abstract

BACKGROUND AND OBJECTIVES: Little information is available concerning the natural history and optimal treatment of chronic nonbacterial osteomyelitis (CNO). We conducted a retrospective review to assess the clinical characteristics and treatment responses of a large cohort of pediatric CNO patients.

METHODS: Children diagnosed with CNO at 3 tertiary care centers in the United States between 1985 and 2009 were identified. Their charts were reviewed, and clinical, laboratory, histopathologic, and radiologic data were extracted.

RESULTS: Seventy children with CNO (67% female patients) were identified. Median age at onset was 9.6 years (range 3–17), and median follow-up was 1.8 years (range 0–13). Half of the patients had comorbid autoimmune diseases, and 49% had a family history of autoimmunity. Patients with comorbid autoimmune diseases had more bone lesions \((P < .001)\), higher erythrocyte sedimentation rate \((P < .05)\), and higher use of second line therapy \((P = .02)\). Treatment response to nonsteroidal antiinflammatory drugs (NSAIDs), sulfasalazine, methotrexate, tumor necrosis factor \(\alpha\) inhibitors, and corticosteroids was evaluated. The only significant predictor of a positive treatment response was the agent used \((P < .0001)\). Estimated probability of response was 57% for NSAIDs, 66% for sulfasalazine, 91% for methotrexate, 91% for tumor necrosis factor \(\alpha\) inhibitors, and 95% for corticosteroids.

CONCLUSIONS: In a US cohort of 70 children with CNO, coexisting autoimmunity was a risk factor for multifocal involvement and treatment with immunosuppressive agents. Disease-modifying antirheumatic drugs and biologics were more likely to lead to clinical improvement than NSAIDs. Pediatrics 2012;130:e1190–e1197

WHAT’S KNOWN ON THIS SUBJECT: Chronic nonbacterial osteomyelitis (CNO) is a sterile inflammatory bone disorder of presumed autoimmune or autoinflammatory etiology predominantly affecting children. There are limited data on the characteristics and optimal treatment of CNO in the United States.

WHAT THIS STUDY ADDS: A US-based cohort of pediatric CNO patients revealed high rates of personal and familial autoimmunity. Coexisting autoimmunity was a risk factor for widespread involvement. Response to nonsteroidal antiinflammatory drugs was inferior to that with immunosuppressive and biologic agents.

AUTHORS: Arturo Borzutzky, MD,a,b Sara Stern, MD,a,b,c Andreas Reiff, MD,a,b David Zurakowski, PhD,a,b Evan A. Steinberg, MD,f Fatma Dedeoglu, MD,a,b and Robert P. Sundel, MDa,b,c

dProgram in Rheumatology, Division of Immunology, Children's Hospital Boston, Boston, Massachusetts. bDepartment of Pediatrics, Harvard Medical School, Boston, Massachusetts. cPediatric Rheumatology Unit, Division of Pediatrics, Pontificia Universidad Catolica de Chile School of Medicine, Santiago, Chile. dDivision of Rheumatology, Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, California. eDivision of Rheumatology, Children's Hospital Los Angeles, Los Angeles, California. fPediatric Infectious Diseases, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California

KEY WORDS: chronic nonbacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, osteomyelitis, autoimmunity

ABBREVIATIONS: CNO—chronic nonbacterial osteomyelitis; DMARDs—disease-modifying antirheumatic drugs; ESR—erythrocyte sedimentation rate; IBD—inflammatory bowel disease; NSAIDs—nonsteroidal antiinflammatory drugs; SAPHO—synovitis, acne, pustulosis, hyperostosis, and osteitis; TNF-\(\alpha\)—tumor necrosis factor \(\alpha\)

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3788
doi:10.1542/peds.2011-3788

Accepted for publication Jun 14, 2012

Address correspondence to Robert Sundel, MD, Children's Hospital Boston, 300 Longwood Ave, Boston MA 02115. E-mail: robert.sundel@childrens.harvard.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2012 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Borzutzky: speaker for Roche, Educational Travel Grant from Pfizer and Abbott. Dr Reiff: consultant and speakers' bureau for Abbott, Amgen, Genentech, Pfizer, and Roche. Dr Sundel: advisory board for Roche. Roche, Pfizer, Abbott, Amgen, Genentech produce biologic disease-modifying antirheumatic drugs, some of which were used in the treatment of some patients reported in this study.

