Chronic Nonbacterial Osteomyelitis and Chronic Recurrent Multifocal Osteomyelitis in Children

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KEYWORDS

• Chronic nonbacterial osteomyelitis • Chronic recurrent multifocal osteomyelitis
• DIRA • Majeed syndrome • NSAID • Whole-body MRI

KEY POINTS

- Chronic nonbacterial osteomyelitis (CNO; also known as chronic recurrent multifocal osteomyelitis) is an inflammatory/autoinflammatory bone disease that primarily affects children and adolescents. It is a diagnosis of exclusion.
- Often the diagnosis of CNO in children is delayed because of a lack of awareness and the occult nature of CNO. Prompt referral to pediatric rheumatology can help establish a diagnosis and determine appropriate treatment.
- Imaging studies, especially MRI with short tau inversion recovery, are essential diagnostic tools.
- Whole-body MRI is the gold standard for disease monitoring.
- Long-term treatment and follow-up are needed to prevent complications, such as vertebral compression fractures and leg-length discrepancies.

INTRODUCTION

Chronic nonbacterial osteomyelitis (CNO; **a.k.a., chronic recurrent multifocal osteomyelitis**) is an inflammatory disorder that presents with bone pain arising from sterile osteomyelitis. It is primarily a pediatric disorder but can persist into adulthood or have an adult-onset presentation. The condition is difficult to diagnose, most commonly suspected to be infectious osteomyelitis or malignancy, with milder cases resembling growing pains. Children may have decreased physical function and poor school

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attendance when bone pain and inflammation are not controlled adequately. Delays in diagnosis can lead to permanent skeletal damage. The cause of the disease remains unknown for most but involves immune dysregulation resulting in inflammation of the bone and sometimes of other tissues, including skin, joints, and the intestine.

NOMENCLATURE

The disease has gone by many names, making nomenclature complicated (**Box 1**). It was first described as a symmetric multifocal osteomyelitis and later given the name chronic recurrent multifocal osteomyelitis (CRMO).[1] However, because the disease may begin or stay unifocal, CRMO may not be an accurate term for these patients. Thus, the term *CNO* has been proposed as an umbrella term.

INCIDENCE AND DEMOGRAPHICS

In 2011, the annual incidence of CNO in Germany was reported to be 0.4 per 100,000 children,[2] as compared with the reported incidence range of infectious osteomyelitis of 10 to 80 per 100,000 children per year.[3] However, during 2004 to 2014 in a single center in Germany, of the 109 children seen for osteomyelitis, 53% were categorized as infectious and 47% as noninfectious, unexpectedly similar proportions.[3] A single center in Britain reported increased patient referral for CNO after a letter was sent to all orthopedic centers to enhance recognition of the disease.[4] Although the actual incidence of CNO is likely to vary from one region to another, these studies suggest that it is more common than previously appreciated and underscore the importance of raising awareness of CNO.[4]

Age

- The average age of disease onset is 9 to 10 years.[2,4–8] Rarely, disease onset occurs before 3 years of age.

Sex

- Girls are more likely to be affected, with a female to male ratio of 2:1.[2,4–8]

Box 1
Reported terms of chronic nonbacterial osteomyelitis

Bone lesions of acne fulminans
Chronic multifocal cleidometaphyseal osteomyelitis
Chronic recurrent multifocal osteomyelitis
Chronic sclerosing osteitis
Chronic symmetric osteomyelitis
Clavicular hyperostosis and acne arthritis
Diffuse sclerosing osteomyelitis
Pustulotic arthro-osteitis
Sclerosing osteomyelitis of Garré
Sternocostoclavicular hyperostosis
Sternoclavicular pustulotic osteitis
Synovitis, acne, pustulosis, hyperostosis osteitis

Race and Ethnicity

- Most reported cases are of European ancestry, although it has been reported in all races.[2,4–8]
- Prevalence among different ethnicities has not been described.

MAJOR DIFFERENCES FROM ADULT CHRONIC NONBACTERIAL OSTEOMYELITIS (ALSO KNOWN AS SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, OSTEITIS)

- Cutaneous involvement in children is not as common as in adults.
- Common bone sites affected are long bones in children compared with the sternum and clavicles in adults.

DELAYS IN DIAGNOSIS ARE COMMON

The median time between initial symptoms and diagnosis of CNO is 2 years.[9] Forty-eight percent of children were not evaluated by a pediatric rheumatologist until at least 12 months after their first symptom occurred. The delay of diagnosis was likely related to the insidious development of pain, minimal findings on clinical examination, relatively normal laboratory studies, and lack of awareness of this condition. A patient survey study discussed delays in diagnosis for 21 patients who had a single symptomatic site and were initially misdiagnosed as bacterial osteomyelitis; 55% of these patients did not have whole-body imaging, and this was hypothesized to contribute to the delay in the diagnosis of CNO.[10]

WHEN TO CONSIDER CHRONIC NONBACTERIAL OSTEOMYELITIS

CNO should be considered in a child who has intermittent or persistent focal bone or joint pain of the lower extremities, clavicle, spine, and/or mandible. The pain is worse at night and may interfere with sleep, and the child usually has point tenderness of the affected site. Children with more superficially affected bones (eg, tibia, fibula, clavicle, and mandible) can also have local swelling and warmth (**Fig. 1**).

