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Whole Body MRI in the Diagnosis of Paediatric CNO/CRMO

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ABSTRACT

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

KEYWORDS: Chronic recurrent multifocal osteomyelitis, children, whole-body magnetic resonance imaging, osteomyelitis, autoinflammatory

KEY MESSAGE

Whole-body MRI protocols for CRMO must include the spine, the hands and feet.

CRMO patterns on WBMRI include multifocal predominantly tibial or clavicular-spinal distribution.

Radiologists need to be aware of the mimickers pitfalls of Whole-body MRI in CRMO.

INTRODUCTION

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).

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).

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 physeal closure.

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

and research results, radiologists should be performing similar WBMRI exams regarding sequences and planes of imaging while also keeping scan times appropriate for children. Beyond performing the examination in the same way, radiologists should be aware which signs are most diagnostic, what a typical CRMO lesion looks like and report it in a comparable manner. In order to predict outcome, scoring systems should not only incorporate lesion burden but also reflect susceptibility for growth disturbance and deformity.

WBMRI is already established for use in CRMO because it has further advantages over localised imaging, in that it can reveal multifocal disease (increasing the likelihood of CRMO), including silent (non-painful) lesions that may have characteristic features of CRMO when the sentinel lesion has non-specific features. Furthermore, having images of the whole skeleton helps to demonstrate patterns of skeletal involvement characteristic of CRMO, e.g. 'bilateral, symmetric pattern' (2), 'tibia multi-appendicular pattern' or 'clavicle pauci-axial pattern' (11), and helps quantify the disease in terms of lesion load (number of lesions in a patient) and lesion severity (e.g. vertebral collapse, proportion of physis involved) for prognosis.

Having established the role of WBMRI in CRMO, technical considerations must be optimised both for minimising the time spent on the scanner and for improving sensitivity of detecting lesions and relevant complications. Despite reports of 40-minute scan times, the addition of sagittal imaging of the spine and diffusion weighted imaging (DWI) can extend scan times by up to and beyond 90 minutes. The radiologist's role in imaging interpretation must also be optimised, by validating characteristic MRI features and patterns of CRMO, highlighting pitfalls and mimickers (such as carpal and tarsal high signal foci), improving prognostication from MRI through determination of lesion 'activity' (signal intensities), lesion load (lesions per patient, scoring systems), lesion extent (proportional metaphyseal, epiphyseal and paraphyseal involvement) and lastly through standardised reporting for improved data collection and diagnosis.

This review summarises current knowledge with regard to important technical aspects and image interpretation of WBMRI for paediatric CRMO, previously presented in abstract format (12)

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

visualisation (2). Arnoldi et al go further in recommending routine sagittal plane scanning with T1WI and STIR, resulting in an additional scanning time of 11 minutes (14). The whole spine can usually be covered with 2 overlapping sagittal sections (1).

Routine additional imaging of the spine in the sagittal plane is important because spinal involvement should be considered a classic feature of CRMO (3). Damasio reported the spine as 'the most frequent radiologically involved skeletal segment' (13). Arnoldi et al reported "regular spine involvement of nearly a fifth" of their cohort and highlighted the role that WBMRI findings can have in management of CRMO (14). Numerous publications report spinal involvement: 8.4% (18), 19% (11) 20% (19), 26% (20), 29% (3), 33 % (13). CRMO involves the thoracic spine predominantly, followed by lumbar, cervical and sacral portions of the spine (5, 11, 21).

Furthermore, identification of spinal involvement is important because vertebral height loss is reported as the most common location of pathologic fracture in CRMO (21, 22) (**Figure 2b**). Falip et al reported vertebra plana in 22% of their patients (3) while Wipff et all reported the risk of vertebral fracture from CRMO lesions as 17.5% (23). Detecting spinal involvement early, is therefore important for preventing vertebral body fracture and resultant vertebra plana (1, 3, 5, 21) (16, 22) because vertebral height is not regained after treatment in CRMO (3, 21, 24). It follows that adequate imaging of the spine should therefore occur at the subclinical stage so that aggressive treatment (e.g. bisphosphonates) can be initiated to prevent deformity (kyphosis and scoliosis) (5, 20, 25).

