

Characteristics and outcomes of chronic non-bacterial osteitis in children

Stefanie Wintrich, Gerd Horneff

Abstract

Objective: To determine patient characteristics, clinical presentation, pattern of involvement, treatment, and outcome of patients with chronic non-bacterial osteitis (CNO).

Material and Methods: Consecutive cases of CNO were analyzed at a single center for pediatrics and adolescent medicine from 2006 to 2013 in terms of patient characteristics, clinical presentation, pattern of involvement, treatment, and outcome.

Results: We identified 32 children aged 1.5–15 years who were diagnosed with CNO between 2006 and 2013. A maximum of 12 bones per patient were affected in a total of 114 documented locations. The pelvis and clavicle (affecting 34% of patients each) were the most frequently affected bones. The foot skeleton was the most commonly affected region in 60% of patients. Skin manifestations were found in 7 (21%) patient. Increased inflammatory signs at presentation were detected in 18 patients. Pathological findings were found in all 30 children examined using magnetic resonance imaging (MRI), in 10 of 11 children examined using radiography, and in 8 of 10 patients examined using skeletal scintigraphy. Bone biopsy was performed in 9 patients. For initial treatment, non-steroidal anti-inflammatory drugs (NSAIDs) or coxibs were used in 28 (87.5%) patients. Remission or satisfactory follow-up was achieved in all patients.

Conclusion: Today, CNO is increasingly diagnosed using MRI and rarely through histological examinations. Therapeutic strategies include NSAIDs, which are often highly effective. All patients in the present study showed good clinical outcomes.

Keywords: Chronic recurrent multifocal osteomyelitis, bone diseases, chronic disease

Introduction

Chronic non-bacterial osteitis (CNO) is a benign noninfectious autoinflammatory disease of the bone tissue with an incomplete etiology (1, 2). The incidence of CNO is 0.4/100.000 children (3). It was first reported by Giedion et al. (4) in 1972. There are several synonyms for CNO, such as chronic recurrent multifocal osteomyelitis (CRMO); non-bacterial osteitis; or synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, all describing the same disease entity (5, 6). CNO generally occurs in children and adolescents, with a peak age of onset of 7–12 years (7). Localized bone pain is the leading symptom, often with local swelling and warmth (8). Patients are usually in good general condition. CNO can appear as a mono-/oligo-focal disease, as well as in chronic recurrent polyfocal stages with a risk of late effects, such as vertebral fractures and severe hyperostotic bone lesions (9). CNO primarily affects the metaphyses of long bones, although lesions can occur in any part of the skeleton (10). Other organs, including the skin, eyes, gastrointestinal tract, and lungs, can also be affected by inflammation (9, 11, 12). Skin inflammation manifests as palmoplantar pustulosis, acne, psoriasis, and rarely as pyoderma gangrenosum (1, 2). The most important differential diagnosis is bacterial osteomyelitis, although it is not usually multifocal (13). Even the pathophysiology of CNO is not completely known; there is evidence of an imbalance between pro- [interleukin-6 and tumor necrosis factor α (TNF- α)] and anti-inflammatory (interleukin-10) cytokines in patients with CNO (14). Children frequently have mild to moderately increased levels of inflammatory markers (7, 15, 16). Nowadays, CNO is usually diagnosed using magnetic resonance imaging (MRI) or through histological examination of bone biopsies, which reveal chronic inflammation and sclerosis without an infectious agent (17, 18). The first-line therapy for CNO is non-steroidal anti-inflammatory drugs (NSAIDs) (19). Among the second-line therapies, corticosteroids, methotrexate, sulfasalazine, TNF- α inhibitors, and bisphosphonates are used (16, 20–22). The aim of this study was to determine patient characteristics, clinical presentation, pattern of involvement, treatment, and outcome of patients with CNO.

Material and Methods

We retrospectively analyzed consecutive children who were diagnosed with CNO between January 2006 and December 2013 at a single center for pediatric rheumatology in a general hospital of pediatrics and adolescent medicine. CNO was diagnosed on the basis of clinical findings, such as localized bone pain,



Department of Paediatrics, Asklepios
Clinic Sankt Augustin, Sankt Augustin,
Germany

Address for Correspondence:
Stefanie Wintrich, Department of
Paediatrics, Asklepios Clinic Sankt
Augustin, Sankt Augustin, Germany

E-mail: s.wintrich@asklepios.com

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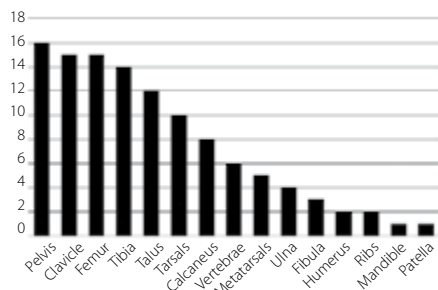


