Editorial

Quantification of Disease Activity in Chronic Nonbacterial Osteomyelitis by Whole-body Magnetic Resonance Imaging

Chronic nonbacterial osteitis (CNO), also termed chronic recurrent multifocal disease (CRMO), is a rare autoinflammatory disease characterized by recurrent flares of inflammatory bone pain related to aseptic osteomyelitis[1,2,3]. It usually affects children and adolescents and the clinical presentations range from mild and limited unifocal disease to severe chronic inflammation in multiple bones[4,5,6]. The long tubular bones of the lower extremities are most commonly involved, followed by the spine and the clavicles[2,3]; there may be extraskeletal skin and bowel manifestations such as palmoplantar pustulosis, psoriasis, and Crohn disease[7].

Diagnostic imaging in CNO relies on a multimodality approach usually consisting of radiography followed by magnetic resonance imaging (MRI)[2]. Because bone marrow edema (BME) is characteristic for active lesions, fat-saturated fluid sensitive MRI sequences such as short-tau inversion recovery (STIR) and T2-weighted fat-saturated sequence are ideal for detecting active lesions, whereas T1-weighted sequences are preferable for detecting chronic structural lesions[2]. The findings by MRI may, however, be nonspecific and the diagnosis is usually a diagnosis of exclusion after ruling out other diseases, such as infectious osteomyelitis and tumors or tumor-like lesions, based on clinical presentation, imaging, and if needed, culture-negative biopsy[1,7,8]. The combination of characteristic imaging findings are usually diagnostic[2,7], such as multiple bone lesions or characteristic metaphyseal lesions in the lower extremities, and clavicular or spinal osteitis with concomitant dermal changes.

To diagnose and monitor the extent of CNO in children/adolescents, a whole-body (WB)-MRI approach is advantageous because radiological disease activity may be underestimated clinically[1,5,9]. WB-MRI gives a simultaneous evaluation of the entire body without exposure to ionizing radiation, and in small children the number of needed MR examinations in sedation can be reduced. Multifocality and clinically silent lesions can be detected by WB-MRI[5]; this is valuable in the decision making regarding treatment and followup because clinical remission does not necessarily

mean radiological remission[9]. WB-MRI is therefore increasingly used to assess the total CNO activity. A valid/reliable scoring system for active as well as chronic lesions detectable by WB-MRI is therefore needed to stage as well as monitor the disease over time. A previous proposal for scoring CNO in children/adolescents by WB-MRI has mainly been based on the number and size of lesions and their anatomical locations[5]. Another scoring method, predominantly used to evaluate region-specific MRI, was more concentrated on CNO characteristics[10]. None of these methods has been validated. This may be due to some inherent difficulties in CNO evaluation related to the variable disease presentations such as a tibio/appendicular multifocal pattern, a claviculo/spinal paucifocal pattern, or mixed presentations[6]. Although the MR appearance of characteristic CNO lesions is well described in areas of predilection, all bones can potentially be involved and the appearance can vary considerably. It is therefore much more difficult to establish a scoring system for CNO lesions than for the rather homogeneous lesions occurring in axial spondyloarthritis[11,12] and rheumatoid arthritis[13].

In this issue of *The Journal*, Zhao, *et al*[14] present a method to score CNO lesions by WB-MRI mainly based on a standardized scoring/grading of the different characteristics of CNO lesions, irrespective of the bone involved. This chronic nonbacterial osteomyelitis MRI scoring (CROMRIS) system is based on CNO features previously used to score region-specific MRI[10], but with modifications developed in consensus by 11 pediatric radiologists from 7 different hospitals in North America and Europe. The following 4 CNO characteristics applicable for all CNO lesions were defined to be scored as shown in Table 1: bone marrow hyperintensity, signal size, soft tissue or periosteal hyperintensity, and bony expansion. The scoring of these features was supported by an atlas, encompassing representative MRI of active CNO lesions.

In addition, the following CNO manifestations were defined to be scored (Table 1): vertebral compression, kyphosis, limb hypertrophy, and joint effusion, and the

Table 1. Variables in the chronic nonbacterial osteomyelitis MRI scoring (CROMRIS) system[14].

CNO characteristics applicable for all CNO lesions	
Variables	Score values
Bone marrow hyperintensity	Absent, < fluid signal, and similar to fluid signal[#]
Signal size	Absent, < 25%, 25–50%, and > 50% of the bone involved
Soft tissue or periosteal hyperintensity	Absent or present
Bony expansion	Absent or present
Region-specific CNO features	
Variables of interest	Score values
Vertebral compression	Normal, some height loss, and vertebra plana
Kyphosis	Absent or present
Limb hypertrophy	Absent or present
Joint effusion	Absent or present
Grouping of bones	
Complex bones	Scapula, sacrum (combine S1–5 for each side), pelvis (ilium, periacetabulum, pubis/ischium), ribs, mandible, skull, patella, clavicle, divided into laterality (right and left side), and sternum (manubrium and sternal body)
Long bones	Humerus, ulna, radius, femur, tibia, fibula. These bones were divided anatomically into proximal epiphysis, proximal metaphysis, diaphysis, distal metaphysis, and distal epiphysis
Less-commonly affected bones	Hand: carpals, metacarpals, and phalanges; hindfoot: talus and calcaneus; fore/mid-foot: tarsals, metatarsals, phalanges
Spine	Sum of individual vertebral bodies from cervical to lumbar region with concomitant dichotomous scoring of abnormal signals within lateral and posterior spinal structures.

