



Whole body magnetic resonance imaging in healthy children and adolescents

Bone marrow appearances of the appendicular skeleton

Pia K. Zadig^{a,b}, Elisabeth von Brandis^{d,e}, Berit Flatø^{e,f}, Lil-Sofie Ording Müller^d, Ellen B. Nordal^{b,c}, Laura Tantarri de Horatio^{b,g}, Karen Rosendahl^{a,b}, Derk F.M. Avenarius^{a,b,*}

^a Department of Radiology, University Hospital of North-Norway, Tromsø, Norway

^b Department of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway

^c Department of Pediatrics, University Hospital of North-Norway, Tromsø, Norway

^d Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway

^e Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

^f Department of Rheumatology, Oslo University Hospital, Oslo, Norway

^g Department of Pediatric Radiology, Ospedale Pediatrico Bambino Gesù, Rome, Italy

ARTICLE INFO

Keywords:

Whole-body magnetic resonance imaging
Bone marrow
Children
Adolescents
Healthy individuals

ABSTRACT

Objective: To describe the appearances of bone marrow in the appendicular skeleton on fat-suppressed T2-weighted sequences as assessed by whole-body MRI in healthy and asymptomatic children and adolescents.

Material and methods: Following ethical approval, we assessed the bone marrow of the extremities on water-only Dixon T2-weighted images as part of a whole-body MRI in 196 healthy and asymptomatic children aged 5–19 years. Based on a newly devised and validated scoring system, we graded intensity (0–2 scale) and extension (1–4 scale) of focal high signal bone marrow areas, and divided them into minor or major findings, based on intensity and extension, reflecting their potential conspicuousness in a clinical setting.

Results: In the upper extremity, we registered 366 areas with increased signal whereof 79 were major findings. In the lower extremities there were 675 areas of increased signal of which 340 were major findings. Hundred-and-fifteen (58.79%) individuals had at least one major finding, mainly located in the hand and proximal humerus, and the feet and knees. We found no differences according to gender, reported hours of sports activity, handedness, or age group, except for more minor findings in the upper extremities amongst 15–18-year-olds as compared to those aged 5–8 years.

Conclusion: Focal areas of high signal intensity on whole-body MRI, T2-weighted fat suppressed images that, in a clinical setting could cause concern, were seen in more than half of healthy, asymptomatic children and adolescents. Awareness of this is important when interpreting whole-body MRI in this age group, particularly in the assessment of clinically silent lesions.

1. Key points

- Whole Body Magnetic Resonance Imaging of healthy individuals reveals many areas of increased bone marrow signal that can resemble pathology.
- Certain patterns of increased bone marrow signal are more often seen than others in healthy individuals.

2. Introduction

Whole-body MRI is increasingly being used in the evaluation of bone marrow pathologies in children and adolescents, such as inflammatory diseases, malignancies, and fractures [1]. There is no unifying protocol for whole-body MRI, but fat suppressed T2 weighted (T2W) with or without T1 weighted (T1W) series are most frequently used [1]. For detection of bone marrow lesions, fat-suppressed T2W-sequences are sometimes applied as the only sequence in a whole-body protocol [1–3].

* Corresponding author at: Department of Radiology, University Hospital of North-Norway, Tromsø, Norway.

E-mail address: derk.avenarius@unn.no (D.F.M. Avenarius).

<https://doi.org/10.1016/j.ejrad.2022.110365>

Received 25 February 2022; Received in revised form 28 April 2022; Accepted 14 May 2022

Available online 20 May 2022

0720-048X/© 2022 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Focal areas of increased bone marrow signal on T2W fat-suppressed images are nonspecific and may represent both pathology and normal growth-related changes. Previous studies have shown that focal T2W hyperintensities in hands, feet, and knees of healthy children may mimic pathology [4–7]. The lower extremities are frequently involved in diseases with bone marrow affection [8–10]. Bone marrow lesions might be asymptomatic, particularly in inflammatory disorders, e.g., chronic non-bacterial osteomyelitis and juvenile spondyloarthritis [11,12], and the ability of whole-body MRI to detect these clinically silent lesions has been emphasized by several authors [11,13,14]. However, the risk of false positive findings in the growing skeleton is rarely mentioned [1] and to the best of our knowledge no previous studies addressing the appearances of the bone marrow based on a whole-body MRI in healthy children and adolescents has been published. The aim of this study was therefore to assess the appearances of bone marrow that may mimic pathology in the appendicular skeleton in healthy, asymptomatic volunteers aged 5–19 years. The axial skeleton is addressed in a separate paper.

3. Materials and methods

3.1. Study design and subjects

This is a prospective, cross-sectional, multicenter study including healthy children and adolescents aged 5–19 years, residing in southern or northern Norway. The study was performed at the Departments of Radiology, University Hospital North Norway (UNN) and Oslo University Hospital (OUS). From November 2018 to February 2020, eligible individuals were invited to undergo a whole-body MR examination. The study was approved by the Regional Ethics Committee (REK; no 2016/1696) and written informed consent was obtained from all the participating individuals and/or their caregivers.

Excluded were individuals having contraindications to MRI, a history of cancer, current infection, chronic or systemic disease, metabolic or musculoskeletal disorder, or a symptomatic trauma within the past four weeks. Also excluded were individuals with musculoskeletal complaints impairing everyday activity and/or necessitating a consultation by a physician within the last six months. Self-reported sport-activities and hours of physical exercise per week were registered, as was height, weight and handedness.

None of the participating individuals reported on disease or symptoms from the musculoskeletal system when contacted within 18 months after the first examination. Children with the most conspicuous nonspecific bone marrow hyperintensities were invited to undergo a dedicated follow-up MRI. Standard ethical practice for research in healthy individuals was followed and incidental findings were managed according to proposed guidelines in the literature [15,16].

3.2. Image protocol

All the included individuals had a whole-body 1.5 T MRI, unседated, with free breathing (Philips medical systems, Best the Netherlands, Inera model release 2.3. or Magnetom Siemens Aera, software e11c). The protocol included a coronal scan from the skull-base to toes in 3–5 steps, with the following sequences: T1W, Dixon T2W and diffusion-weighted (DWI) sequences (b50 and b1000). The calvarium was included in 81 examinations. During the examination the child could either listen to music or watch a movie and total scan time was approximately 30–45 min. The imaging protocol is available online (Supplement 1).