Sequences for WBMRI in CRMO

WBMRI is intended to serve as a screening examination for revealing bone marrow oedema and therefore uses STIR as the default imaging sequence (17). There is also currently strong support for the use of T1 weighted images and recent papers reported using additional DWI in CRMO (11, 13). Few authors use additional T2 sequences and only occasionally are regional post contrast images performed. A summary of the sequences reported for use in WBMRI of CRMO is provided in **Supplementary Table S2,** available at *Rheumatology* online. Damasio et al report that T1-weighted sequences are essential in imaging CRMO (13). This is because T1 hyperintensity on unenhanced

sequences may suggest an alternate diagnosis including fat, blood products and proteinaceous material (22). T1 is most useful in CRMO for differentiating true lesions from normal bone marrow conversion (13). Differentiation of red (haematopoietic) marrow from a CRMO lesion may not be possible with STIR imaging alone as both can have a moderately high signal. T1 assists the radiologist because **red marrow is of intermediate signal on T1** while **CRMO lesions have a low T1 signal** (26). Considering the extended scan times, especially with the routine addition of sagittal imaging, T1 could be added for problem solving on a lesion by lesion basis, until sequence times are improved all around.

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

abdomen and to include them in the abdominal or pelvic portion of the WBMRI or to place the hands under buttocks during the pelvic portion of the WBMRI (**Figure 3b**) as described by Andronikou et al (11) thereby splaying the hands and avoiding air-skin interface artefact. Note should be made that according to Avenarius et al, joint fluid, bone marrow oedema-like changes, and ganglion cysts may mimic pathologic abnormalities in the paediatric wrist (31).

CRMO is more common in the small bones of the feet than in the hands (21) occurring in around 40% of CRMO cases (**Supplementary Table S5**, available at *Rheumatology* online). The calcaneus and talus, which are metaphyseal equivalents, are reported to be involved most often (21) and while most papers report that the metatarsals are only rarely involved in CRMO, Andronikou et al reported abnormality involving the metatarsals in 22% of patients (11). A poor anatomical match in the feet can justify targeted MRI (14) which includes an optional sagittal scan of each foot (17). Purposefully positioning both feet in the lateral view (**Figure 3c**) is an optional solution for the last station of a WBMRI (11) or adding a sagittal scan of the feet to improve visualisation of the talus and calcaneus. Most important is to note that MR signal abnormalities of the talus and calcaneus may not be pathological (**Figure 3d**) and need to be considered alongside other lesion identified and clinical findings (6, 32). Our own experience with WBMRI protocols and technical considerations is discussed in a prior publication (11).

IMAGING INTERPRETATION

Classic MRI CRMO lesions

Two main imaging features of CRMO are multi-focality and the involvement of specific skeletal sites. These characteristic sites include the juxtaphyseal/periphyseal portions of the tibia and femur, the clavicle and thoracolumbar spine (5, 14)(1, 6, 25, 33)(3, 4). *Clavicular* involvement is expected to comprise 30% of all CRMO lesions (21) and is reported as the most common non-neoplastic cause of a clavicular lesion in children and adolescents (21). These lesions typically involve the medial third of the clavicle with marked periosteal reaction, soft-tissue signal abnormality and hyperostosis (3, 21) (**Figure 4 a-c**). The clavicle is an atypical location for bacterial osteomyelitis,

and as such, an inflammatory lesion in this location on MRI is highly suggestive of CRMO (3, 5, 14). Hence, even when unifocal, clavicular lesions in children and adolescents are sufficient to meet the Bristol criteria for CRMO (19, 25, 33).

Tibial involvement occurs in up to 71% and femoral involvement in up to 47% of patients (**Figure 5a**) (1). Von Kalle et al suggested that because individual lesions are non-specific in CRMO, particular combinations of multi-focal skeletal sites may offer 'diagnostic patterns' (2). They reported that '*three quarters of the diagnoses in their patients could have been made through identification of multifocal, hyperintense 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). This typical phenotypic pattern of distribution was also noted by Fritz et al who reported that multifocal symmetric lesions in the lower extremities were important (6). Khanna et al also reported bilateral tibial disease as being common (21) (**Figure 5b**). Andronikou and colleagues identified two distinct patterns of involvement in CRMO using WBMRI: a more common *tibio-appendicular multi-focal pattern seen in more than half of children with CRMO, presenting with* tibial lesions, multifocal involvement and **no** clavicular involvement; and a *claviculo-spinal pauci-focal* pattern*, seen in a third of children with CRMO and presenting with* clavicular lesions and few other, mainly spinal, lesions with no tibial involvement (11).