HOW CHRONIC NONBACTERIAL OSTEOMYELITIS PRESENTS

CNO typically presents as insidious bone pain with or without systemic features; however, it can also present as acute onset of pain. Young children may stop using an affected limb. Common features of CNO are shown in **Box 2**. Often there are minimal to no objective changes overlying the lesions, but point tenderness is common when the disease is active. The pain often results in reduced physical activities;

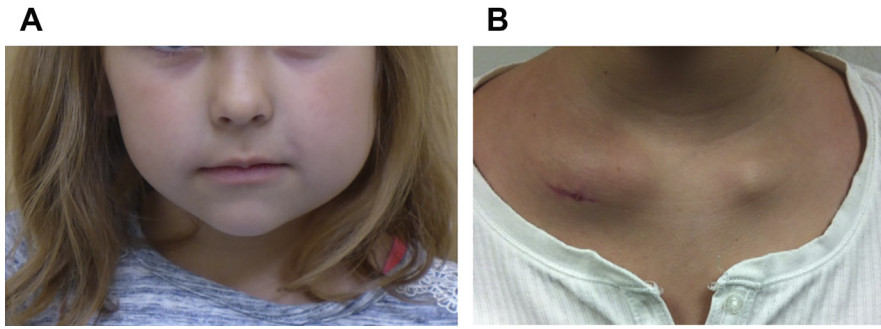

Fig. 1. (*A*) Left mandibular CNO with facial swelling and asymmetry in a child. (*B*) Swelling of right medial clavicle in a child with CNO.

Box 2
Clues to the diagnosis of chronic nonbacterial osteomyelitis

- Point tenderness with or without swelling or warmth
- Pain worse at night
- Limited function/use of affected limb
- Coexisting psoriasis, inflammatory bowel disease, or inflammatory arthritis
- Absence of constitutional symptoms

school attendance may be affected, particularly if lower extremities and/or axial bones are involved.

Approximately 40% of patients present with or develop arthritis with their CNO, which is associated with joint swelling and stiffness.[6] These symptoms often occur in joints adjacent to active areas of osteomyelitis of the long bones but can occur in areas without bone involvement. Even without arthritis, many patients have functional limitation of the joints.

Patients may present with constitutional symptoms, such as fever (20%)[7] and weight loss; however, most patients with CNO appear well. Fatigue is common in children with CNO.[9]

Pattern of bone involvement (**Fig. 2**)

- It most commonly affects the metaphyseal regions of long bones.
  - Diaphyseal regions of the long bones are rarely affected.

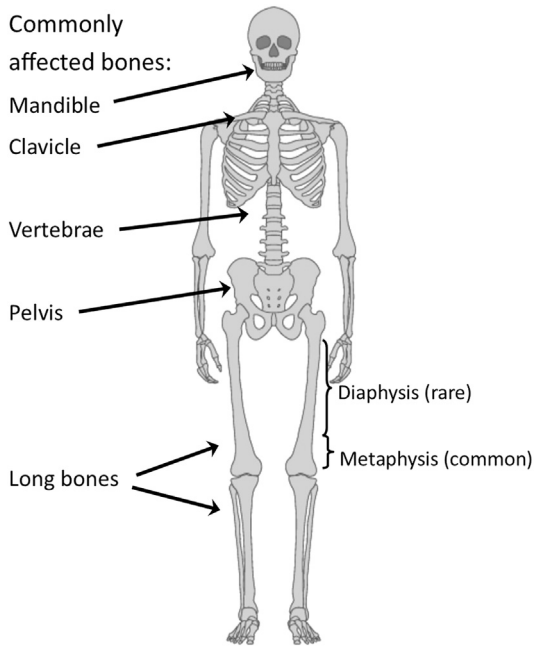

Fig. 2. Common sites affected in CNO. Metaphysis is indicated as the ending of long bones and diaphysis is indicated as the middle part of long bones. (*Adapted from* Vecteezy.com with free license. Accessed February 1, 2018.)

- The commonly affected sites are lower extremity long bones, vertebrae, clavicles, and mandible
  - In these sites, the trabecular bone is enriched and bone turnover is higher.
- There is asymmetric involvement in approximately 60% and symmetric involvement in approximately 40%.[7]
- Unifocal bony involvement at presentation is up to 30%.
  - Over time, most develop multifocal disease (93% in one study after mean of 4 years).[5]
- Clavicular and mandibular lesions are more likely to present as unifocal lesions and remain so throughout the disease course.
- Asymptomatic bone lesions are common.

DISEASE MORBIDITY

The most common complications of CNO are fractures in affected bones (especially of the vertebrae) and deformities due to growth alterations. Kyphosis may occur in patients with multiple vertebral compression fractures. Pathologic fractures in the long bones may occur when there is accelerated bone resorption. Leg-length discrepancy may result after the growth plate is damaged by CNO (**Fig. 3**A) or due to bony overgrowth of the epiphysis from excess inflammation. Angulation of a joint may occur when the growth plate is damaged asymmetrically, and often this complication requires surgical intervention (**Fig. 3**B). Aggressive treatment of patients with physeal damage before closure may reduce the risk of leg-length discrepancy or joint angulation. Untreated or inadequately treated patients may have increasing bony expansion (see **Fig. 3**B). One large study reported that 26% of children with CNO have complications, including localized deformation (particularly of the clavicle) (15%), vertebral fractures (4%), and growth asymmetry (6%).[5]

IMPACT ON QUALITY OF LIFE

CNO causes a significant impact on the quality of life in affected children. School absence due to pain, fatigue, and frequent medical visits are common. Assistive devices may be needed in some children. Inability to participate in desired sports activity because of limited function is frequent. Based on a family survey, most parents reported that their child with CNO was challenged to perform daily tasks or hobbies because of pain, fatigue, and physical limitation.[9] Another family survey study in Germany also reported a negative influence on family life in 80% of children with CNO.[10] Psychosocial support should be considered to improve the quality of life for these children and their families. Nearly half of these families reported a desire to contact other patients/families for mutual support.[10] A pamphlet for families of children with CRMO has been developed by a parent group and can be accessed on the Web site (www.crmoawareness.org). Other sites that allow families to seek further information and connect have been developed (https://www.facebook.com/groups/CRMOawareness, www.kailaskomfort.org).