3.3. Image analysis

Prior to this study, we developed and validated a child specific scoring system for bone marrow, with signal intensity on a 0–2 scale and signal extension on a 0–4 scale being the more reliable features, with

moderate to good kappa values for both inter- and intra-observer variability [17]. MR-images of the lower limbs were analyzed in consensus by two radiologists at UNN (PZ/DA, with 6 and 20 years of experience in pediatric radiology, respectively), while the upper limbs were analyzed by two radiologists at OUS (EvB/LSOM, both with 15 years of experience in pediatric radiology), using high resolution screens. Based on the water-only Dixon T2W images, the location, signal intensity and extension of high signal intensity areas (as compared to the fatty marrow) in the bone marrow was registered for the long bones (diaphysis, metaphysis and epiphysis), trochanter major, patella, and for the hands and feet (phalanges / metatarsals / tarsals), and scored as follows: a) signal intensity on a 0–2 scale (0 = absent, 1 = mildly increased, 2 = moderately increased up to fluid-like signal compared to fatty marrow, and b) extension on a 1–4 scale (1 = < 5% followed by increments of 1/3 of the volume of the bone segment). All available images and reconstructions (T1W, fat-only Dixon T2W, DWI, ADC) were used for further description of findings, when necessary, to secure protocolled follow-ups. High signal intensity areas were grouped into major or minor findings (Table 1) where “major findings” are more likely to cause concern in a clinical setting. Symmetry of high signal intensity areas and high signal intensity in the periosteum and/or adjacent soft tissue, was registered.

In the long tubular bones, high signal intensity areas with a speckled appearance in the epi-, meta-, or diaphysis (defined as two or more roundish/punctuated high signals, size 2–5 mm) was scored as a separate feature and defined as major findings.

A punctate high signal pattern in carpals or tarsals (multiple signal foci with a diameter less than 5 mm) were scored, in the carpals as present or not and in the tarsals graded on a 0–2 scale (0 = absent, 1 = mild, 2 = extensive). These punctate signals were not included in the definition of major or minor findings. Additional areas of increased signal with a diameter more than 5 mm were scored separately and divided into major and minor findings.

Hyperintensities with specific features, i.e., findings suggestive of desmoid, fibroxanthoma, bone cyst, osteochondral lesion, enchondroma, or hyperintensities related to a patella bipartita, were registered and scored as a high signal intensity area as described above, but a note was made to be able to differentiate these findings from the remainder high signal areas.

Focal high signal areas in the long bones, centered at the physis and extending into both the adjacent metaphysis and epiphysis, previously described as focal periphyseal edema (FOPE) [7], were registered as separate features, and not scored according to intensity grade or extension.

Diffusely increased signal intensity in the epi-, meta-, and diaphysis, thin and/or punctate (<2 mm) high signal intensities in the epiphysis of long bones, high signal intensity along the calcaneal apophysis and, vessel like, vertical high signal lines in the diaphysis of the long bones were noted but not included in further analysis. Suboptimal visualized areas due to artifacts were registered and excluded from the analysis.

3.4. Statistical analysis

Descriptive statistics were reported as numbers with percentages, means with standard deviations or medians with IQRs, where

Table 1

Subclassification of MRI-findings into minor or major on water-only Dixon T2W images, based on signal intensity on a 0–2 scale and signal extension on a 0–4 scale.

	Signal intensity on a 0–2 scale / extension on a 0–4 scale
Major MRI findings	-Signal intensity 1 and extension 3–4 or -Signal intensity 2 and extension 2–4
Minor MRI findings	-Signal intensity 1 and extension < 3, or -Signal intensity 2 and extension < 2

appropriate. Differences in the number of high signal intensity findings between genders and according to handedness were examined using Mann-Whitney-*U* test, while differences according to four age groups (5–9, 10–12, 13–15, 16–19 years), sport activity (none, 1–2 h per week, 3–6 h or 7–15 h) and localisation were examined using Kruskal-Wallis test. Pearson Chi-Square test was used to explore differences in the location of major and minor findings in the lower extremities (femur, patella, tibia, fibula, hindfoot, midfoot, metatarsals, phalanges) across the four age groups. Information on sport activity for Norwegian adolescents aged 6–18 years was retrieved from the Statistics Norway [18]. All statistical analyses were performed using Predictive Analytics Software (SPSS) version 27 (IBM, Armonk, NY), and a *p*-value < 0.05 was considered statistically significant.

4. Results

A total of 196 individuals (101 females, 51.5%), mean age 12 years (SD 3.6), with 47–52 individuals per age group, were included. Demographic details on the study cohort as compared to the general population are listed in Table 2.

A total of 971 high signal areas were identified, of which 419 were classified as major findings and 552 as minor. The distribution according to age group is listed in Table 3.

There were no differences in the total number of high signal intensity areas according to gender (*p* = 0.787 lower limb, *p* = 0.057 upper limb), thus, the results were pooled. No differences in the number of high signal intensity areas were found according to sports activity, neither for the lower limb (*p* = 0.730 for major and *p* = 0.558 for minor findings) nor for the upper limb (*p* = 0.761 and 0.841, respectively). For the lower extremities, although the total number of major findings peaked at 9–12 years of age and minor findings peaked at 13–15 years, no statistically differences were found across age groups (*p* = 0.054 for major and 0.584 for minor findings). For the upper limbs, no differences were found for major findings (*p* = 0.988), whilst there was a significant difference for minor findings (*p* = 0.042), with more findings amongst the 15–18-year-old as compared to those aged 5–8 years.

4.1. Lower extremities

In the lower extremities we identified a total of 674 high signal areas. Three-hundred-and-forty (50.4%) were defined as major findings, whereof 64 (18.8%) were symmetrically distributed according to side (Fig. 1). Two-hundred-and-seventeen major findings (63.8%) had signal intensity 2, whereof 35 (16.1%) had extension ≥ 3 , e.g. involvement of $\geq 1/3$ of the bone (15 midfoot bones, 7 metatarsals, 7 phalanges, 2 calcanei, 1 talus, 1 proximal tibial metaphysis and 1 distal fibular epiphysis (Figs. 2–5). Ninety-seven major findings (28.5%) were

Table 2

Demographic details on the healthy pediatric cohort compared to the general population.