Spinal involvement has more recently been recognised as a classic CRMO feature, and in contrast to older studies it is currently considered one of the most common sites of involvement (3) with a reported prevalence of up to 30% (5, 23). The thoracic spine is reported to be involved most often (5, 21) (Hospach 60%; Falip et al 75%) (3, 20) (**Figure 2a and b**).

Spinal lesions show altered MR signal intensity of the vertebral marrow and endplate irregularity (3, 21, 22). Spinal involvement is also reported to be multifocal in two thirds of cases which is further support for using WBMRI (2, 3). An important aspect of spinal CRMO, is the possibility for complications such as vertebral fractures (2). When multifocal, CRMO of the spine typically involves non-contiguous vertebrae without crossing the disc - this is considered the distinguishing feature of CRMO from an infectious spondylodiscitis (3, 21, 22). However,

involvement of the disc in some patients has prompted a description of spinal CRMO as a spondylodiscitis (22). Falip et al reported disc involvement in 2 of 9 patients with spinal involvement (22%) and recorded contiguous vertebral involvement in 1 patient (11%) (3) while Andronikou et al reported disc involvement in 14% of patients (5 of their 7 patients with vertebral involvement) (11).

According to the Bristol criteria, CRMO lesions are diagnosed irrespective of their location, preferably by STIR MRI and typically show bone marrow oedema, bone expansion, lytic areas and periosteal reaction (33). Lesions are also described as ranging from **'**ill-defined' to 'confluent' bone marrow oedema (6, 14). **More subjective descriptions of** peri-physeal CRMO lesions include 'veld-fire' appearance with 'flames' projecting into the metaphyses (**Figure 5c**) (11). Periosteal reaction is part of the spectrum of the disease (6, 11, 14, 21) with 11% of patients demonstrating periosteal reaction in the study by Andronikou et al (11), as is soft-tissue inflammation (reported in up to 52% of children) which can be marked, mimicking a soft-tissue mass (3, 21).

Epiphyseal and Physeal Involvement

There are ten reports mentioning involvement of the epiphysis in children with CRMO (**Supplementary Table S6**, available at *Rheumatology* online). Andronikou et al reported 35% epiphyseal involvement (11), Arnoldi et al in 46% (14) and Fritz et al in 67% of long bone sites in children with CRMO (6). However, epiphyseal lesions without involvement of the metaphysis are not currently considered 'classic' CRMO lesions.

Two reports also specifically describe physeal involvement by CRMO on MRI in a way that suggests growth arrest may occur as a complication: Falip et al described a pseudo-widening growth plate of the distal fibula (3) and Khanna et al described radiological crossing of the physis in CRMO (21) (**Figure 5d**). In addition to isolated reports of leg length discrepancy (34) a paper by Huber et al describes a series of children with growth disturbances resulting from CRMO (35). These authors reported significant bony deformities either important for cosmetic or functional reasons in 11/ 23 (48%) patients with CRMO, presumably due to early physeal closure, but there is no correlation with imaging in this report (35). Physeal and epiphyseal lesions should be reported individually and should

have additional weighting in future scoring systems because of the possibility of complicating with deformity.

Mimickers: Carpal / Tarsal high signal

High signal in the metatarsals, tarsals and carpals should be treated with caution because of the likelihood this represents a normal variant (31, 32) (**Figure 3d**). Therefore, recording of potential lesions in the carpal and tarsal bones should continue but not be attached a full weighting towards lesion load or be considered diagnostic on their own [i.e. without the presence of one or more other classic lesions].

Mimickers: vertebral end-plate / disc involvement

23 papers have reported data of CRMO involvement of spine in children, with incidence ranging from 2-43% (more often between 20% and 35%) (**Supplementary Table S7**, available at *Rheumatology* online, summarises 20 of those with available data). Exams should only be considered adequate when they have excluded spinal involvement (5). Lesions that may mimic CRMO of the spine range from abnormal vertebral body signal to end-plate irregularity and complications of CRMO that may cause confusion with other pathology include sub-endplate fracture, height loss and vertebra plana (5) (21) (**Figure 3**). According to Jansen et al, nearly half of the patients with vertebral fractures develop scoliosis (36).

The most typical spinal manifestation resembles spondylodiscitis, describing signal abnormality in the vertebral body, endplate irregularity and extension into the disc (11, 22) with disc signal abnormality or height loss (21). Therefore, differentiating CRMO spinal lesions from bacterial spondylitis and spondylodiscitis may be difficult (2). However, only rarely in CRMO are there reports of disease crossing a disc to involve contiguous vertebrae, which differentiates CRMO from infectious discitis (5) (21, 24).