FUNDING: No external funding.
Chronic nonbacterial osteomyelitis (CNO) is a sterile inflammatory bone disorder of unknown etiology. It typically affects children and most commonly presents with bone pain and/or swelling. CNO bone lesions have a typical radiologic appearance characterized by osteolysis, sclerosis, and hyperostosis. Chronic recurrent multifocal osteomyelitis is the most widespread form of CNO, but unifocal or nonrecurrent patterns also have been recognized. The acronym SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis) has been used in adult patients with sterile bone lesions as well as joint and skin inflammation, but this entity is seen infrequently in children.

Infectious etiologies have long been suspected in the pathogenesis of CNO. Although some early studies identified specific bacteria in bony lesions, these are now generally thought to have reflected contaminants. More recent microbiological studies in large CNO cohorts, including universal 16S ribosomal DNA polymerase chain reaction in bone tissue samples, have been consistently negative. CNO is currently thought to be in the spectrum of autoimmune and autoinflammatory disorders. This is supported by the high rates of systemic inflammatory conditions, particularly psoriasis and inflammatory bowel disease (IBD), in patients and family members.

Treatment of CNO has been directed at reducing pain and inflammation, with the intent of halting bone destruction and disease progression. Due to the low prevalence of this disease, most treatment reports involve small series or individual cases. Nonsteroidal antiinflammatory drugs (NSAIDs) are generally used as first-line therapy, but frequently patients require additional treatments. Small series have reported successful treatment of CNO with bisphosphonates. However, caution is warranted in their use in children because of long drug half-life in bone, and reports of secondary osteopenosis and delayed fracture healing. On the basis of the hypothesis that CNO is an autoimmune disease, treatment with disease-modifying antirheumatic drugs (DMARDs), immunosuppressive agents, and biologics is increasingly reported to be effective in case reports and small series.

There are few data on patients with CNO treated in the United States; most literature has been generated in Europe. In this study, we report on the clinical characteristics and responses to anti-inflammatory and immunosuppressive therapy in 70 patients with CNO evaluated at 3 tertiary care pediatric centers in the United States.

METHODS

Inpatient and outpatient databases at Children's Hospital Boston, Children's Hospital of Los Angeles and Kaiser Permanente Los Angeles Medical Center were screened for patients diagnosed with chronic osteomyelitis, recurrent osteomyelitis, or nonbacterial osteomyelitis between January of 1985 and March of 2009. The medical records of patients who were identified were reviewed and clinical, laboratory, histopathologic, and radiologic data of children were redacted. Because of the small number of patients from Kaiser Permanente Los Angeles Medical Center and geographic proximity to Children's Hospital of Los Angeles, these 2 institutions were analyzed together.

Data collection included age at diagnosis, gender, time to diagnosis, follow-up duration, clinical presentation, number and location of bone lesions, comorbidities, family history of autoimmune diseases, laboratory data at presentation, imaging studies, histopathology, response to treatments, complications, and outcomes at last evaluation. The institutional review boards for all participating institutions approved this study.

The diagnosis of CNO was established by the presence of unifocal or multifocal bone inflammation, typical radiologic and/or histopathologic findings, and negative evaluation for infectious etiologies. Imaging studies performed included plain radiographs \( (n = 69) \), CT \( (n = 42) \), MRI \( (n = 57) \), and Tc99 bone scan \( (n = 57) \). Treatments used included NSAIDs (naproxen or ibuprofen, \( n = 69 \) ), DMARDs (methotrexate, \( n = 30 \ ); sulfasalazine, \( n = 22 \ ); corticosteroids (prednisone or methylprednisolone, \( n = 19 \ )); and tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)) inhibitors (\( n = 11 \); etanercept [Enbrel], \( n = 7 \ ); adalimumab [Humira], \( n = 2 \ ); infliximab [Remicade], \( n = 5 \)). Doses were in accordance with standard pediatric prescribing practices. Response to treatment was assessed by improvement in pain and serologic markers of inflammation, as well as radiographic proof of bone healing. Responses were generally assessed \( >3 \) months after starting treatment. Treatment responses were categorized as “no response” (unchanged pain and radiologic appearance), “partial response” (decrease in pain, inflammatory parameters, and/or radiographic improvement), or “clinical remission” (resolution of pain, normalization of inflammatory parameters, and radiographic improvement).