Variables	Study subjects, n = 196	Data from Statistics Norway*
Oslo University Hospital / University Hospital North Norway, n (%)	78 (39.8%) / 118 (60.2%)	
Female, n (%)	101 (51.5%)	- 374,152 (48.8%) **
Age, years (range)	12.0 (6.0 – 18.9)	- (6.0–15.0)
Median BMI, kg/m ² (range)	18 (13–30)	18 (-)
Sports-activity at least once a week, n (%)	167 (85%)	- (84% – 89%)

*Statistics Norway, Helseforhold, levekårsundersøkelsen. Statistisk Sentralbyrå, statistikkbanken.

<https://www.ssb.no/statbank/table/06658>. Accessed 24. May 2021.

**<https://www.ssb.no/a/barnogunge/2020/tabeller/befolkning/bef0000.html>. Age 6–17.

Table 3

High signal areas on water-only Dixon T2W images in the appendicular skeleton in 196 healthy children and adolescents by age group.

	5–9 years (n = 47)	10–12 years (n = 52)	13–15 years (n = 47)	16–19 years (n = 50)	Total (n = 196)
Major findings (upper extremity)	88 (15)	124 (11)	119 (29)	88 (24)	419 (79)
Minor findings (upper extremity)	72 (40)	89 (60)	90 (53)	83 (62)	552 (215)

speckled appearances (Fig. 3a,b) in the epi-, meta and/or diaphysis of which 72 (74.2%) were symmetrically distributed in both extremities (Fig. 4b,c).

Hundred-and-fifteen out of 196 (58.79%) subjects had at least one major finding (median 1.0, IQR = 3), with the majority located in the feet (142/340, 41.8%), the proximal tibia (52/340, 15.3%) distal femur (51/340, 15.0%) and distal tibia (46/340, 13.5%) (Fig. 1a). There was a statistically significant association between localization and age group (*p* < 0.001), with calcaneus, talus, midfoot and proximal tibia predominating in children aged 5–12 years as compared to distal femur, proximal tibia and metatarsals in children between 13 and 15 years and phalanges in those over 15 years (Fig. 2a).

A total of 137 (69.9%) subjects had at least one minor finding (median 1.0, IQR = 3) with a similar distribution as for major findings. The majority were in the metatarsals, proximal tibia, and distal femur epi-, and metaphyses, again; with a statistically significant association between localisation and age group (*p* = 0.009).

A punctate high signal pattern in the tarsals was registered in 136/185 (73.5% %) individuals; of which 75 (55.1%) were graded as mild and 61 (44.9%) as severe. The distribution was always symmetrical according to side and was, with exception of two individuals, not observed in individuals older than 15 years.

There were 21 major and 33 minor findings in or around specific findings such as patella bipartita (2 major), desmoids (1 major, 21 minor), osteochondral defects (3 major, 4 minor), fibroxanthoma (7 major, 3 minor), bone cysts (7 major, 4 minor) and enchondromas (1 major, 1 minor).

4.2. Upper extremities

In the upper extremities we identified a total of 294 high signal intensity areas. Seventy-nine (26.9%) were defined as major findings, whereof 5 were symmetrically distributed. Twenty-seven major findings (34.2%) had signal intensity 2, whereof 10 had extension ≥ 3 (4 metacarpals, 2 phalanges, 2 proximal humerus epiphysis, 1 proximal humerus metaphysis and 1 proximal radius epiphysis) (Fig. 1b).

Twenty-eight out of 196 subjects (14.3%), had at least one major finding (median 0.0, IQR = 1). with the majority located in the humerus (27/79, 34.2%), either in the proximal epiphysis (12), proximal metaphysis (10) or in the diaphysis (5). Thirty-five (44.3%) of the major findings were in the hand with no differences between age-groups (Fig. 6).

118 subjects (60.2%) had at least one minor finding (median 1.0, IQR = 2), distributed in a similar pattern as for major findings.

A punctate high signal-pattern in the wrist bones was registered in 118/153 (77.1%) children and was always bilateral, symmetrical and with no differences according to age. One major finding, in the proximal humerus epiphysis, had a specific appearance consistent with an enchondroma.