Periosteal reaction is reported accompanying spinal CRMO, but identification of any paravertebral mass should suggest a different diagnosis (37) (2, 24). CRMO should therefore be

included in the differential diagnosis when vertebral end-plate and discs disease are identified i.e. in the differential diagnosis of a spondylodiscitis.

Mimickers: enchondral ossification related to cyclical bisphosphonate therapy

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

Scoring systems and recording of disease burden

The RINBO scoring system is the only dedicated scoring system proposed for WBMRI findings of CRMO (14). It has been shown to be a significant predictor for the presence of clinically active lesions, which supports the idea of RINBO offering a means to grade the intensity of disease and to simplify the evaluation of progression, stability or remission during the course of the disease (14). The RINBO score allocates points (to a maximum of 10) according to increasing numbers of lesions (out of a 3-point scale), increasing size of lesions (out of a 3-point scale), any acute or chronic inflammatory reactions of the periosteum / soft tissues (1 point for each) and for any vertebral body signal and deformation (1 point for each) (14). The creators of the score, indicate that the purpose of RINBO 'is to encourage standardized reporting, improve reproducibility and ease stratification of WBMRI findings' to improve therapeutic decisions (14). However, considering that clinical activity is already evident through visual analogue scaled (VAS) scores, the usefulness of correlating the RINBO score with clinically active lesions is not clear (14). This is especially because patients

present with pain, and management is customised to this pain. From a prognostic perspective, only spinal involvement is weighted into the score, whereas from a diagnostic perspective, no weighting is given to the likelihood of CRMO based on the distribution pattern (14).

Future iterations of RINBO or an alternative scoring system should aim to correlate with outcome (i.e. deformity), for it to be used as a prognostic tool. To this end, the likelihood of future physeal fusion with growth restriction / deformity and possibility for vertebral collapse/spinal deformity should be weighted into the score. Furthermore, the scoring system should provide weighting depending on whether lesions are 'classic', 'probable' and 'possible' and downgrade carpal/tarsal bone signal abnormalities. A standardised reporting system could also reflect lesion load and spinal involvement in more detail than RINBO currently does, (e.g. actual lesion load rather than categories of lesions numbers as recorded in RINBO).

To achieve this one of the several anatomic maps have been published to demonstrate proportional lesion distribution in CRMO, which may also be used to record individual findings and may assist in revealing diagnostic and prognostic distributional patterns of disease (2, 6, 11, 23, 29, 43). Such a pictorial tick-sheet could assist in revealing WBRMI distribution patterns and inform modifications of scoring systems to indicate the likelihood of CRMO as the diagnosis. Phenotypic groupings (e.g. by Wipff et al and Andronikou et al) have not only correlated with severity of inflammatory disease but were also linked to outcome, likelihood of response to treatment and relapse rates, and include details of peri-physeal lesions which should in turn influence scoring (11, 23). Most clinicians who have expertise in CRMO currently use WBMRI to prognosticate on need for immunomodulatory therapies (e.g., pamidronate or anti-TNF) and depending on sites involved potential long-term outcomes at least after 6 -12 months of treatment to assess response. WBMRI remains for clinicians, in the absence of other clinical or laboratory markers, the most important tool to help in management of children and adolescents with CRMO.

Finally, work is in progress for developing artificial intelligence platforms for automated lesion detection from MRI, scoring and decision making, but the numbers of children with CRMO and

issues with ground truth especially when trying to differentiate lesions from normal marrow without biopsy, are proving to be obstacles at the initial stages.

CONCLUSION

WBMRI has found its role in the diagnosis and management of CRMO in children. This review summarises technical aspects to assist diagnosis while keeping scan times practical and describes MRI features of CRMO. Sagittal STIR imaging of the spine should be routine in CRMO while improved imaging of the hands and feet can be achieved by simple positioning manoeuvres. T1 can be used to differentiate pathology from normal red marrow in children. Important areas to highlight, include that CRMO lesions are not only metaphyseal but also epiphyseal and physeal, because these can cause growth disturbance and deformity; that spinal lesions are common and important because they cause vertebral collapse; that there are typical CRMO patterns on WBMRI including multifocal tibial pattern (bilateral, symmetric metaphyseal lesions, around the knee) and the paucifocal pattern with few lesions involving the clavicles and spine, with predictable presentation and course of disease. The review also highlights important WBMRI pitfalls such as marrow signal, metaphyseal signal appearances early on in bisphosphonate therapy and signal in the hands and feet.