Figure 1. Absolute numbers of osteomyelitis-affected bones in the examined group of children with CNO during the entire observation period

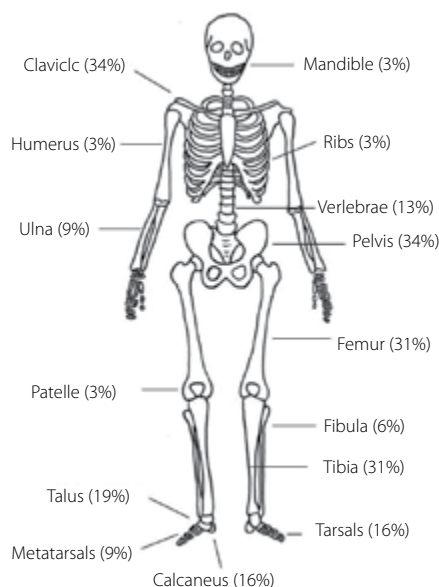


Figure 2. Relative frequency of CNO-affected bones, reflecting the percentage of patients in whom the bones were affected

swelling and warmth, regions with suspected osteomyelitis on magnetic resonance imaging (MRI) examination, or well-determined osteomyelitis of bone biopsies without an infectious origin. Patients were analyzed in terms of characteristics, such as gender and age, onset of symptoms, and clinical presentation. Data were retrieved for the pattern of involvement, typical laboratory findings, treatment options, and clinical outcomes. Clinical remission was defined as the absence of pain and swelling, inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] in the normal range (CRP: ≤ 5 mg/L; ESR: ≤ 20 mm/h), and absence of inflammatory changes on fluid-attenuated inversion recovery (FLAIR) MRI sequences, with missing or resolved contrast enhancements.

Because this was a retrospective, non-interventional study, approval of the ethics committee and informed consent was not neces-

sary. Statistical analysis was performed using Microsoft Excel and Microsoft PowerPoint (version 2010) for Windows (Microsoft Corporation, Redmond, United States). Results are expressed as total numbers and percent of cases.

Results

We identified 32 children with CNO from 2006 to 2013. The age at symptom onset ranged from 1.5 to 15 years (median: 7.7; I interquartile range (QR): 7.7–12.1), with 19 (60%) children aged ≥ 10 years. Twenty-five (78%) patients were female. Symptom duration until diagnosis ranged between 1 month and 5 years (median: 3.5 month). Twenty-six (81%) children were diagnosed within 1 year of onset. The patients were followed-up for a period of up to 8 years. We documented a total of 114 CNO-affected skeletal locations (Figure 1).

On average, each patient had 3.6 affected bones. The number of affected bones was 1 in 10 patients, 3 in 6 patients, 6 in 3 patients, 5 and 7 in 2 patients each, and 4, 8, 10, and 12 in 1 patient each. Ten (31%) patients had monofocal disease and 22 (69%) had multifocal disease. In the monofocal form of manifestation, the clavicle was the most commonly affected bone (40% patients). Overall, in the total patient cohort, 8 upper extremity bones, 60 lower extremity bones, and 46 axial skeleton bones (including mandible, clavicle, and pelvis) were affected. The pelvis, femur, and vertebrae were most commonly affected, whereas the mandible and patella were rarely affected (Figure 1). The pelvis, clavicle, femur, and tibia were the most frequently affected bones according to the number of patients affected (Figure 2).

The pelvis or clavicle was affected in 34% of patients, followed by the femur in 31% of patients. The most frequently affected region was the foot skeleton in 12 (38%) patients.

Skin manifestations were observed in 7 (21%) children, with palmoplantar pustulosis in 5 (15%) children and acne in 2 (6%) children; all these children were ≥ 9 years. One of the 5 children with palmoplantar pustulosis had only 1 affected bone, whereas the other 4 children had ≥ 6 affected locations. In the 2 children with acne, there was a single affected location in one and 5 affected locations in the other. Thus, there was no correlation between skin manifestations and the extent of bone disease. Increased inflammatory signs at presentation were detected in 18 patients. Increased CRP levels (>5 mg/L) were found in 15 (47%) patients and increased ESR levels (>20 mm/h) were found in 13 (40%) patients. In 10 (31%) patients, both CRP and ESR levels were increased, whereas in 5 (16%) and 3

(10%) children, only CRP or ESR levels were increased, respectively. In 14 (44%) patients, there were no detectable inflammatory signs. Eleven (34%) children were radiographically examined. Among these, 10 showed pathological findings such as osteolysis or hyperostosis (sensitivity, 91%). All 30 children examined by MRI showed CNO foci (sensitivity, 100%). Skeletal scintigraphy revealed positive findings in 8 of the 10 children (sensitivity, 80%). A biopsy of bone lesions was performed in only 9 (28%) patients. All these samples showed evidence of lymphoplasmacellular infiltration and sclerosis (sensitivity, 100%).