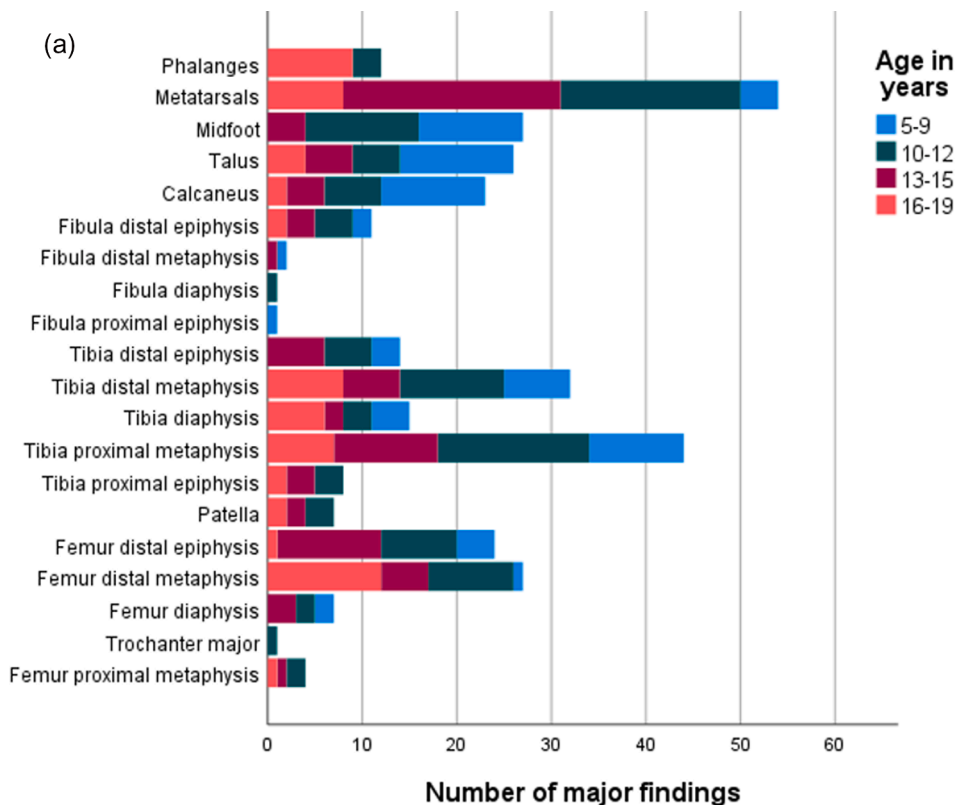
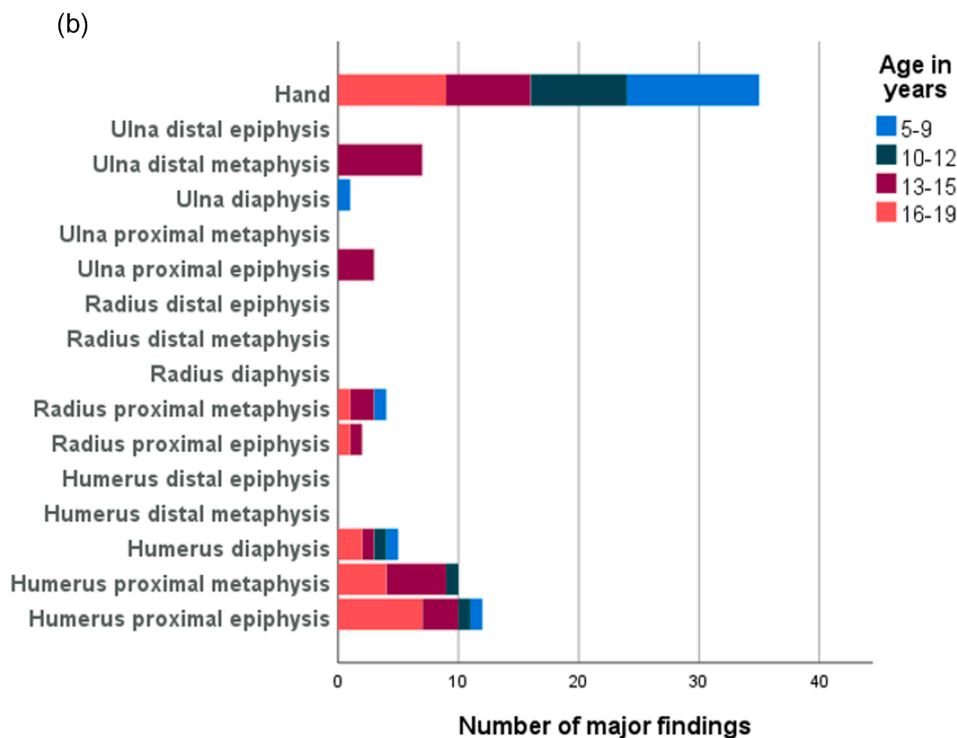


Fig. 1. a and b: Number and distribution of major findings (based on T2-w Dixon water only images) by anatomical area in 196 healthy volunteers aged 5–19 years. a; Lower extremities (n = 340 major findings, including areas of speckled appearance in the long bones and findings with a specific appearance) and b; upper extremities (n = 79 major findings). For the lower extremities, 50 (26%) forefeet, 24 (10%) hind feet, 20 (10%) distal legs, 16 (8%) distal femur / proximal leg, and 14 (7%) proximal femur were hampered by artifacts, and thus excluded from the analysis. For the upper limbs, the figures were 48 (24.5%) hand, 83 (42.3%) ulna, 71 (36.2%) radius, and 54 (27.6%) humerus, respectively.



4.3. Periphyseal edema (FOPE) in the extremities

A total of 156 FOPEs were found in 79 subjects, with a maximal number of 5 in one individual and maximum of three in the same anatomical area. The majority were seen in the proximal tibia (112) and distal femur (30) (Fig. 2d). We registered three FOPEs in the distal tibia,

4 in the proximal fibula and 6 in the distal fibula. Only one FOPE was registered in the upper extremities, located in the proximal humerus. We found FOPE-like lesions in all age-groups with a median age of 12.8 (IQR = 5.3). High signal in the periosteum /soft tissues was seen adjacent to four major lesions and two minor lesions in the lower extremities and to one major lesion in the upper extremities (Figs. 2b, 3d, 5a,b).

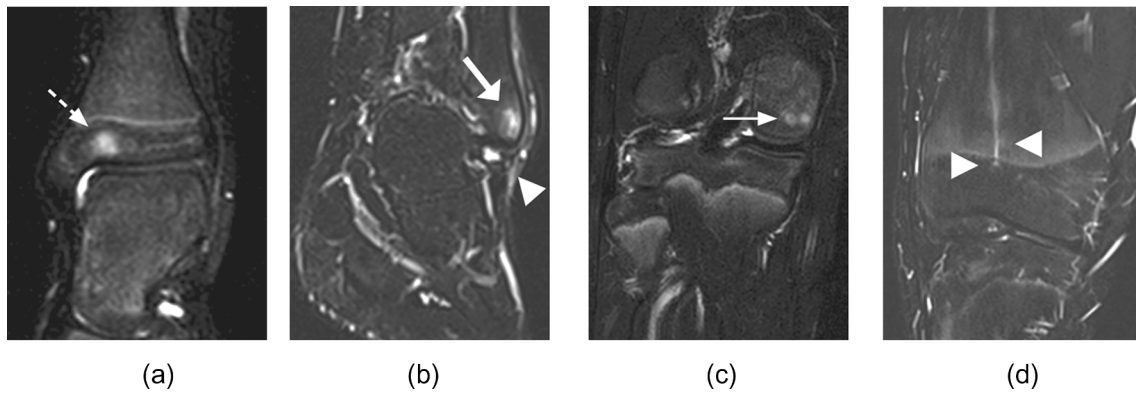


Fig. 2. a) 8-year-old boy with a high signal intensity area in the distal tibia epiphysis (dashed arrow). b) 17-year-old girl with a high signal intensity areal in the distal fibula epiphysis (thick arrow), and increased signal in the adjacent subcutaneous tissue (small arrowhead) c) 16-year-old boy with two round high signal intensity areas in the medial femur epiphysis (thin arrow) d) 17-year-old boy with a high signal intensity area on both sides of the epiphysis consistent with a FOPE (arrow heads).