ASSOCIATED CONDITIONS

In a minority of patients, other coexisting conditions, including psoriasis vulgaris, palmar plantar pustulosis, and inflammatory bowel disease, may occur before, concurrently with, or after the diagnosis of CNO. Psoriasis has been reported in 2% to 17% (**Fig. 4**), palmar plantar pustulosis (PPP) in 3% to 20%, and inflammatory bowel disease (IBD) in 3% to 7% of patients with CNO.[5–8] One proposed diagnostic criterion considers the presence of one of these comorbid conditions to help support

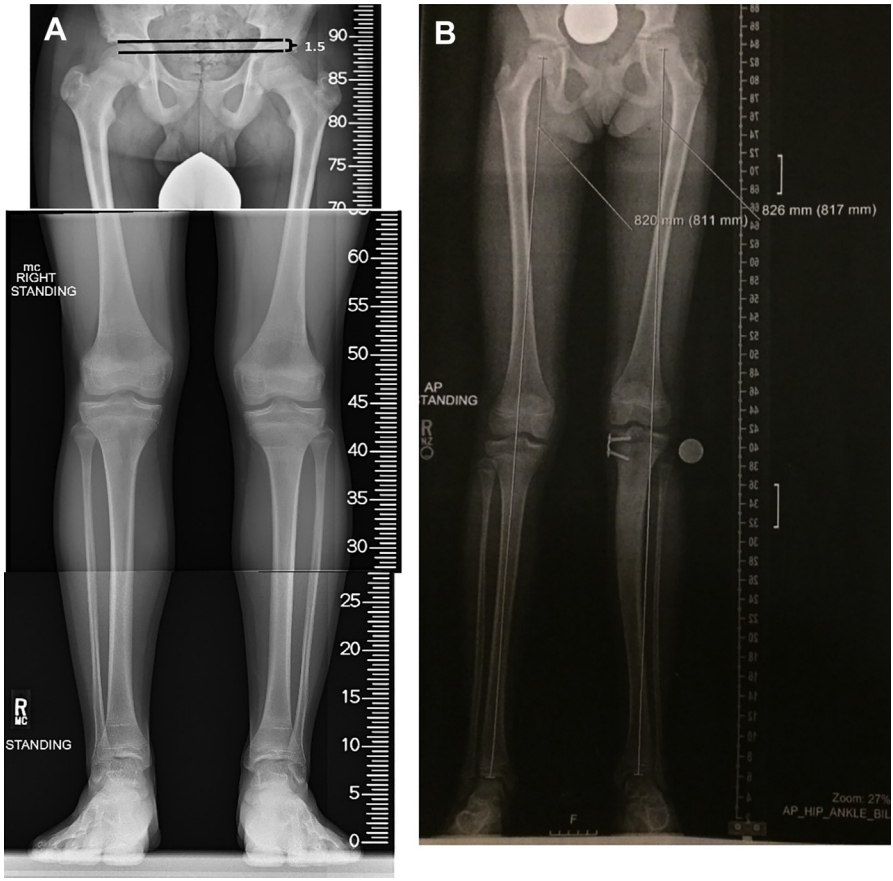

Fig. 3. (*A*) Radiographs of a child with CNO show a 1.5-cm discrepancy between the total lengths of 2 legs (right > left) due to growth plate damage in left proximal tibia. (*B*) Radiograph of a child with CNO shows persistent angulation of left knee a year after stapling of the medial proximal tibia.

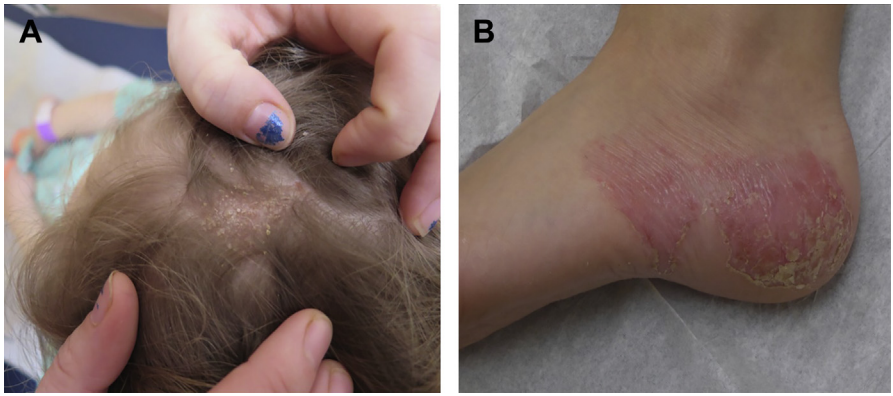

Fig. 4. (*A*) Plaque psoriasis on the scalp of a child with CNO. (*B*) Plantar psoriasis on heel of a child with CNO.

the diagnosis of CNO.[7] These comorbid conditions are also present in a high proportion of close relatives of patients with CNO. Up to 50% of patients with CNO have a first- or second-degree family member with psoriasis, PPP, Crohn disease, ulcerative colitis, or inflammatory arthritis. Family history of these diseases increases the positive predictive value of a diagnosis of CNO.[5–7] One category of treatments used for CNO, tumor necrosis factor (TNF)–alpha inhibitors, has also been associated with the development of psoriasis in patients with CNO.[11]

DIFFERENTIAL DIAGNOSIS OR MIMICS

The differential diagnosis of CNO is broad and includes infections of the bone or joint, malignancy, benign bone lesions, metabolic bone disease, amplified pain syndromes, and nutritional deficiencies.

The common differential diagnosis of CNO includes the following

- Leukemia
- Lymphoma
- Langerhans cell histiocytosis
- Primary malignant bone disease
- Benign bone tumor (osteoma, endo-chondroma)
- Infectious osteomyelitis
- Septic arthritis
- Avascular necrosis (osteonecrosis)
- Vitamin C deficiency (scurvy with bony changes)
- Enthesitis-related arthritis
- Psoriatic arthritis
- Amplified musculoskeletal pain syndrome/complex regional pain syndrome
- Hypophosphatasia
- Occult fracture
- Benign limb pain of childhood (growing pains)

A thorough physical examination is essential to help differentiate CNO from malignancy and infection, assessing for the presence of other areas of bone or joint swelling, lymphadenopathy, hepatosplenomegaly, mass, or rash. Lesions in the diaphysis should prompt evaluation for alternative diagnosis, including benign and malignant bone tumors. Lactate dehydrogenase (LDH) and uric acid are useful to screen for increased cell turnover in children with leukemia and lymphoid malignancies. Alkaline phosphatase and serum phosphorus are useful to screen for hypophosphatasia.