Four children demonstrated spontaneous remission. NSAIDs (such as naproxen, ibuprofen, diclofenac, or indomethacin) or coxibs (etoricoxib) were used for initial treatment in 28 (88%) children. Of these, 20 (71%) children achieved remission without further therapy (Figure 3a, b). In 7 children, additional therapy with a short (5 day) course of oral corticosteroids was undertaken. Three children required further therapy, either with methotrexate, sulfasalazine, or bisphosphonates, to achieve remission (Figure 4). The average treatment duration of the patients at last presentation ranged from 8 to 66 months. Eleven patients are still being followed-up regularly and are currently in a controlled stage of the disease. All patients showed improvement without further complications.

Discussion

In our study, 78% of patients with CNO were females, with a median age of 8 years. This is consistent with the findings of earlier studies that investigated the distribution of patient characteristics in CNO cases (23, 24). There was no evidence that one gender was affected with CNO at an earlier age than the other. The median number of bone lesions per patient was 3.6, similar to that reported previously (15, 24). With regard to the number of affected bones per patient, we cannot exclude that affected bones could have been overlooked for several reasons. In agreement with the literature, the clavicle was one of the most commonly affected bones (34% of patients) (25). With 60 bone lesions identified, the lower extremity was the most affected part of the skeleton, similar to the findings of previous studies (15, 16, 26). A previous study showed an association between CNO and different skin manifestations, such as palmoplantar pustulosis and acne, in up to 23% of children (24). In our study, we found an association rate of 21%. There appears to be no correlation between the presence of skin manifestations and the severity of the disease. Our investigation demonstrates that MRI is a very sensitive examination method to substantiate CNO diagnosis. Every child



Figure 3. a, b. T1 weighted and fat suppressed of the right foot of an 11-year-old male patient with osteomyelitis of the distal tibia at presentation (a) and after 8 months of monotherapy with NSAIDs (b)

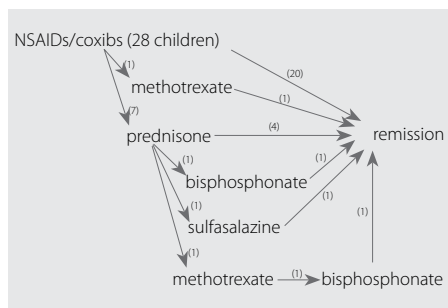


Figure 4. Flowchart of the different therapeutic strategies utilized in our patients with CNO, all patients eventually achieved remission

examined using MRI had confirmed bone lesions. CNO diagnosis can be almost definite if bone lesions on MRI are accompanied by typical skin lesions (9). In such cases, biopsy appears to be unnecessary (27). In our study, 28% of patients were biopsied; none of these had palmoplantar pustulosis. Differential diagnoses were bacterial osteomyelitis, other benign bone diseases, including fibrous dysplasia or osteofibroma, and malignant processes. When bacterial osteomyelitis is suspected, children are often initially treated with antibiotics for months before CNO is diagnosed.

In our study, 62% of patients with CNO achieved remission after monotherapy with NSAIDs, which is lower than the value reported in most earlier investigations (maximum 80%) (16, 24). In contrast, some studies have reported that only 13% of patients achieved clinical remission using NSAIDs (28). Thus, the outcome of our patients appears to be very favorable. In our study, the number of children achieving remission with NSAIDs might have increased if they had continued monotherapy for a longer duration. Furthermore, lesions are known to heal spontaneously; therefore, the magnitude of the effect of NSAIDs remains unclear. Different studies have demonstrated

very high response rates to corticosteroids in relapsing cases (29). Probably because of the short duration of the therapy, our results revealed that 43% of children treated with corticosteroids still required additional therapies, such as sulfasalazine, methotrexate, or bisphosphonates, to achieve remission. These therapies are listed in the literature as options for children with a very active or relapsing disease; however, double-blind controlled trials are lacking (15). Surgical intervention does not have any positive therapeutic effects (30).

Our study had some limitations. The sample size was small and the study involved only descriptive, retrospective analysis. Furthermore, the results of the study would probably have a greater significance if all patients had histologically confirmed CNO.

In conclusion, in the present study, all children achieved complete remission or reached a controlled stage of the disease without any symptoms on a stable dose of medications, indicating that the clinical outcomes of children with CNO are mostly good. NSAIDs are well-suited as a first-line therapy to achieve remission, with a minority of children requiring further therapy.

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