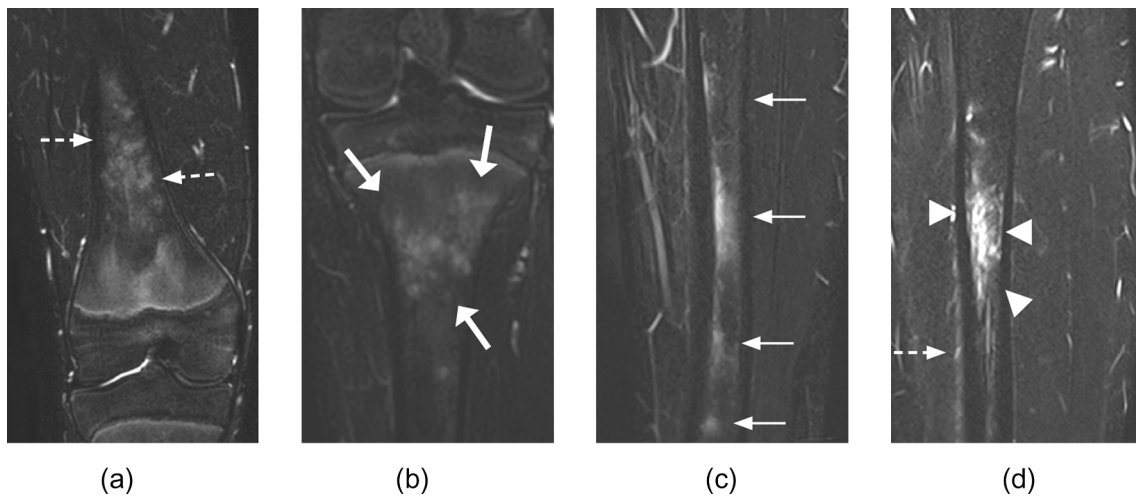


Fig. 3. a) Coronal water-only Dixon T2W image of the distal femur shows hyperintense signal with an inhomogeneous, flame shaped pattern in the metaphysis and a speckled appearance in the distal diaphysis (dashed arrows) in a 16-year old boy. b) 12-year-old girl with speckled appearance of high signal intensity areas in the proximal tibia metaphysis (thick arrows) c) 15-year-old boy with a high signal intensity area in the diaphysis of the tibia (thin arrows) d) Example of a major finding with an extensive and symmetrical distribution in a 16-year-old girl (arrowheads), and increased signal from the periosteum (dotted arrow).



Fig. 4. a)15-year-old boy with a major finding in the right proximal epiphysis (dashed arrow). b)14-year-old girl with extensive symmetrical areas of increased bone marrow signal in the metaphysis(arrows) c)16-year-old girl with symmetrically distributed increased signal in both tibia diaphysis(arrowheads).

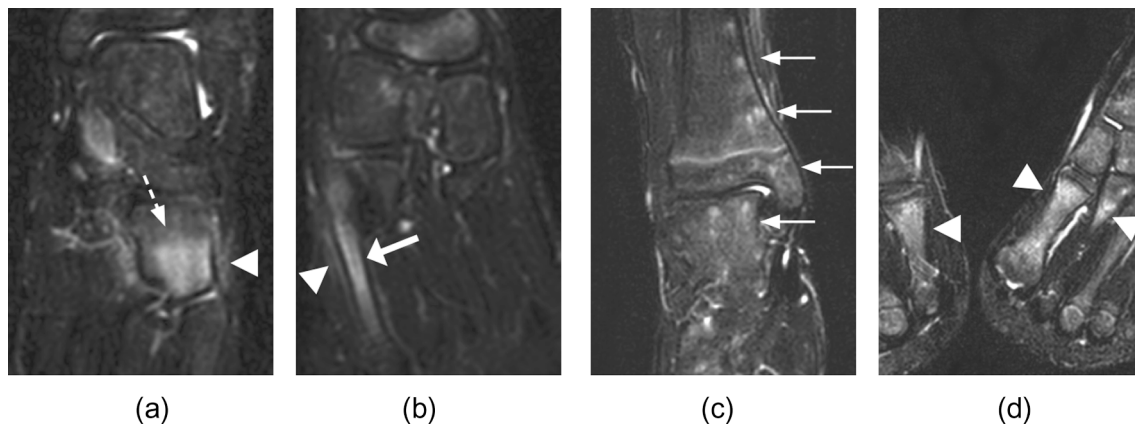


Fig. 5. a) 6-year-old girl with a high signal intensity area in the cuboid bone (dashed arrow), and increased signal from nearby subcutaneous tissue (small arrowhead) b) 7-year-old girl with a high signal intensity area from the fifth metatarsal bone (thick arrow), and increased signal from the periosteum (small arrowhead) c) 12-year-old girl with speckled high signal intensity in the tarsal bones, the tibia epiphysis, and the distal tibial metaphysis (thin arrows) d) 12-year-old boy with a high signal intensity area within both first metatarsal bones and base of left second metatarsal bone (arrowheads).