Biopsy of multiple bone sites or repeated bone biopsies may need to be performed, especially when there is a concern of a CNO-mimicking disease, such as intraosseous lymphoma.[12] Bone marrow biopsy may also be obtained in patients with strong suspicion of leukemia (cytopenia, episodic pain, nocturnal pain, elevated LDH, raised uric acid). Infectious workup is routinely performed on the biopsied bone samples, and additional blood culture is needed when the concern for infection is high.

Jansson and colleagues[13] developed a scoring system to guide the diagnostic workup based on the presence or absence of 7 components (**Table 1**). This scoring system was intended to distinguish nonbacterial osteomyelitis from infectious osteomyelitis as well as from benign and malignant bone tumor in adults and children. A total score of 28 or less had a negative predictive value of 97% for CNO, whereas a total score of 39 or greater had a positive predictive value of 97% or greater for CNO.

The pattern of pain may also help differentiate CNO from other diseases. Pain is often worse at night and interferes with sleep. This pattern is also seen in children

Table 1
Diagnostic scoring system of chronic nonbacterial osteomyelitis by Jansson and colleagues

Clinical, Laboratory, and Imaging Findings	Points
Normal blood cell count	13
Symmetric lesions	10
Lesions with marginal sclerosis	10
Normal body temperature	9
Vertebral, clavicular, or sternal lesions	8
Radiologically proven lesions ≥2	7
C-reactive protein ≥1 mg/dL	6

Total possible score is 63. This scoring system was intended to distinguish nonbacterial osteomyelitis from infectious osteomyelitis as well as from benign and malignant bone tumor in adults and children. A total score of 28 or less had a negative predictive value of 97% for CNO, whereas a total score of 39 or greater had a positive predictive value of 97% or greater for CNO.

Data from Jansson AF, Muller TH, Gliera L, et al. Clinical score for nonbacterial osteitis in children and adults. Arthritis Rheum 2009;60:1152–9.

who have growing pains (also known as benign limb pain of childhood, see Jennifer E. Weiss and Jennifer N. Stinson's article, "Pediatric Pain Syndromes and Noninflammatory Musculoskeletal Pain," in this issue). Episodic severe bone pain with significantly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should raise concerns for osseous infiltration from leukemia or lymphoma. Diffuse body pain and tenderness to touch (allodynia) may be an indication of amplified musculoskeletal pain syndrome (discussed in Chapter 10) rather than active CNO. Some children with CNO may also have amplified musculoskeletal pain syndrome, which can make it challenging to determine if they have active disease; in such cases, MRI can be helpful.[14]

IMAGING, LABORATORY, AND BIOPSY STUDIES FOR DIAGNOSIS IN CARE

Imaging

Whole-body MRI is considered the gold standard imaging modality by experts. Patients almost always have a radiograph taken initially. However, MRI is preferred for its sensitivity and lack of radiation. Typical findings of CNO from each imaging modality are listed next.

Radiographs

- Most common findings
  - Lytic lesion during early phase (**Fig. 5**A)
  - Sclerosis, bony expansion, or mixed picture during later stage (**Fig. 5**B)
  - Normal in 80% of patients
- Other findings
  - Pathologic fracture during acute lytic phase (rare)
  - Compression fracture of vertebrae
    - Can lead to kyphosis or vertebra plana (**Fig. 5**C)
- Advantages
  - Quick
  - Least expensive
- Disadvantages
  - Least sensitive with a high false-negative rate
  - Radiation

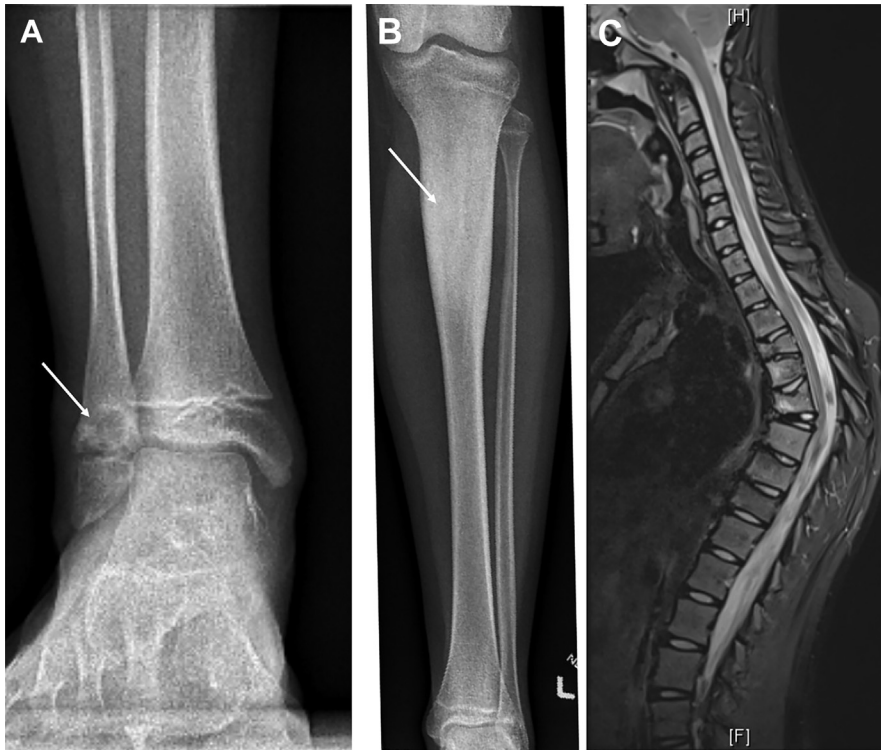

Fig. 5. (*A*) CNO lytic lesion (*arrow*) in fibula. (*B*) Sclerosis (*arrow*) of tibia. (*C*) Height loss of T3 to T6 and plana of T7 due to CNO on MRI, which resulted in 47° of kyphosis.