Using a pictorial reporting format for recording both first-time and follow-up of CRMO lesions on WBMRI can be partnered with a scoring system that reflects not only the lesion load but also the lesion distribution and likelihood for growth disturbance / deformity.

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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 show 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.

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.

Figure 4 Coronal STIR WBMRI demonstrating clavicular involvement considered characteristic of CRMO

(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

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

(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

lesion in the left tibial metaphysis (*black arrow*). Note that while the (physeal) aspect of the signal abnormality is well defined, the internal (diaphyseal) margin is not.

(d) Coronal STIR providing a distal tibial view of a CRMO lesion involving the metaphysis and epiphysis of the right distal tibia with destructive changes involving the physis itself, concerning for a future growth disturbance or deformity.

Figure 6 Metaphyseal bands associated with pamidronate therapy

(a) Coronal STIR WBMRI in a child who received pamidronate treatment for the first time, demonstrating a symmetric thick band of high signal in the distal femoral metaphyses (*thin arrows*), separable from the thinner linear band of high signal of the physis (*thick arrows*). The non-physeal aspect of the signal has a sharp margin, which differentiates this from the 'veld-fire' appearance or 'flame-shaped' CRMO lesions. It is thought that this represents the visible expanded zone of endochondral ossification (present early on in Pamidronate therapy), which has a reported high signal on T2.

(b) A coronal STIR image from a WBMRI study in a patient with CRMO who received a single dose of pamidronate demonstrates a typical Pamidronate line which is seen as a thin, low-signal linear band mirroring the metaphyseal edge (*arrow*), which (as a result of growth) has migrated some distance away from the physis (a high signal band).

(c) A coronal STIR image from a WBMRI study in a patient with CRMO who received multiple, evenly-spaced, doses of pamidronate. The image demonstrates the typical zebra-line pattern (*rectangle*). Note that the last course was some time previously, as noted by the large distance between the most distal pamidronate line and the high signal physis (*arrow*).

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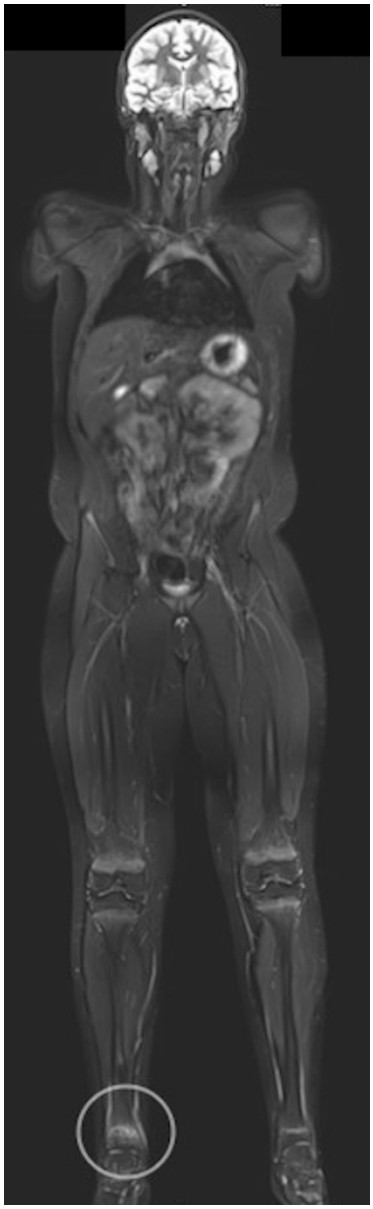