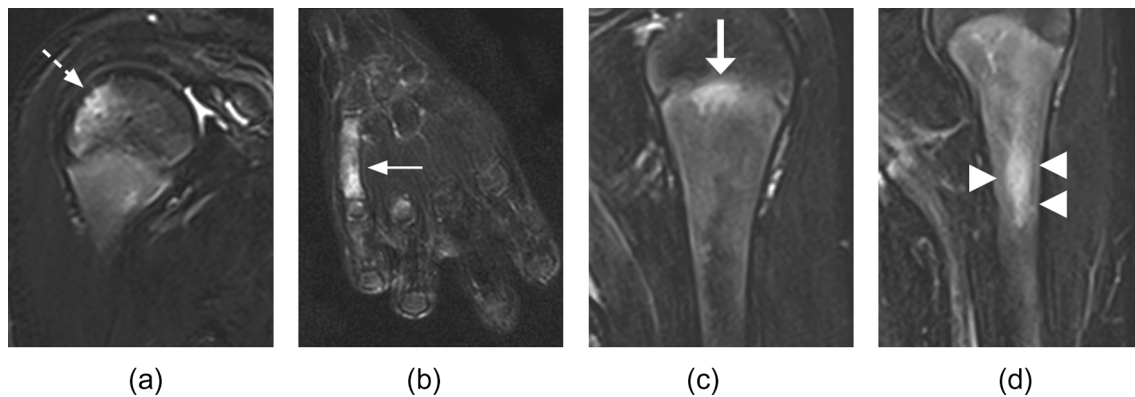


Fig. 6. Coronal water-only Dixon T2W image of the of the proximal humerus in: a) a 7-year-old boy, showing a major finding in the lateral part of the epiphysis (dashed arrow), b) a 7-year-old boy with a major finding involving the whole fifth metacarpal bone (thin arrow), c) a 14-year-old boy with a major finding in the proximal humerus metaphysis (thick arrow) and d) a 10-year-old boy with a major finding in the proximal humeral diaphysis (arrowheads).

5. Discussion

We have shown that a high proportion of healthy, symptom-free children and adolescents have at least one major high signal finding in the extremities, of which most are in the feet or around the knees. Periosteal reaction was rarely seen. There were no statistically significant differences in the total number of high signal intensity areas according to age, gender, level of sports activity or handedness, however, for the lower extremities the numbers of major findings peaked at 10–12 years of age and minor findings peaked at 14–16 years of age.

We believe our study cohort to represent the general population as those included were recruited from two different cities, sharing common characteristics with the general population such as gender, BMI and level of sports activity. On the other hand, the study did not fulfill the strict criteria of a population-based study.

The MRI appearances of bone marrow in children differs from that in adults. The process of conversion from red to yellow bone marrow occurs throughout childhood in a well-known pattern [19,20]. In addition, the process of skeletal growth and ossification continues until skeletal maturation. The higher vascularization and pliability of the growing skeleton combined with a higher activity level as compared to adults, makes the pediatric skeleton more prone to physiological stress. All these processes may influence the bone marrow signal on MRI [21,22]. Diffuse, homogenous low-grade background signal was not scored in the present study. Other than this, except for the findings with specific features, an effort was made to perform an objective and unbiased

scoring of all focal inhomogeneous or patchy high signal areas.

A high proportion of major findings in the long bones of the lower extremities were located around the knees and were most common in the older age-groups (Figs. 2c, 4a, b). Patchy or inhomogeneous flame-shaped patterns of residual red bone marrow in the metaphysis of the knee is a normal finding in adolescents [19,20]. We also registered a higher number of major findings in the epiphysis of the knee in individuals aged 10–15 years (Fig. 1a). Such patterns may be indistinguishable from early inflammatory lesions in chronic non-bacterial osteomyelitis, typically found in the same age-group and at the same location [23].

A speckled pattern of high signal was frequently found in dia-, epi-, and most often the metaphysis of the long bones. This pattern is probably equivalent to what is previously described as focal islands of red marrow [19,21] but occasionally it had a striking appearance (Fig. 3a,b, 5c). Major findings with a more confluent appearance were commonly seen in the diaphysis, particularly in the tibia, and were often symmetrical and sometimes relatively extensive (Fig. 3c,d, 4c).

Our study showed numerous findings in the feet, whereof the majority were found in the metatarsals, more so in adolescents than in the younger age groups. Of particular interest was high-grade signal involving most of, or even the whole of metatarsals or phalanges (Fig. 5b,d). In a clinical context these findings could resemble osteitis as an early sign of tarsitis in juvenile enthesitis-related arthritis (ERA) [13,24] or inflammatory lesions in chronic non-bacterial osteomyelitis [25]. The frequent finding of metatarsal involvement contrasts with

previous reports addressing healthy individuals [6,26].

In the tarsals, major findings were most commonly found in the calcaneus and talus and in the younger age-groups. A punctate high signal pattern, occasionally quite pronounced and always symmetrical, was registered in most children up to 15 years of age. These results are similar to what was reported by Shabshin et al in 34 healthy subjects 0–18 years [6]. Occasionally the high-grade signal was confluent in one or several tarsal bones. Similar signal has recently been described as abnormal when present in the calcaneus or talus [25]. A 6-year-old girl had high-grade hyperintensity areas involving nearly the whole extent of the navicular and cuboid bones (Fig. 5a) She was asymptomatic, but on direct questioning her parents remembered a minor foot sprain 4 weeks earlier. This example highlights previous observations, that even an insignificant trauma may cause prominent T2W hyperintensities within the pediatric bone marrow [5,27].

Major findings in the long bones of the upper extremities were rare, and, when present, less frequently registered in the diaphysis than in the epi- or metaphysis (Fig. 6a,c,d). Analogously, the upper extremities are less commonly involved in disease processes than the lower extremities [8–10 28–30], and in inflammatory or infectious disorders, isolated involvement of the diaphysis is uncommon [8,31].

In agreement with previous studies on healthy children and adolescents, bone marrow hyperintensities in the hand were a common finding [4,5]. Occasionally the signal involved an entire metacarpal or phalanx (Fig. 6b), a finding that could be misinterpreted as pathology in patients with e.g., CNO, psoriatic arthritis, or as a manifestation of Raynaud phenomenon [32–34].

We identified high signal in or around several specific findings such as bipartite patellas, and osteochondral lesions in the talus, which, in a clinical setting, would suggest a clinically relevant lesion.

FOPE-like lesions were mainly found around the knees (Fig. 2d) and occasionally in the ankles, consistent with existing literature [7,35]. This finding is suggested to present early stages of physiologic physeal closure [7] which implies that also physes in other locations may be involved. FOPE has been reported to be a non-traumatic cause of pain [7,36,37]. In accordance with previous publications, the highest number of FOPEs were in the adolescent age-group [7], but we also found FOPE-like lesions in younger children. One individual had a FOPE-like lesion in the proximal humerus. To our knowledge, there exists no published data on FOPEs in the upper extremities. No detailed definition of FOPE exists which may explain slightly diverging published results regarding age distribution.

