Chronic Recurrent Multifocal Osteomyelitis

The Prevalence of Lower-Limb and Foot Involvement

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Background: Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory condition. The lesions are reported to present most frequently in the long bones. This study aimed to review the presenting features of CRMO in a cohort of children diagnosed as having CRMO and to compare the level of agreement between the clinical and published diagnostic criteria.

Methods: A case notes review was undertaken of patients with a clinical diagnosis of CRMO. Patients were younger than 16 years at the time of diagnosis. Features were identified in each patient that agreed or disagreed with the published diagnostic criteria. The location of bone lesions in the lower limb at onset and disease progression was recorded.

Results: A total of 37 patients were included. There was a high prevalence in white individuals. Agreement with the diagnostic criteria of Jansson et al and El-Shanti and Ferguson was poor, with levels of agreement of 40.5% and 43%, respectively, and low kappa scores ($\kappa = 0.07$ and 0.09, respectively). The lower limb was affected in 49% of patients at onset and in 72% overall.

Conclusions: This study presents one of the largest published cohorts of pediatric patients with CRMO and also presents racial/ethnic group data that have not previously been reported in other studies. Despite being a condition considered to affect the metaphysis of long bones, the ankle area and foot bones were also frequently affected. The agreement between the clinical diagnosis and the published diagnostic criteria was weak. (J Am Podiatr Med Assoc 104(6): 583-587, 2014)

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, noninfectious autoinflammatory disorder. It is reported to have frequent associations with other inflammatory conditions, such as palmoplantar pustulosis, psoriasis, Crohn's disease, ulcerative colitis, and Sweet's syndrome.[1,2] The condition was first reported by Giedion et al[3] in 1972, who described a subacute and chronic symmetrical process comprising multiple lytic lesions affecting the metaphysis of long bones. The histopathologic findings of bone lesions from biopsy are regarded as the gold standard in the diagnosis of this condition because they will reveal the absence of infectious and malignant processes, although Girschick et al[4] stated that the diagnosis cannot be made by biopsy alone but requires a combination of the presenting clinical and radiographic features. Imaging on its own may not be able to exclude malignancies such as osteosarcoma or bacterial subacute osteomyelitis. The etiology currently remains unknown.

Nonbacterial osteitis (NBO) is an umbrella term that includes three subgroups, including CRMO. The classic clinical picture of CRMO is characterized by recurring and relapsing bone pain and fever. The onset is almost always insidious with pain and tenderness, whereas swelling and fever are not always present.[2] There is a strong female predominance, but racial/ethnic predominance has not been described. Although the primary site of disease is the long bones of the lower limb, other sites affected include the clavicle, pelvis, spine, mandibulae, and neighboring joints.[5] It is known that the foot bones can be affected in CRMO, with a large cohort study and several case studies identifying calcaneum, talus, and metatarsal lesions and tarsometatarsal joint lesions,[3,6-10] but the prevalence of lesions in other foot bones from a large cohort has

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not been reported. Acute and chronic NBO compose the other two subgroups of NBO. Acute NBO involves a single bone lesion, with symptoms lasting less than 6 months. Chronic NBO may have single or multiple sites, with persistent symptoms continuing for longer than 6 months.[11]

Imaging modalities, such as bone scintigraphy and whole-body magnetic resonance imaging (MRI), are valuable tools to detect the multiple sites involved, many of which may be silent, and thus help aid the clinical diagnosis, which is more difficult when a single symptomatic site presents. Imaging also helps determine the progression of the condition or the effect of treatment.[12]

A panel of diagnostic criteria was developed by Jansson et al,[11] who suggested that when few criteria were met, the diagnosis of NBO could more likely be reached; when a greater number of criteria were met, a diagnosis of CRMO would be more likely. Thus a threshold for diagnosis was set with NBO requiring the fulfilment of two major or one major plus three minor criteria for diagnosis and the diagnosis of CRMO being made when three major plus four minor criteria are met (Table 1). El-Shanti and Ferguson[2] later stated that for the diagnosis of classic CRMO, the following criteria should be met: multifocal bone lesions, prolonged clinical disease over several years with relapses and remissions, unresponsiveness to antimicrobial drug therapies, and radiologic findings evidencing multiple osteolytic foci surrounded by sclerosis.