Computed tomography

- Common findings
  - Lytic lesions, sclerosis, bony expansion, or mixed pattern
- Advantages
  - Three-dimensional rendering of affected bone to guide the biopsy
- Disadvantages
  - Limited use in determining disease activity
  - Radiation

Bone scintigraphy

- Common findings
  - Increased uptake at affected sites (**Fig. 6**)
- Advantages
  - Whole-body level scanning when whole-body MRI is not available
- Disadvantages
  - Not as sensitive as MRI[15]
  - Challenging to distinguish inflamed sites from the physiologic increased uptake at the growth plates
  - Radiation

PET–computed tomography

- Common findings
  - Increased tracer uptake

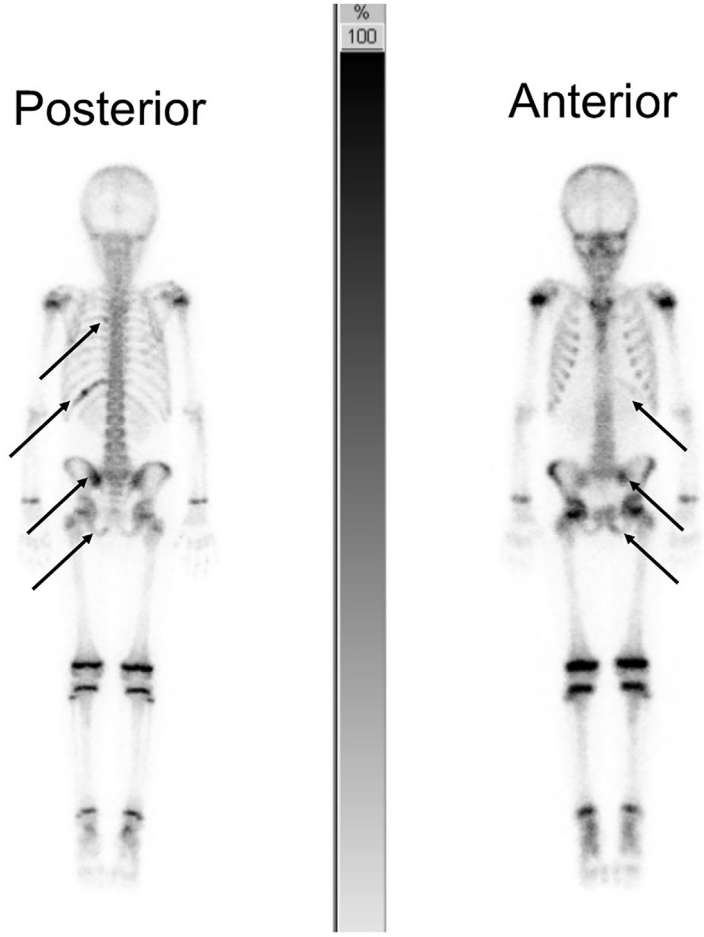

Fig. 6. Bone scintigraphy of a child with CNO reveals increased uptake of radioisotope (*arrows*) in the left third and eleventh ribs, left ilium, and left ischium indicating active inflammation.

- Advantages
  - Correlates with disease activity based on increased metabolism
  - Detailed localization of inflamed sites
- Disadvantages
  - Radiation

MRI

- Common findings
  - Hyperintensity within bone marrow in short tau inversion recovery (STIR) or T2 fat saturation sequences
  - Hyperintensity within surrounding soft tissue in STIR or T2 fat saturation sequences
  - Bony expansion during late stages
- Other findings
  - Physis irregularity or complete bony bar

- Compression vertebral fracture
- Advantages
  - Most sensitive in detecting inflamed sites (Figs. 7 and 8)
  - Assesses both disease activity and skeletal damage
- Disadvantages
  - Requires sedation in young children

Whole body MRI

- Useful protocol of whole-body MRI (Fig. 9)[16]
  - Coronal STIR of total body in 4 to 5 stations
  - Sagittal STIR of entire spine
  - Sagittal STIR of feet
  - Axial STIR of pelvis and knee
- Advantages
  - Whole-body screening
  - Most sensitive in detecting inflamed sites
  - Assesses both disease activity and skeletal damage
- Disadvantages
  - Requires sedation in young children

Frequency of imaging monitoring

There is no consensus on how often imaging should be performed to monitor disease activity of CNO. In North America, about half of the surveyed pediatric rheumatologists use imaging regularly, with 54% of them repeating imaging every 6 months and 25% every 12 months.[17] Because of the occult nature of the disease and lack of reliable biomarkers or physical findings, more frequent radiation-free imaging may be necessary to provide an accurate estimate of disease activity in order to guide the treatment. In general, early in the disease, repeating MRI 3 to 6 months after initiation of the treatment is reasonable. In patients who have a completely normal MRI and remain on stable medications or are off medications, repeating MRI every 6 to 12 months is appropriate.