Statistical Analysis

Clinical and demographic differences between Children's Hospital Boston and Children's Hospital of Los Angeles/Kaiser Permanente Los Angeles Medical Center patients were assessed by \( \chi^2 \), Mann-Whitney \( U \) test, and Student \( t \) test for independent variables. Pearson bivariate correlation was used to assess associations between numerical variables. Multivariable logistic regression was used to identify variables associated with treatment response. A...
Laboratory data

- Leukocytes (× 10^3/L): 8.8 ± 2.7
- Hematocrit (%): 36 ± 5
- Platelets (× 10^3/L): 401 ± 130
- ESR (mm/h): 47 ± 33

Disease pattern:
- Unifocal nonrecurrent: 3 (4%)<br>- Unifocal recurrent: 17 (25%)<br>- Multifocal nonrecurrent: 9 (13%)<br>- Multifocal recurrent: 40 (58%)

*One patient in the Boston cohort was lost to follow-up and was not included in the analysis of CNO pattern.

Results

Patient Characteristics

Seventy patients (67% female) were evaluated during the study period. Age had a unimodal distribution with a median age at presentation of 9.8 years (range 3–17). Demographic, clinical, and laboratory characteristics of patients are shown in Table 1. Bone lesions were distributed throughout the body, affecting the axial and appendicular skeleton (Fig 1). Twenty patients had unifocal disease. Among these, the most commonly affected bone was the mandible (12 patients). The pattern of disease, previously characterized by Girschick et al, was significantly different between the Boston and Los Angeles centers (P < .001), with the latter group having less recurrent disease (96% vs 57%, P < .01; Table 1).

Recurrence rates did not differ between patients with unifocal (85%) and multifocal disease (82%; P = .21). Female patients had more lesions than their male counterparts (4.8 ± 3.3 vs 3.1 ± 2.2, P = .02) and higher rates of psoriasis (26% vs 0%, P < .01). There were no other statistically significant differences between genders in terms of clinical, laboratory, or radiologic data.
vs 54%, $P < .001$). They had more bone lesions on average (5.7 ± 3.2 vs 2.7 ± 2.1 lesions, $P < .001$), and higher rates of involvement of the feet, tibia, pelvis, and humerus. Family history of autoimmune disease in first- or second-degree relatives was seen in 49% of CNO patients (Fig 3), most frequently psoriasis (22%) and rheumatoid arthritis (13%).

**Laboratory**

Eighty-one percent of patients had an elevated erythrocyte sedimentation rate (ESR) (mean 47 ± 33 mm/hr, median 36 mm/hr) at presentation. Patients with comorbid autoimmune diseases had higher average ESR (55 ± 36 vs 38 ± 22, $P < .05$) and lower average hematocrit values (35 ± 6 vs 38 ± 4, $P = .03$). The white blood count was elevated >12.0 × 10⁹/L in only 7% of patients and thus was not a sensitive marker for CNO. A platelet count >400 × 10⁹/L was seen in 42%.

**Imaging**

Ninety-nine percent of patients had plain radiographs performed at their initial visit. Characteristic sclerotic, osteolytic, and/or hyperostotic bone lesions were detected in 77% of plain films. CT was performed in 42 patients, of which 93% had bone lesions. Localized MRI studies were available in 51 patients. Bone lesions were detected in 86% (including fractures in 8%), bone marrow edema in 49%, soft tissue edema in 31%, and synovitis in 12%. Tc99 nuclear medicine studies were performed in 57 patients. A circumscribed increase in tracer uptake corresponding with the clinical location of lesions was detected in 96% of the studies. Positron emission tomography/CT scan was performed in 2 patients, demonstrating increased bone lesion ¹⁸F-fluorodeoxyglucose uptake in both cases. Combining imaging results, all patients had at least 1 abnormal imaging study, including sclerotic bone lesions in 68%, osteosclerosis in 71%, and hyperostosis in 23% of patients (see Supplemental Information).