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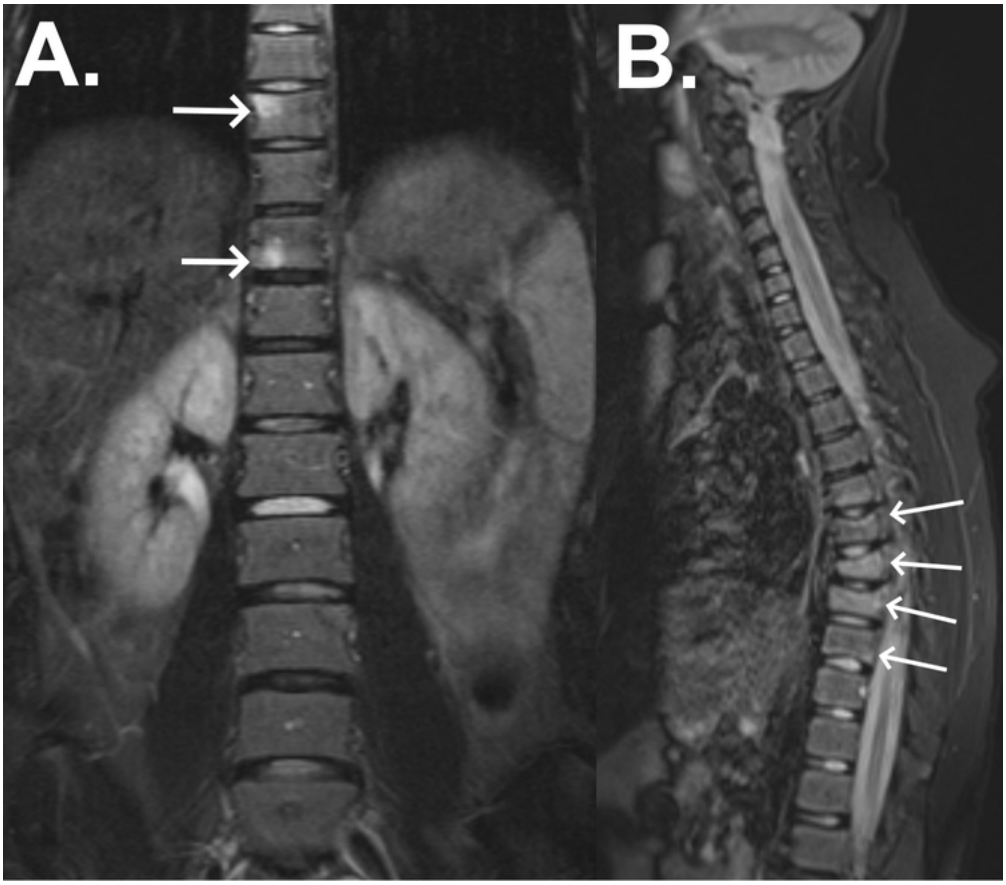

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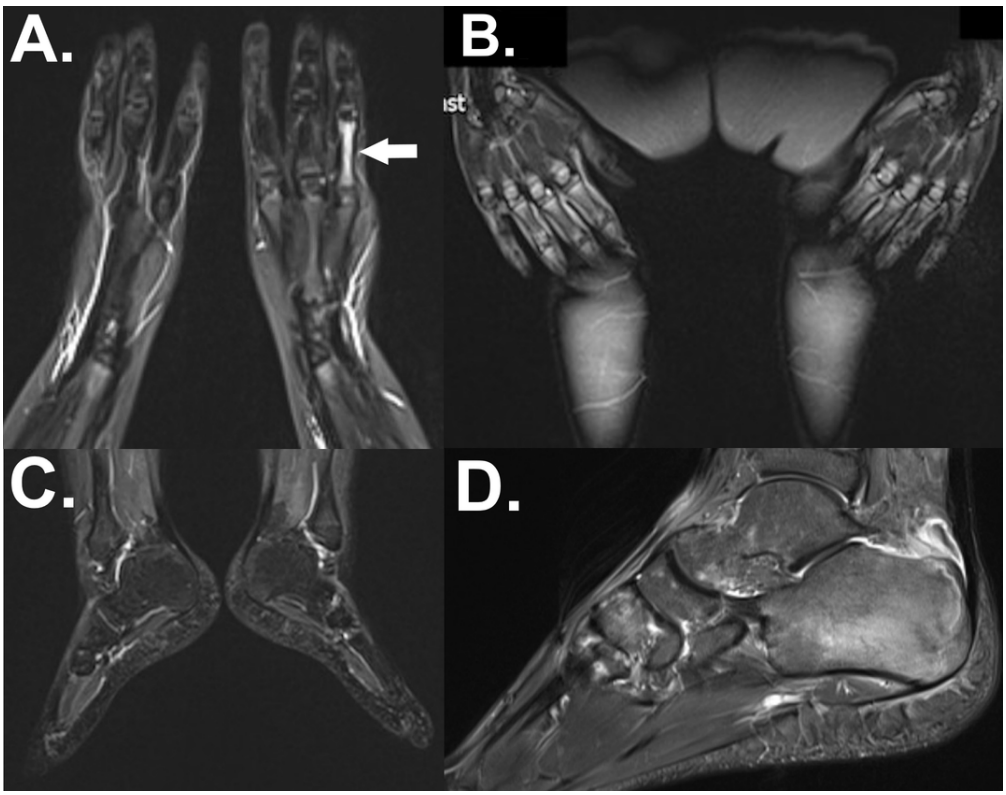