Despite their initial development almost 10 years ago, the criteria proposed for CRMO have never been validated, and most cases presented in the literature seem to be labeled CRMO even when the condition has a single focus or is continuous without remitting. This study aimed to review the usefulness of the published diagnostic criteria when applied to a large cohort of children and to identify the prevalence of foot lesions in this population.

Table 1. Diagnostic Criteria for Nonbacterial Osteitis/ Chronic Recurrent Multifocal Osteomyelitis[11]

Major criteria
Radiologically proven osteolytic/sclerotic bone lesion
Multifocal bone lesions
Palmoplantar pustulosis or psoriasis
Sterile bone biopsy with signs of inflammation or fibrosis, sclerosis
Minor criteria
Normal blood cell count and good general health
C-reactive protein level and erythrocyte sedimentation rate mildly to moderately elevated
Observation time longer than 6 months
Hyperostosis
Associated with other autoimmune diseases apart from palmoplantar pustulosis or psoriasis
Grade I or II relatives with other autoimmune or autoinflammatory disease or with nonbacterial osteitis

Methods

Approval for the retrospective case note review was granted by the Great Ormond Street Hospital for Sick Children (London, England) institutional ethics review board. A computer search of medical correspondence for all patients registered with the rheumatology team at Great Ormond Street Hospital for Sick Children was undertaken using the search terms *chronic recurrent multifocal osteomyelitis* and *CRMO*. The correspondence was reviewed to exclude patients with a diagnosis of other conditions. The medical records of the remaining identified patients were accessed and scrutinized. Patients were included in the study if they were younger than 16 years at the time of diagnosis and if a diagnosis of CRMO was made by a pediatric rheumatologist. All identifiable information was anonymized. Data were collected for age at onset, sex, and racial/ethnic group, as well as for the criteria suggested by Jansson et al[11] and El-Shanti and Ferguson.[2] The sites of the initial presenting lesion and of later lesions as the disease progressed and associated joint swelling were recorded. The recorded site of pain or swelling was identified by clinical records rather than from imaging reports.

Percentage agreement was used to analyze agreement between the published diagnostic criteria and clinical diagnosis. The kappa coefficient was calculated for the level of agreement for categorical data (yes/no agreement).[13]

Results

The computer search of medical correspondence identified 47 potential participants extending over 13 years. Of these patients, five were excluded owing to having a diagnosis other than CRMO as stated in the electronic information. Medical records were sought for 42 patients, and, of these, two sets of medical records were missing. Three additional patients were excluded owing to an early change in diagnosis to SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) syndrome (two patients) and juvenile idiopathic arthritis (one patient). The remaining 37 patients were

included in the study, including four whose diagnosis was considered CRMO initially but was changed to "unlikely" at a later stage of their management, although a further diagnosis was not made.

The cohort included 17 boys and 20 girls. Age at onset ranged from 4 to 14 years, with a mean age of 9.2 years. All of the patients had disease for greater than 6 months. The cohort was predominantly from a white UK racial/ethnic group (n = 29), with a minority from a white European racial/ethnic background (n = 3) or African and Arabic backgrounds (n = 3). In two cases, the racial/ethnic group was not stated in the medical records.