**Histopathology**

A bone biopsy was performed in 81% of patients. Chronic inflammation with lymphocytic infiltrates was observed in 83% of samples, marrow fibrosis in 57%, osteonecrosis in 10%, and granulomas in 8%. Bacterial cultures were negative in all samples.

**Treatments**

Thirty patients received antibiotic therapy before diagnosis or rheumatologic evaluation. All had incomplete responses or subsequent recurrence of disease, and 69 of the 70 patients ultimately received treatment with NSAIDs, DMARDs, or immunosuppressive agents. The remaining patient was lost to follow-up before starting treatment. No standardized treatment protocol was followed. Generally, NSAIDs were used as first-line therapy, with DMARDs used next when response to NSAIDs was inadequate. Most patients who failed methotrexate were placed on TNF-α inhibitors. Corticosteroids were generally used briefly for acute relief of pain and inflammation. No patient received bisphosphonates.

Patients with any comorbid autoimmune disease were significantly more likely to receive second- or third-line therapy (83% vs 57%, $P < .02$). Partial and complete response rates for each agent are depicted in Fig 4. The highest rates of clinical remission were observed with TNF-α inhibitors (46%), followed by corticosteroids (37%), methotrexate (20%), sulfasalazine (18%), and NSAIDs (13%).

For additional analysis, patients with partial or complete responses to treatment were grouped together as “responders.” The only significant predictor of response was the treatment used (likelihood ratio test = 19.77, $P < .0001$). Age ($P = .22$), gender...
Less frequently, children manifest systemic symptoms such as fever. The locations and number of lesions among patients are extremely variable. Individual lesions in our series were found most frequently in long bones of the lower extremities, as well as in the pelvis, spine, clavicle, and mandible, but unusual locations also were seen. Rates of unifocality in previous publications have varied between 10% and 56%\(^1,2,3,7,45\), consistent with our series (29%). The mean number of lesions in our series (4.2 ± 3.1) was also similar to previous findings\(^2,3,7,44\).

Ancillary studies, including laboratory, radiologic, and pathologic investigations, are primarily useful for confirming the diagnosis of CNO and defining its extent and severity. They are not sufficiently specific, however, to replace clinical information. Plain radiographs are not sensitive for detecting asymptomatic lesions, nor do they provide information regarding ongoing inflammation. We found that \(^99m\)Tc bone scintigraphy has high sensitivity for detecting bone lesions but is limited by poor specificity in defining the location and extent of pathology. MRI permits detailed morphologic evaluation and assessment of disease activity, typically reflected by marrow edema.\(^46\) Novel imaging studies such as positron emission tomography/CT scan and whole-body MRI may hold promise for evaluating disease extent and activity.\(^47,48\)

We found that CNO patients with comorbid autoimmune diseases had a more aggressive phenotype during follow-up with higher rates of multifocality and higher ESR. Half of our patients had comorbid autoimmune disorders, and 49% of the patients had family history of autoimmunity in first- or second-degree relatives, similar to previous reports.\(^2\) The most common autoimmune comorbidities of CNO in this and other series have been arthritis, psoriasis, and IBD.

Evaluating treatment responses in CNO is difficult because of its recurrent pattern and the protean nature of the condition precluding simple outcome measures. Furthermore, in the absence of prospective, controlled trials, a natural fluctuation in disease severity could be misinterpreted as a therapeutic response. Nonetheless, we believe that our findings provide guidelines for a therapeutic approach to children with CNO. Antibiotics, used before rheumatologic evaluation, were nearly always unsuccessful in inducing remission of CNO flares. Contrary to other reports, we found that NSAIDs rarely provided durable control of bony lesions. Only 13% of our patients achieved a clinical remission using NSAIDs alone. This differed from a recent prospective German study in which 51% of 37 children with CNO treated only with naproxen were symptom-free after 12 months.\(^27\) The higher response rates to NSAIDs in German patients may reflect population differences or the fact that the German cohort included only newly diagnosed patients. Strikingly, 41% of this cohort had new radiologic lesions despite treatment. Thus, it appears that even in early disease, NSAIDs do not block progression of the inflammatory process, although they may ameliorate symptoms.