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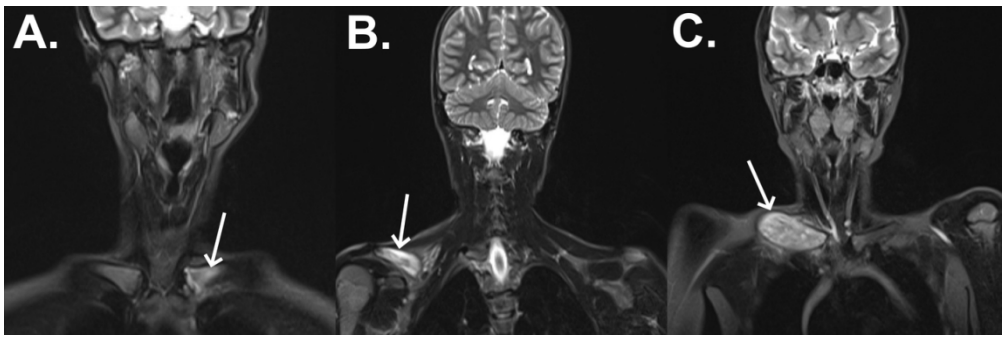

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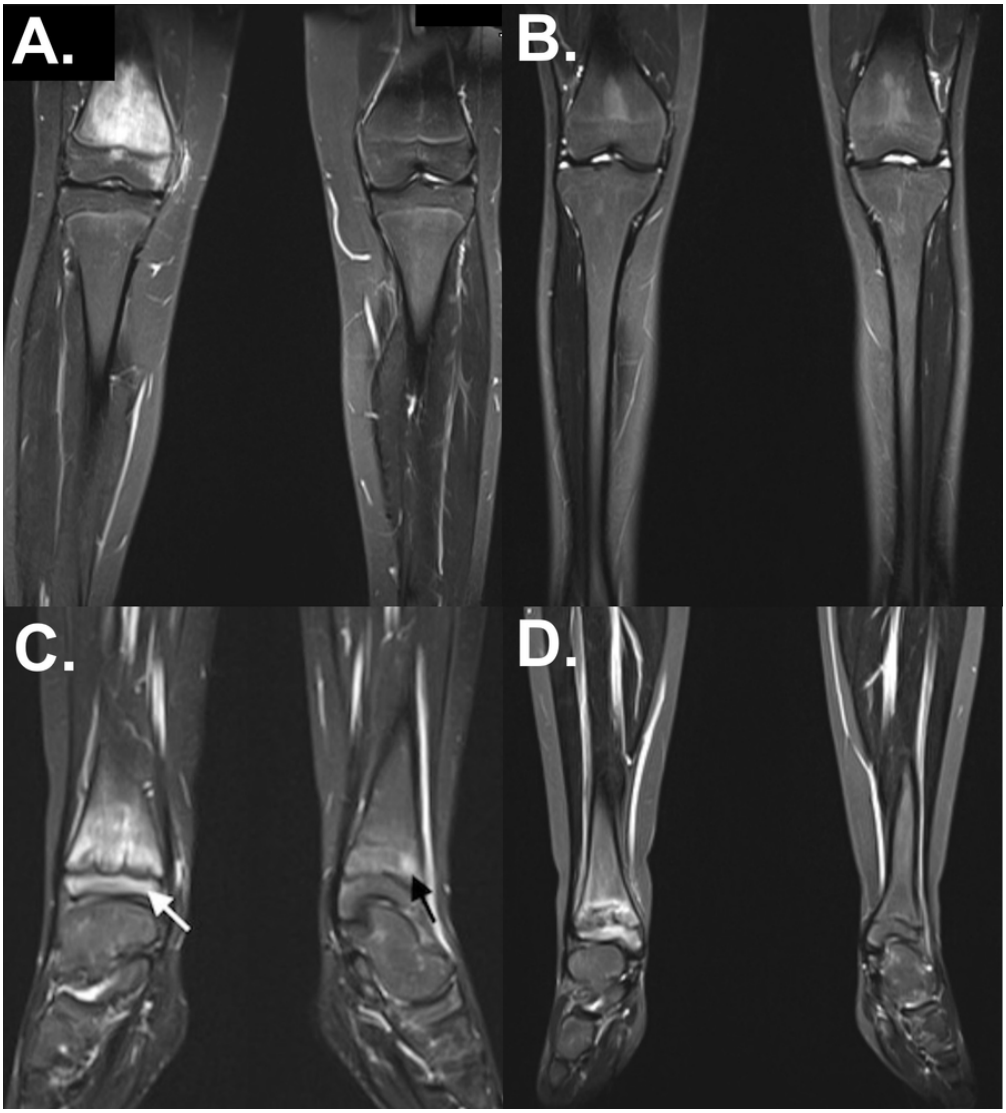

