bones (70 anatomic sites), metaphysis (86%, 60 of 70) and epiphysis (67%, 47 of 70) were involved.
Beck 2010 (18)	Single patient - Further lesions are seen in the metaphyses of both proximal and distal femurs, proximal tibias and fibulas predominantly in the epiphyses/metaphyses
Guérin-Pfyffer 2012 (15)	'Both metaphysis and epiphysis of long bones were involved'
Costa-Reis 2013 (5)	It can affect all bones, but lesions usually occur at the metaphyses and epiphyses of long bones, with a predilection for the lower extremities
Habibi 2013 (49)	Case report This showed multiple areas of high-signal lesions involving distal femur, tibial metaphyses and epiphyses , distal fibulae, bilateral sacral alae, distal right radius, bilateral medial clavicles and collapse of multiple cervical and thoracic vertebral bodies
Ract 2015 (50)	Single patient with metaphyseal abnormality spreading to epiphysis
Moussa 2017 (47)	One patient had epiphyseal lesions and metaphyseal involvement.
Arnoldi 2017 (14)	Of 33 patients - The most common anatomic locations were long tubular bones (85 % metaphyseal, 46 % epiphyseal , 7 % diaphyseal)
Andronikou 2019 (11)	35% of all lesions were epiphyseal Commonest site was the distal metaphysis (42% of long bone lesions), except at the humerus, where the proximal metaphysis was more common