Comparison was made between the symptoms presented in the medical records and the diagnostic criteria published in the literature and was tested using percentage level of agreement and the kappa coefficient. The number of patients meeting each diagnostic criterion is given in Table 2. The patients generally showed good agreement with the major criteria suggested by Jansson et al[11] to the level where nearly all of the patients fulfilled the criteria for NBO; the minor criteria were less likely to be met. For example, in most cases there was a radiologically proven osteolytic/sclerotic lesion seen on radiographs or MRIs, but in one case, only a bone scan seemed to have been performed, and, therefore, the specific radiologic criteria was not fulfilled. Most patients had multifocal lesions, although nine (24%) were unifocal, affecting the clavicle, mandible, ilium spine, femur, or tibia. The major criterion of palmoplantar pustulosis or psoriasis was met in only five patients, with all of these patients presenting with psoriasis. Sterile bone biopsy was not undertaken in four patients despite it being considered the gold standard for diagnosis. In these cases, the biopsy was reported as unnecessary owing to other obvious clinical features. Overall, the level of agreement for the diagnostic criteria for CRMO and the clinical diagnosis was 40.5%, with a poor kappa score ($\kappa = 0.07$).[13]

The diagnostic features published by El-Shanti and Ferguson[2] generally performed well, with greater than 84% agreement in three of the four criteria. Only the criterion related to the response to antibiotic drug therapy was poorly met owing to lack of detail regarding responsiveness in the medical records. The level of agreement with all four of the criteria and the clinical diagnosis reached only 43%, with a poor kappa score ($\kappa = 0.09$).

Most patients demonstrated multifocal involvement. The onset of disease presented in the lower limb in 49% of patients. When the onset initiated outside of the lower limb, it progressed to involve further sites in 47% of the remaining patients, with all but one patient showing progression in the lower limb. Thus 27 patients (73%) had lower-limb involvement during the course of their disease. In the medical records, this involvement was named as either a bone site or joint area with associated swelling. Table 3 demonstrates the location of presenting bone lesions or joints affected in the

Table 2. Frequency of Diagnostic Criteria Presenting in the CRMO Cohort

Criteria Required for Diagnosis of CRMO	Participants (No.)			
	Positive for Criteria	Negative for Criteria	Not Performed	Not Stated
Radiologically proven osteolytic/sclerotic bone lesion	32	4	1	0
Multifocal bone lesions	33	4	0	0
PPP or psoriasis	5	32	0	0
Sterile bone biopsy with signs of inflammation and sclerosis	28	5	4	0
Normal blood cell count and general health	34	3	0	0
Mild or moderately raised erythrocyte sedimentation rate/C-reactive protein level	32	4	0	1
Duration >6 months	37	0	0	0
Hyperostosis	9	11	0	17
Association with autoimmune diseases other than PPP or psoriasis	1	35	0	1
Grade I or II relatives with autoimmune or autoinflammatory disorders or with nonbacterial osteitis	11	24	0	2
Prolonged course relapsing/remitting	31	4	0	2
Lack of response to antimicrobial drug therapy	14	4	10	9

Abbreviations: CRMO, chronic recurrent multifocal osteomyelitis; PPP, palmoplantar pustulosis.

Table 3. Prevalence of Lower-Limb Bone/Joint Involvement

	Reports (No.)	
Lower-Limb Lesion	At Onset	With Progression
Hip	2	3
Femur	2	4
Knee	7	2
Tibia	3	1
Fibula	2	0
Ankle	8	4
Talus	0	0
Calcaneum	3	1
Navicular	0	0
Cuneiforms	0	0
Cuboid	0	1
Metatarsals	1	0
Phalanges (hallux)	2	0
"Foot"	1	1

cohort. Overall, there were eight cases (22%) initiating in the foot or ankle. There were reports of lesions in many of the foot bones, with the calcaneum being the most frequently affected. Two patients were described as having foot involvement, but the specific bones involved were not named.

Discussion

This study presents one of the largest cohorts of pediatric patients diagnosed as having CRMO published to date. The cohort of 20 girls and 17 boys conflicts with the female predominance in the condition reported in other studies.[1,2,5,6] The mean age at onset of 9.2 years (range, 4–14 years) seems typical for pediatric cases.[1,5] Previous publications have not suggested predominance in any ethnic groups. The present findings suggested a higher predominance in white UK (78%) than in other European backgrounds (8%) and African and Asian backgrounds (8%). However, the racial/ethnic spread is similar to the population distribution for England for 0- to 15-year-olds (82% white UK, 3% white other, 11% black and Asian) but is less similar to the London ethnic distribution (54% white UK, 7% white other, 29% black and Asian),[14] where the unit is located. Case studies for CRMO have been reported from countries worldwide, but they usually do not state the race/ethnicity of the individual, so although the data would suggest a slight predominance in white racial/ethnic groups, the condition is by no means confined to that population.