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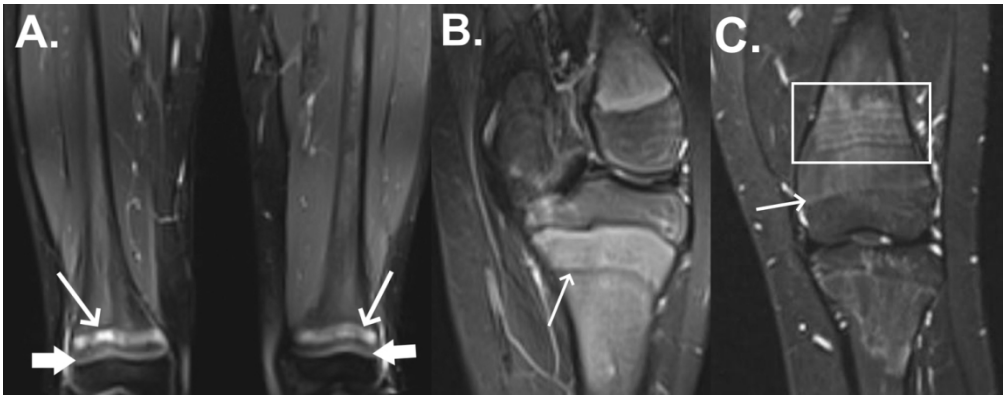

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SUPPLEMENTAL MATERIAL

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 Coronal T1 Sagittal STIR	480x336mm 480x336mm 400x400mm	320x259 384x307 384x326	5-6 stations 2 sections	
Leclair 2016 (16)	Coronal STIR	500x500mm	448x336	6-8 depending on height	Paper mainly on DWI
Merlini 2017 (28)	Coronal STIR Coronal T1	448x448mm 400x400mm	300x320 360x360	'According to size'	General paper on WBMRI in children
Andronikou 2019 (11)	Coronal STIR		450X310	5-7 depending on height	

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

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

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

References	DWI plane	Whole body?	Technique used, if specified	ADC	Result	Comments
Neubauer 2012 (27)	Axial (8 additional sagittal and coronal)	Regional only	B values: 0-50, 800-1000, Slice 6mm 1.5 and 3T	Yes	DWI can reliably detect and characterise lesions Sagittal and coronal images had marked artefact (distortion and ghost artefact) Limited in-plane resolution	Only 13 of 52 with CRMO Some with non-specific marrow oedema and arthritis
Leclair 2016 (16)	Axial	Whole body	B values: 800 3T, slice 4mm reconstructed in coronal plane 5mm and as thick 3d MIP	Yes Used ADC ratio to normal side	ADC values substantially elevated in CRMO lesions, Problems with artefact (2 patients DWI non-diagnostic)	16 patients Did not look at sensitivity of DWI compared to STIR Only used to help characterise Useful as additional scan 12-16min scan time
Merlini 2017 (28)	Axial	Whole body		No	DWI did not enhance lesion conspicuity compared to STIR	General paper on WBMRI in children only 8 children with CRMO (n=54)
Arnoldi 2017 (14)	Axial	Not known	B values: 800	?	Not presented	Mention of DWI in the discussion; showed high signal in some lesions when performed; suggest inclusion in future
Andronikou 2019 (11)	Axial	Whole body	**Head:** 7,400 ms TR, 89 ms TE, B-values of 0 and 800, 230x230 mm FOV, 25 section of 4 mm thick with a 1.2 mm gap **Body:** 5,320 ms TR, 64 ms TE, B-values of 0 and 800, 300x420mm FOV, 40 sections of 4 mm thick with a 0.4 mm gap.	No		Not used for analysis

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

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. Both measures entail adding an imaging stage and thus, increase the scan duration.
Khanna 2009 (21)	Review	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 5th, tarsals 6th, calcaneus 7th and metatarsals 9th 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