5.1. Limitations and strengths

There are some limitations to our study. First, there is an inherent subjective nature of the scoring process and standardization of the signal intensity scale on MRI [25,38]. The MRI-image is dependent on hardware, software and sequence parameters and may therefore differ between institutions. To reduce the risk of bias, we performed a meticulous calibration and validation of the scoring system prior to the study. Second, our definitions of minor and major findings may not correspond to the clinical significance in every case. Third, bone marrow hyperintensities with similar size and signal intensity may be weighted differently based on shape, contour, and location. Finally, the bone marrow may appear differently based on large field of view protocols as compared to focused protocols. However, the aim of this study was to describe the appearances of the bone marrow as assessed on whole-body MRI.

The strengths of our study were the prospective, population-based design, the large number of healthy volunteers and thorough calibration. Efforts were made to ensure that there were no underreported or underlying pathological conditions, both in terms of follow-up interviews and imaging.

6. Conclusion

Focal areas of high signal intensity are frequently seen on whole-body MRI, T2W fat suppressed images of healthy, asymptomatic children and adolescents. More than half had findings that could cause concern in a clinical setting, often in an asymmetrical distribution. Awareness of this is important when interpreting whole-body MRI in this age group, particularly in the assessment of clinically silent lesions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements:

We wish to thank Bac Nguyen, from Oslo University Hospital, for his help in MR sequence design, and Eddie-Andre Elde from the University Hospital of North Norway for his help in implementing and adjusting the local scan protocol.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejrad.2022.110365>.

References

- [1] P. Zadig, E. von Brandis, R.K. Lein, K. Rosendahl, D. Avenarius, L.S. Ording Müller, Whole-body magnetic resonance imaging in children - how and why? A systematic review, *Pediatr. Radiol.* (2020). doi: 10.1007/s00247-020-04735-9:11.
- [2] L. Merlini, M. Carpentier, S. Ferrey, M. Anoooshiravani, P.-A. Poletti, S. Hanquinet, Whole-body MRI in children: Would a 3D STIR sequence alone be sufficient for investigating common paediatric conditions? A comparative study, *Eur. J. Radiol.* 88 (2017) 155–162.
- [3] T.S. Sato, P.J. Ferguson, Whole-body MRI imaging is an essential tool in diagnosing and monitoring patients with sterile osteomyelitis, *J. Rheumatol.* 48 (5) (2021) 635–637.
- [4] D.F.M. Avenarius, L.-S. Ording Müller, K. Rosendahl, Joint fluid, bone marrow edemalike changes, and ganglion cysts in the pediatric wrist: features that may mimic pathologic abnormalities-follow-up of a healthy cohort, *AJR Am. J. Roentgenol.* 208 (6) (2017) 1352–1357.
- [5] L.-S. Müller, D. Avenarius, B. Damasio, O.P. Eldevik, C. Malattia, K. Lambot-Juhan, L. Tanturri, C.M. Owens, K. Rosendahl, The paediatric wrist revisited: redefining MR findings in healthy children, *Ann. Rheum. Dis.* 70 (4) (2011) 605–610.
- [6] N. Shabshin, M.E. Schweitzer, W.B. Morrison, J.A. Carrino, M.S. Keller, L. E. Grissom, High-signal T2 changes of the bone marrow of the foot and ankle in children: red marrow or traumatic changes? *Pediatr. Radiol.* 36 (7) (2006) 670–676.
- [7] A.M. Zbojniczewicz, T. Laor, Focal Periphyseal Edema (FOPE) zone on MRI of the adolescent knee: a potentially painful manifestation of physiologic physeal fusion? *AJR Am. J. Roentgenol.* 197 (4) (2011) 998–1004.
- [8] T.S. Sato, P. Watal, P.J. Ferguson, Imaging mimics of chronic recurrent multifocal osteomyelitis: avoiding pitfalls in a diagnosis of exclusion, *Pediatr. Radiol.* 50 (1) (2020) 124–136.
- [9] C. Jaimes, M. Jimenez, N. Shabshin, T. Laor, D. Jaramillo, Taking the stress out of evaluating stress injuries in children, *Radiographics* 32 (2) (2012) 537–555.
- [10] J.-L. Labbé, O. Peres, O. Leclair, R. Goulon, P. Scemama, F. Jourdel, C. Menager, B. Duparc, F. Lacassin, Acute osteomyelitis in children: the pathogenesis revisited? *Orthop. Traumatol. Surg. Res.* 96 (3) (2010) 268–275.
- [11] A.P. Arnoldi, C.L. Schlett, H. Douis, L.L. Geyer, A.M. Voit, F. Bleisteiner, A. F. Jansson, S. Weckbach, Whole-body MRI in patients with Non-bacterial Osteitis: radiological findings and correlation with clinical data, *Eur. Radiol.* 27 (6) (2017) 2391–2399.
- [12] A.C. Rachlis, P.S. Babyn, E. Lobo-Mueller, et al., Whole body magnetic resonance imaging in juvenile spondyloarthritis: Will it provide vital information compared to clinical exam alone? in: *Arthritis and Rheumatism Conference: Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals* 63.
- [13] M.R. Aquino, S.M.L. Tse, S. Gupta, A.C. Rachlis, J. Stimec, Whole-body MRI of juvenile spondyloarthritis: protocols and pictorial review of characteristic patterns, *Pediatr. Radiol.* 45 (5) (2015) 754–762.
- [14] A. Schnabel, U. Range, G. Hahn, T. Siepmann, R. Berner, C.M. Hedrich, Unexpectedly high incidences of chronic non-bacterial as compared to bacterial osteomyelitis in children, *Rheumatol. Int.* 36 (12) (2016) 1737–1745.