The cohort included in this study did not show good agreement with the diagnostic criteria for CRMO defined by Jansson et al.[11] There was agreement with the major criteria, with nearly all of the participants being able to meet three of the major criteria. However, the criterion related to associated skin conditions (psoriasis/palmoplantar pustulosis) was included as a major and a minor criterion, and few patients met this criterion. This is similar to another large cohort[6] in which only three of 40 patients had skin conditions on presentation, and so the use of this feature as a diagnostic aid should be questioned. The criteria published by Ferguson and El-Shanti[2] performed very well, except for the criterion of responsiveness to antibiotic drug therapy. This was generally not reported in the medical records and is likely to be due to the fact this unit is a quaternary center and it would be expected that the patients had visited general practitioners and pediatricians before referral to this center. It would be unlikely that antibiotic drug therapy would not have been prescribed at some point during the initial presenting symptoms, and unresponsiveness to therapy is no doubt a factor as to why onward referral was required; however, the medical records failed to record the use or response to previous antibiotic drug therapy. There were no reports of antibiotic agents being prescribed specifically for the condition in the unit. The level of agreement would also have been increased if unifocal cases were included in the published criteria. In this unit, and as evidenced from published case studies, the term *CRMO* is often used even when the case is unifocal, and a distinction between the NBO subgroups is not always made. Recent studies have shown that the presentation of CRMO is rarely unifocal because silent lesions often exist and are revealed only on whole-body MRIs or bone scans.[11,15] This new knowledge may mean that the subgroups of NBO may not be correct and perhaps have to be reconsidered.

The disease is reported to predominantly affect the long bones and clavicle,[2] although many other bones have been reported in single case studies. This was not generally reflected in this cohort, with only 13 patients (35%) presenting with long bone lesions at onset, and others having lesions in the clavicle, mandible, vertebrae, and foot bones. The lower limb did predominate as the initial site of bone lesions, in agreement with the findings of Girschick et al,[5] but more frequently the neighboring joint was reported as pathologic rather than the bone area. Ankle soft-tissue swelling is most likely

related to a neighboring tibial or fibular bone lesion. Knee swelling is most likely associated with a neighboring femoral lesion. Thus, when the ankle is considered with tibial lesions, and the knee is considered with femoral lesions, the long bones are most frequently affected in lower-limb involvement equating to 62% of lesions. The affected sites reported in this cohort are similar to those reported by Catalano-Pons et al[6] in their cohort of 40 patients, where 57.5% had distal tibial involvement. The awareness of this condition by the podiatric physician should be raised by this high level of lower-limb, ankle, and foot involvement. In agreement with Catalano-Pons et al,[6] in the foot, the calcaneum was most frequently affected in this study, identifying involvement in 8% of patients. Although involvement of all of the foot bones was not identified in this study, case reports have shown that most foot bones can be involved.

Conclusions

It was found that many of the patients did not fulfill the individual criteria suggested by the two published diagnostic criteria, and small bones were frequently affected compared with sites in the long bones as previously reported. Differences in presentation of the site of the disease in this cohort may be related to the specialist rheumatology service involved, whereby the more typical patterns of presentation and lesion patterns may have been diagnosed and treated at a local hospital level, with the more unusual cases presenting to this quaternary service. The time from disease onset to referral to such a center is often prolonged, and, therefore, full recall of affected sites at onset may not be accurate, and, typically, use of retrospective data does potentially weaken the associations identified.

This study highlighted the potential for CRMO to predominantly affect the white population. The ankle and foot bones are frequently affected in the condition, and so consideration of this diagnosis should be made when a generally well child presents to the podiatric physician with bone pain.

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