[#] Additional scoring of confidence level as low, medium, or high. CNO: chronic nonbacterial osteitis; MRI: magnetic resonance imaging.

bones were grouped into complex bones, long bones, less-commonly affected bones, and the spine.

The interrater agreement and reliability of the scoring system was tested by 11 readers based on 45 WB-MRI; 41 patients with CNO and 4 with other diseases. The results regarding the presence or absence of BME in the different regions are not given, but it is stated that there is a low absolute agreement of signal hyperintensity in the commonly affected bones (tibia and femur). Therefore, a predefined 70% agreement was used as a threshold to determine whether there was a "true" abnormal bone marrow signal. The absolute interrater agreement of the signal intensity of BME was low (< 60%) in more commonly affected bones such as the femur, tibia, fore/mid-foot, hind foot, and clavicle. Most of the low- and medium-confidence readings were from commonly affected sites such as femur, tibia, and foot, whereas the absolute agreement was near or greater than 80% in the majority of less-commonly affected bones. The agreement regarding the size of BME was in most segments of the femur and tibia lower than in other long bones. These relatively lower agreements regarding the most commonly involved sites indicate a need for further calibration regarding the detection of BME areas and scoring of their features for intensity and size. It is important to have a valid detection and grading of lesions in commonly affected bones, if the scoring system is used to monitor the disease over time, including to monitor the effect of therapy.

The authors are, however, to be congratulated on their effort and the resulting cross-sectional validation analysis, which is an important step toward a common scoring system in CNO.

The scoring system it a potential research tool, but may be too complicated to be used in clinical practice, where the standardized reporting of WB-MRI findings proposed by Arnoldi, et al[5] may be more feasible. Their radiologic index for nonbacterial osteitis (RINBO) includes the absolute size of active lesions and clustering the number of active lesions into 3 categories: unifocal, paucifocal (2–4 lesions), and multifocal (5 or more lesions; Table 2). Soft tissue inflammation, periosteal reaction, and hyperostosis were classified as extramedullary findings, and spinal involvement was divided into active with abnormal STIR signal and chronic lesions with deformation (Table 2)[5]. The use of a relative lesion size in CROMRIS is more appropriate for the pediatric population, indicating a need for modifications of the RINBO when used. Although less detailed, RINBO gives the possibility of estimating a total score of up to 10. This is not yet a feature of CROMRIS, because further studies were deemed necessary to determine the weight of each variable. A score taking all lesions into account is needed because the fluctuating course implies that new lesions may occur while others are vanishing[4,9].

Future studies within WB-MRI scoring methods in CNO should be focused on the following aspects:

Table 2. The radiologic index for WB-MRI in patients with CNO and RINBO[5].

Variables of Interest	RINBO Criterion	Value
No. of patient's radiologically active lesions (RAL)		
Unifocal	1	1
Paucifocal	2–4	2
Multifocal	≥ 5	3
Maximum size of patient's RAL		
Minor	< 10 mm	1
Average	10–100 mm	2
Major	> 1000 mm	3
Extramedullary involvement		
Acute	Periostal reaction and/or soft tissue edema	1
Chronic	Hyperostosis	1
Spinal involvement		1
Acute	Radiologically active vertebral lesion	1
Chronic	CNO-related vertebral body deformation	
Maximum index point		10

WB-MRI: whole-body magnetic resonance imaging; CNO: chronic nonbacterial osteitis; RINBO: radiologic index for nonbacterial osteitis.

(1) Validity and sensitivity to changes of CNO activity by WB-MRI in longitudinal studies

(2) Elaboration of a total score for radiological disease activity on a whole-body level

(3) Standardization of the WB-MRI protocol between pediatric centers.

There is currently no consensus among centers regarding protocols for pediatric WB-MRI, leading to divergent approaches and limiting comparison among centers[15]. Standardizing WB-MRI protocols will ease the implementation of uniform scoring. In this context, it is important to remember that a coronal STIR sequence can be regarded as an inverted bone scan, and may not alone be sufficient for CNO evaluation. A T1-weighted sequence will provide further information about the bone marrow, which often is needed to handle the major challenge defining thresholds for normality versus pathology in children taking the gradual conversion of the bone marrow into account[16].

A protocol consisting of coronal body slices in addition to sagittal imaging of the spine may have a low sensitivity regarding some anatomical structures such as the ribs and sternum[1]. This can probably be overcome by acquiring a 3-D STIR sequence with axial reconstructions[17] or performing an axial WB sequence[18]. In accordance with that practice, axial STIR or T2 fat-saturated sequence was obtained in over half of pediatric patients in North America, whereas coronal T1 was performed in about half of the patients[15].

A universal problem with WB-MRI is that the upper extremities may not be included in the scan field in large children. In an analysis by Arnoldi, *et al*, restricted coverage of the upper extremity occurred in 58% (n = 23) of the patients (15 elbow and 16 distal radius)[5]. It may therefore be necessary to perform additional sequences of the arms[1].

Functional MR techniques such as diffusion-weighted MRI (DWI), which is widely used in oncology[16], should be kept in mind. Although its reliability has not been assessed in patients with CNO, it has been shown that the DWI-apparent diffusion coefficient (ADC) values are significantly higher in lesions compared to normal reference tissue[19], and DWI can be used to differentiate CNO lesions from tumors with lower ADC values[19].

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