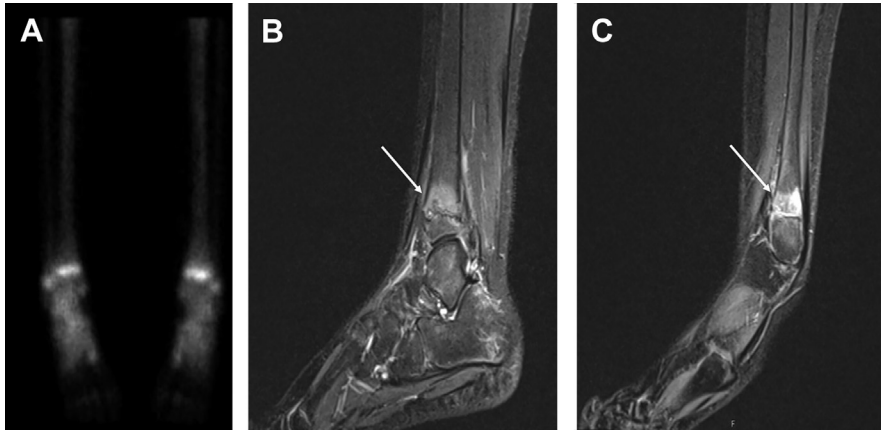

Fig. 7. (*A*) Normal bone scintigraphy of a child. (*B*) Abnormal STIR signal (*arrow*) on MRI within left distal tibia of the same child. (*C*) Abnormal STIR signal (*arrow*) on MRI within right distal fibula of the same child.

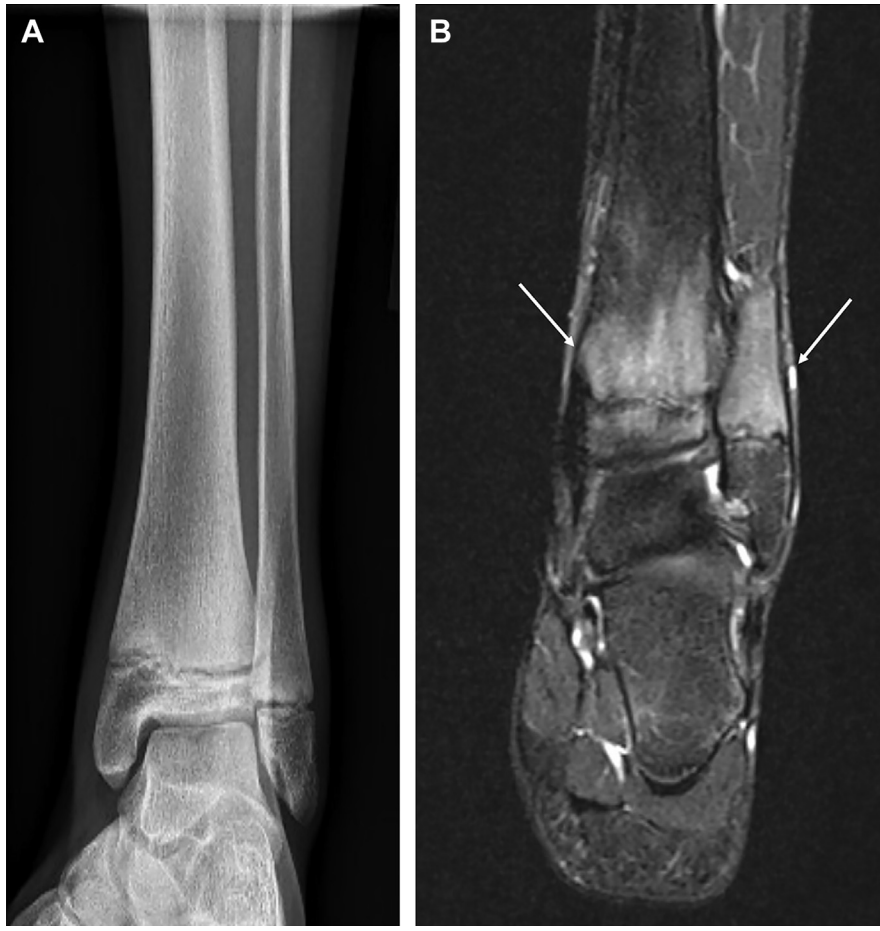

Fig. 8. (*A*) Normal leg radiograph of a child. (*B*) Abnormal STIR signal (*arrow*) on MRI within distal tibia and fibula of the same child.

Laboratory Evaluation

There is no diagnostic test for CNO. Most children have a normal complete blood cell count (CBC) at presentation.[5–7] Because of the broad differential diagnoses for CNO, laboratory tests are most useful to rule out alternative diagnoses. Inflammatory markers, such as ESR and CRP, are elevated in some patients with CNO, but most have normal levels at presentation.[4,7,8,13,18,19] The use of urinary N-terminal telopeptide (NTx) as a disease-monitoring tool in CNO has been reported in a small cohort,[20] with the test found able to identify some children with disease flares. More study is needed to determine the normal range of NTx in healthy children and evaluate the sensitivity and specificity of NTx for screening children for CNO. HLA-B27 positivity and low titer antinuclear antibody positivity have been reported in only a small fraction of these patients.[5,7] Serum TNF-α was increased in 66% of patients in one study.[7] Total immunoglobulin (Ig) G and its subclasses, IgG1, IgG2, IgG3, as well as IgD were elevated in 7% to 33% in one cohort.[7]