As in other autoimmune diseases,\(^49,50\) more aggressive immunomodulatory treatments seemed to be necessary to control CNO adequately in our cohort. Treatment with DMARDs and biologic agents in CNO previously has been reported only in cases and small series.\(^2,25–37\) In our study, we generally saw a sequential progression from NSAIDs to DMARDs, and then to TNF-\(\alpha\) inhibitors, with correspondingly improving response rates as therapy intensified. In a previous report, multifocality of lesions was associated
with failure of response to NSAIDs. However, in our study, only the agent used independently correlated with an improved outcome. Although autoimmune comorbidity was associated with more aggressive therapy, its presence was not predictive of treatment response, suggesting that response of CNO to treatments is independent of associated conditions.

Similar to other series, short courses of corticosteroids proved effective. However, steroids are not a feasible long-term option for treating CNO. In a previous report, sulfasalazine (together with a brief course of steroids) was added to NSAIDs in 4 CNO patients with progressive or stagnant disease. This therapy resulted in improved subjective well-being, but radiologic lesions nonetheless increased in half of the patients. Likewise, our data show no significant differences in response between sulfasalazine and NSAIDs, suggesting that sulfasalazine adds little except symptomatic relief.

Methotrexate has become a first-line DMARD in arthritis, but there are few publications describing its use for CNO. In our series, treatment with methotrexate was significantly more effective than NSAIDs, but similar to the findings of Jansson et al., it was not uniformly effective. TNF-α inhibitors have been reported as effective treatment of CNO in small series and a few case reports. In our cohort, 10 of 11 patients refractory to other therapies that received TNF-α inhibitors responded, including remission in 46%. These results are even more relevant considering that patients who received TNF-α inhibitors had already failed a median of 3 other treatments. In view of the apparent relationship of CNO to arthritis, psoriasis, and other TNF-dependent conditions, such findings are not unexpected. However, higher costs and potential side effects due to immunosuppression of TNF-α inhibitors should be taken into account when considering this therapy.

Several limitations of this study affect interpretation of our results. The retrospective nature of this study limits our ability to calculate associations accurately. For example, standardized medical and family history were not obtained, so estimations of incidence of associated conditions, prevalence of autoimmunity, and other factors represent minimal estimates. Treatments were not standardized or stratified, length of follow-up was variable, and choice of therapy might have been affected by perceived disease severity. It is possible that patients with milder disease were not referred to the centers involved in this study, skewing outcomes. Furthermore, broadly accepted outcome measures do not exist for CNO. We used both subjective (pain, swelling) and objective (acute phase reactants, radiographs) measures of treatment response in an attempt to reduce bias. However, because radiologic follow-up was not mandated, asymptomatic lesions might have been missed.

Ideally, prospective, randomized controlled trials will be organized to better answer questions concerning CNO. Comparison of DMARDs with bisphosphonates will be important as well, because our cohort did not include any patients treated with these agents. However, the rarity and heterogeneity of CNO, as well as the unpredictability of disease flares, render such studies difficult. Despite these limitations, we believe that our report provides important data to help improve the diagnosis and treatment of CNO.

CONCLUSIONS

We report the largest CNO cohort from the United States and provide evidence of improved responses to DMARD and biologic treatments over NSAIDs in this rare inflammatory disease. The rates of comorbid and familial autoimmunity observed in our study are higher than those previously described, supporting a potential autoimmune basis of CNO. Studies of genetic and immunologic mechanisms of CNO may further elucidate the pathogenesis of this disease and better define potential molecular targets for therapy. On the basis of these data and similarity to other rheumatologic diseases, we believe that early diagnosis and more aggressive treatments are important for improving outcomes for children with CNO.

REFERENCES


34. Massara A, Cavazzini PL, Trotta F. In SAPHO syndrome anti-TNF-alpha therapy may induce persistent amelioration of osteo-articular complaints, but may exacerbate cutaneous manifestations. Rheumatology (Oxford). 2006;45(6):730–733


Pediatric Chronic Nonbacterial Osteomyelitis
Arturo Borzutzky, Sara Stern, Andreas Reiff, David Zurakowski, Evan A. Steinberg, Fatma Dedeoglu and Robert P. Sundel

Pediatrics 2012;130;e1190; originally published online October 15, 2012;
DOI: 10.1542/peds.2011-3788

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/130/5/e1190.full.html