- [15] T.C. Booth, A.D. Waldman, J.M. Wardlaw, S.A. Taylor, A. Jackson, Management of incidental findings during imaging research in “healthy” volunteers: current UK practice, *Br. J. Radiol.* 85 (1009) (2012) 11–21.
- [16] S.M. Wolf, F.P. Lawrenz, C.A. Nelson, J.P. Kahn, M.K. Cho, E.W. Clayton, J. G. Fletcher, M.K. Georgieff, D. Hammerschmidt, K. Hudson, J. Illes, V. Kapur, M. A. Keane, B.A. Koenig, B.S. LeRoy, E.G. McFarland, J. Paradise, L.S. Parker, S. F. Terry, B. Van Ness, B.S. Wilfond, Managing incidental findings in human subjects research: analysis and recommendations, *J. Law Med. Ethics* 36 (2) (2008) 219–248.
- [17] P. Zadig, E. von Brandis, P. d’Angelo, et al., Whole-body MRI in children aged 6-18 years. Reliability of identifying and grading high signal intensity changes within bone marrow. *Pediatr Radiol.* (2022). doi: 10.1007/s00247-022-05312-y.
- [18] Statistics Norway, Helseforhold, levekårsundersøkelsen. Statistisk Sentralbyrå, statistikkbanken. Available at: <<https://www.ssb.no/statbank/table/06658>>. Accessed 24. May 2021.
- [19] A. Taccone, M. Oddone, A. Dell’Acqua, M. Occhi, M.A. Ciccone, MRI “road-map” of normal age-related bone marrow. II. Thorax, pelvis and extremities, *Pediatr. Radiol.* 25 (8) (1995) 596–606.
- [20] S.G. Moore, K.L. Dawson, Red and yellow marrow in the femur: age-related changes in appearance at MR imaging, *Radiology* 175 (1) (1990) 219–223.
- [21] T. Laor, D. Jaramillo, MR imaging insights into Skeletal maturation: what is normal? *Radiology* 250 (1) (2009) 28–38.
- [22] C. Jaimés, M. Jiménez, D. Marin, V. Ho-Fung, D. Jaramillo, The trochlear pre-ossification center: a normal developmental stage and potential pitfall on MR images, *Pediatr. Radiol.* 42 (11) (2012) 1364–1371.
- [23] Y. Zhao, P.J. Ferguson, Chronic nonbacterial osteomyelitis and chronic recurrent multifocal osteomyelitis in children, *Pediatr. Clin. North Am.* 65 (4) (2018) 783–800.
- [24] S. Phatak, N. Mohindra, A. Zanwar, A. Aggarwal, Prominent midfoot involvement in children with enthesitis-related arthritis category of juvenile idiopathic arthritis, *Clin. Rheumatol.* 36 (8) (2017) 1737–1745.
- [25] Y. Zhao, T.S. Sato, S.M. Nielsen, et al., Development of CROMRIS (ChRonic nonbacterial Osteomyelitis MRI Scoring) tool and evaluation of its interrater reliability, *J. Rheumatol.* 47 (2019) 739–747.
- [26] C.R. Pal, A.D. Tasker, S.J. Ostlere, M.S. Watson, Heterogeneous signal in bone marrow on MRI of children’s feet: a normal finding? *Skeletal Radiol.* 28 (5) (1999) 274–278.
- [27] R.B. Soder, J.D. Simões, J.B. Soder, M. Baldisserotto, MRI of the knee joint in asymptomatic adolescent soccer players: a controlled study, *AJR Am. J. Roentgenol.* 196 (1) (2011) W61–W65.
- [28] S.F. Baumbach, V. Pfahler, S. Bechtold-Dalla Pozza, I. Feist-Pagenstert, J. Fürmetz, A. Baur-Melnyk, U.C. Stumpf, M.M. Saller, A. Straube, R. Schmidmaier, J. Leipe, How we manage bone marrow edema-an interdisciplinary approach, *J. Clin. Med.* 9 (2) (2020) 551, <https://doi.org/10.3390/jcm9020551>.
- [29] P. d’Angelo, L.T. de Horatio, P. Toma, L.-S. Ording Müller, D. Avenarius, E. von Brandis, P. Zadig, I. Casazza, M. Pardeo, D. Pires-Marafon, M. Capponi, A. Insalaco, B. Fabrizio, K. Rosendahl, Chronic nonbacterial osteomyelitis - clinical and magnetic resonance imaging features, *Pediatr. Radiol.* 51 (2) (2021) 282–288.
- [30] S. Patel, Primary bone marrow oedema syndromes, *Rheumatology (Oxford)* 53 (5) (2014) 785–792.
- [31] D. Jaramillo, J.P. Dormans, J. Delgado, T. Laor, J.W. St Geme 3rd, Hematogenous osteomyelitis in infants and children: imaging of a changing disease, *Radiology* 283 (2017) 629–643.
- [32] S. Andronikou, J.K. Kraft, A.C. Offiah, et al., Whole-body MRI in the diagnosis of paediatric CNO/CRMO, *Rheumatology (Oxford)* 59 (2020) 2671–2680.
- [33] D. Spira, I. Kötter, J. Henes, J. Kümmerle-Deschner, M. Schulze, A. Boss, M. Horger, MRI findings in psoriatic arthritis of the hands, *AJR Am. J. Roentgenol.* 195 (5) (2010) 1187–1193.
- [34] E. Smitaman, B.P.G. Pereira, B.K. Huang, M.M. Zakhary, E. Fliszar, D.L. Resnick, Abnormal bone marrow signal intensity in the phalanges of the foot as a manifestation of raynaud phenomenon: a report of six patients, *AJR Am. J. Roentgenol.* 207 (6) (2016) 1252–1256.
- [35] W.R. Walter, L.H. Goldman, Z.S. Rosenberg, Pitfalls in MRI of the developing pediatric ankle, *Radiographics* 41 (1) (2021) 210–223.
- [36] E. Giles, A. Nicholson, M.S. Sharkey, C.W. Carter, Focal periphyseal edema: are we overtreating physiologic adolescent knee pain? *J. Am. Acad. Orthop. Surg. Glob Res. Rev.* 2 (4) (2018) e047, <https://doi.org/10.5435/JAAOSGlobal-D-17-00047>.
- [37] J.N. Speirs, T.G. Shields, M.J. Morrison, Focal periphyseal edema: an uncommon cause of adolescent knee pain: a report of three cases, *JBJS Case Connect* 9 (3) (2019) e0391.
- [38] L. Tanturri de Horatio, M.B. Damasio, D. Barbuti, C. Bracaglia, K. Lambot-Juhan, P. Boavida, L.-S. Ording Müller, C. Malattia, L. Ravà, K. Rosendahl, P. Tomà, MRI assessment of bone marrow in children with juvenile idiopathic arthritis: intra- and inter-observer variability, *Pediatr Radiol* 42 (6) (2012) 714–720.