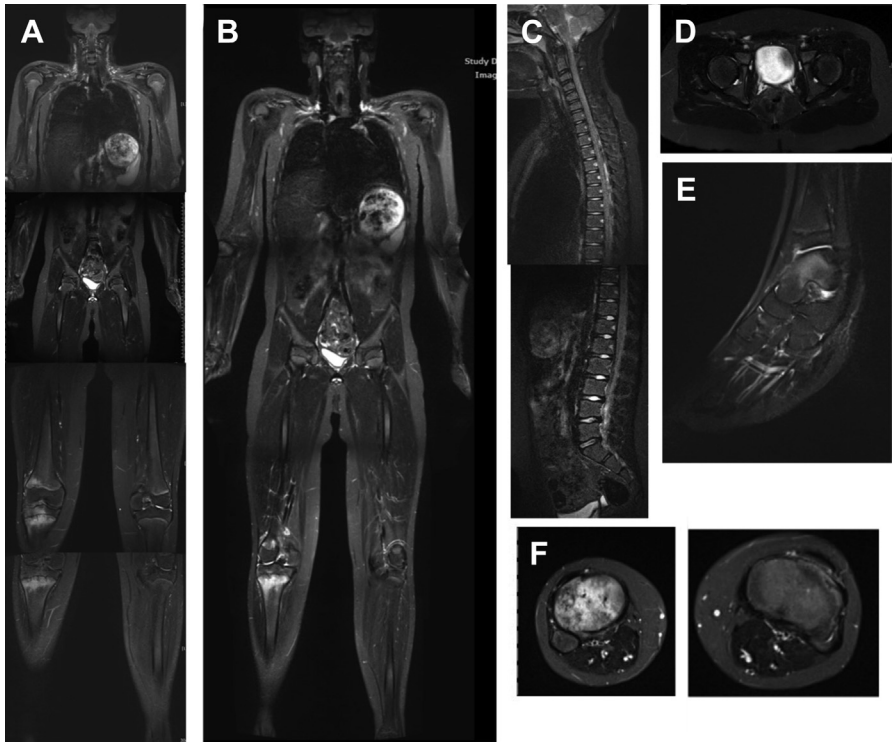

Fig. 9. Whole body MRI of a child with CNO includes coronal STIR of total body in 4 to 5 stations (*A*) with stitched image (*B*), sagittal STIR of entire spine (*C*), axial STIR of pelvis (*D*), sagittal STIR of feet (*E*), and axial STIR of the knee (*F*). It demonstrates active inflammation in right proximal tibia and left talus.

Initial screening laboratory tests in a child with typical chronic nonbacterial osteomyelitis usually show

- Normal CBC; sometimes anemia from chronic disease
- Normal or mildly elevated ESR, CRP
- Normal LDH, uric acid
- Normal serum calcium, phosphorus, alkaline phosphatase

Bone Biopsy

It may be necessary to obtain a bone specimen to exclude infection and malignancy. Most rheumatologists request a bone biopsy when there are constitutional symptoms or a single bone lesion or an atypical presentation. Conversely, patients with the following characteristics may not need a bone biopsy because of the higher confidence in the likelihood of CNO:

- Bone lesion at a typical site (clavicle, metaphysis of long bones, vertebral body) with normal laboratory test results and no constitutional symptoms
- Multiple bone lesions
- CNO-associated conditions (ie, psoriasis or Crohn disease)[4,17]

When indicated, bone biopsy can be obtained via an open biopsy or needle biopsy depending on the affected sites. Usually a decision of how to obtain biopsy is left to

the discretion of the surgeon. Common histologic findings include acute and/or chronic inflammation, marrow fibrosis, osteonecrosis or normal bone.[6,7,17,21,22] No specific staining can confirm the diagnosis of CNO but may exclude other diagnoses. Adequate sample should be obtained to allow for pathologic review as well as for an infectious workup including stains and cultures for bacteria, fungi and mycobacteria.

PATHOGENESIS OF CHRONIC NONBACTERIAL OSTEOMYELITIS

CNO is considered an autoinflammatory disease. Components of the innate immune system, including neutrophils, macrophages, monocytes, and associated cytokines, contribute to disease pathogenesis. Increased proinflammatory cytokines, such as TNF-α and interleukin (IL)-6, and decreased antiinflammatory cytokines, especially IL-10, were reported in children with CNO.[23] IL-6 and C-C motif chemokine 11/eotaxin have been shown to sufficiently differentiate patients with CNO from healthy children and those with other inflammatory diseases in a German cohort.[24] Recently, a serum cytokine profile has been proposed as a marker for CNO.[25] Persistently elevated monocyte chemoattractant protein-1, IL-12, and soluble interleukin-2 receptor were associated with refractory CNO in one cohort; but their use as biomarkers needs to be validated.[25] Imbalanced cytokines cause increased osteoclast activity that results in accelerated bone breakdown during the early phase of disease. Overall bone turnover is increased, and excessive bone formation occurs as a response during the later stage.

There is evidence of a genetic component to CNO, including reports of clustering in some families and a reported association of CNO with a rare allele of marker D18S60 on chromosome 18.[26] For a small minority of patients, CNO may be genetically driven. There are 2 monogenic autoinflammatory bone diseases called deficiency of IL-1 receptor antagonist (DIRA) and Majeed syndrome in which sterile osteomyelitis is a prominent phenotype. These two diseases have distinct clinical features, which can aid in diagnosis. DIRA presents as neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis. Clinical symptoms typically start within the first month of life.[27] DIRA is due to recessive mutations in *IL1RN*, which encodes the IL-1 receptor antagonist, a regulatory protein that binds IL-1 receptors on cells and blocks the binding and activity of IL-1. Affected children respond only partially to glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) but respond very well to replacement treatment with recombinant human IL-1 receptor antagonist, anakinra.[27] Majeed syndrome presents with sterile multifocal osteomyelitis with onset in the first 2 years of life and is associated with congenital dyserythropoietic anemia; a few patients with Majeed syndrome also have a neutrophilic dermatosis resembling Sweet syndrome.[28,29] Majeed syndrome is due to recessive mutations in *LPIN2*. Recently a homozygous missense mutation in the gene *FBLIM1* was reported by Cox and colleagues[30] as the cause of CNO and psoriasis in 2 unrelated children.

HOW CHRONIC NONBACTERIAL OSTEOMYELITIS IS TREATED

Nonsteroidal antiinflammatory drugs (NSAIDs) are often used as the first-line treatment of children with CNO.[8,17,31] Naproxen at 10 mg/kg (maximum 500 mg) twice daily is the most commonly used NSAID. Other NSAIDs used for treatment are indomethacin and meloxicam. Based on the study of Beck and colleagues,[8] responders have significant pain relief and a decrease in the number of bone lesions on MRI by as early as 3 months. Patients who have persistent bone pain and hyperintense signal within bone marrow on STIR imaging after 3 months of NSAID treatment are considered NSAID treatment failures. These patients need treatment with a second-line agent.[31,32]

Second-line treatments include methotrexate, TNF inhibitors (TNFi; most commonly monoclonal antibodies), and bisphosphonates.[5–8,17,19,20,22,32–34] Depending on the severity of disease, one or more of the aforementioned medications may be used sequentially or concurrently after a child fails to achieve a favorable response to NSAIDs. Comparative effectiveness studies have not been done to determine relative efficacy. Retrospective studies suggest that nonbiological DMARDs (such as methotrexate or sulfasalazine) have lower efficacy than TNFi and bisphosphonates.[6] When other associated conditions, such as IBD or enthesitis-related arthritis, are present, TNFi with or without DMARDs are more appropriate to treat both CNO and these coexisting conditions. When spinal lesions are present, bisphosphonates may prevent further compression and allow some recovery of vertebral body height.[18,35] Combining TNFi and bisphosphonates has been reported to provide substantial disease control in children with CNO and a poor response to NSAIDs.[19]

There have been limited reports of the use of other biological medications. The IL-1 inhibitor anakinra has been reported to be effective in 2 small cohorts of patients, associated with a decrease in the CRP after 6 to 8 months of treatment.[36,37] Pardeo and colleagues[37] reported a favorable response in 5 of 9 patients who had refractory CNO (failing NSAIDs, glucocorticoids, pamidronate). After 6 months of anakinra at a median dosage of 2 mg/kg/d, 5 of 9 patients had normalized CRP and ESR. The total number of bone lesions detected by bone scintigraphy at baseline decreased from 77 to 35, although 20 new asymptomatic lesions were identified. At a median of 1.7 years of follow-up, 6 of 9 patients maintained a zero or minimal physician global assessment score.

Of note, glucocorticoids are not recommended during the initial workup or as long-term treatment due to adverse long-term side effects and the potential for harm should the child turn out to have a lymphoid malignancy. Short-term use (up to 6 weeks) in patients with a well-established diagnosis of CNO as a transitional medication may be appropriate.[32]

Without treatment guidelines, there is variability in which medications are used for NSAID failures. The selection and dosing of second-line medications differs among rheumatologists. However, consensus treatment plans (CTPs) have been developed based on the best available evidence and current treatment practices of North American pediatric rheumatologists for the treatment of pediatric CNO refractory to NSAIDs and/or with active spinal lesions.[32] These CTPs will allow future comparative effectiveness studies to identify the most effective therapies.

In a CNO cohort, aggressive combination treatment with a TNFi plus methotrexate with or without bisphosphonate induced clinical remission along with significantly decreased active lesions on MRI compared to treatment with NSAIDs.[19] Further study is needed to determine if early aggressive treatment of children with CNO results in better long-term outcomes[19] and to determine the optimal treatment duration.

CLINICAL MONITORING

Different criteria have been reported to define clinical responses to treatments in CNO. Most of these criteria included 3 main components: pain due to CNO, inflammatory markers (ESR and CRP), and imaging findings. Effective treatments may lead to complete resolution of pain and normalized ESR and CRP, which may precede the complete resolution of lesions on MRI. A composite score, PedsCNO score, includes ESR, number of lesions on MRI, physician global assessment of disease activity, patient/parent global assessment of disease activity, and childhood health assessment questionnaire.[8] PedsCNO 30, 50, and 70 were defined as 30%, 50%, and 70% improvement in at least 3 of 5 variables with no more than one of the remaining variables

deteriorating by more than 30%, 50%, and 70%. Recently, proposed criteria of treatment failure were suggested[32] as no improvement in more than 50% of available criteria or at least 4 of the following 6 criteria: patient pain; total number of clinically active lesions; total number of radiological lesions by whole body MRI or bone scintigraphy; size and degree of marrow edema of CNO lesions; and/or presence of soft tissue swelling/inflammation related to CNO lesion on imaging, physician global assessment, abnormal ESR, and/or CRP after exclusion of other potential causes.

MANAGEMENT OF CLINICALLY ASYMPTOMATIC LESIONS SHOWN IN MRI

Asymptomatic lesions have often been reported, and their clinical significance has not been fully elucidated.[8,14,37] Currently, most physicians do not make clinical decisions based on asymptomatic lesions unless vertebral bodies are affected, which potentially poses a high risk of spinal fracture.

WHAT IS THE PROGNOSIS FOR CHRONIC NONBACTERIAL OSTEOMYELITIS?

Long-term observational studies have reported an average 40% rate of clinical remission (defined as absence of bone pain) in children with CNO after 1 to 5 years of follow-up.[5–8,34] The only long-term follow-up study done on adult patients with childhood onset of CNO showed a persistent presence of active bone lesions, defined as increased signal intensity on STIR images, in 10 of 17 patients who were available for a median of 15-year follow-up.[14] Among these 10 patients, 6 had ongoing clinical symptoms, whereas the other 4 patients were completely asymptomatic. This study underscores the importance of regular imaging monitoring in patients with CNO and demonstrates that, for some, the disease may persist into adulthood. Pediatric rheumatologists manage these patients in collaboration with other specialists (eg, orthopedic surgeon, oral surgeon, neurosurgeon, dermatologist) and assist these patients in their transition into adult rheumatologists for the optimal care.

Recurrence of disease is very common, with 50% of patients relapsing after a median of 2.4 years in a large German cohort study.[34] The relapse rate was even higher (83%) in a large cohort from North America after a median of 1.8 years of follow-up.[6]

In a large cohort study, factors associated with severe disease and a poor outcome include male sex, multifocal disease, extrarheumatologic manifestations, family history of associated disease, and CRP greater than 1 mg/dL.[5] These patients were more likely to receive bisphosphonates and/or TNFi as a result of refractory disease.

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