Chronic nonbacterial osteomyelitis in children: a multicentre Belgian cohort of 30 children

Sara Kaut

UZ Leuven: Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven

Ine Van den Wyngaert

Katholieke Universiteit Leuven (KUL)

Davy Christiaens

University Hospital Leuven

Carine Wouters

University Hospital Leuven

Nathalie Noppe

UZ Leuven: University Hospital Leuven

Nele Herregods

Ghent University Hospital

Joke Dehoorne

Ghent University Hospital

Lien De Somer (✉ lien.desomer@uzleuven.be)

Leuven University Hospitals <https://orcid.org/0000-0002-8488-5090>

Research article

Keywords: Chronic Non-Bacterial Osteomyelitis (CNO), Chronic recurrent multifocal osteomyelitis (CRMO), paediatrics, bone pain, radiology, whole-body MRI, management, tocilizumab

Posted Date: November 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1060789/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

To evaluate clinical characteristics, imaging findings, therapeutic approach and outcome of paediatric patients with Chronic Non-Bacterial Osteomyelitis (CNO).

Methods

Retrospective review of 30 children diagnosed with CNO at two tertiary care centres in Belgium. Imaging data were evaluated by blinded paediatric radiologists.

Results

Mean age at onset was 10.3 years and mean age at diagnosis was 11.7 years. Bone pain was the leading symptom (29/30 patients). Out of 180 symptomatic lesions, 131 were confirmed on MRI as hyperintense geographic lesions on STIR images at the metaphysis and epiphysis adjacent to growth plates of tubular bones. The most common sites of involvement were the lower limbs, spine, sternoclavicular joint and humerus. For nearly half of the patients (14/30) monotherapy with NSAIDs was sufficient to obtain remission. The remaining 16 patients received second-line therapy: bisphosphonates (n=15/30), disease-modifying antirheumatic drugs (n=7/30), etanercept (n=4/30) and tocilizumab (n=1/30). 26/30 Patients reached remission after a mean time of 37.6 months. The prognosis was worse for patients with spinal involvement, resulting in more long-term sequelae.

Conclusions

We present a multicentre paediatric cohort of 30 CNO patients. A typical pattern of bone involvement could be found on MRI. NSAIDs were administered as first-line treatment. Second-line strategies included bisphosphonates, corticosteroids, methotrexate, etanercept and tocilizumab.

Trial registration

Retrospectively registered.

Background

Chronic nonbacterial osteomyelitis (CNO), also known as Chronic Recurrent Multifocal Osteomyelitis (CRMO) was first described in 1972 (1). It is a rare autoinflammatory disorder, characterized by chronic, sterile osteomyelitis in one or more bones presenting with recurrent episodes of bone pain. The metaphysical area of long bones, spine and clavicle are typically involved (2-5). The pathophysiology still remains unclear. There are arguments that a dysregulation between Toll-like receptor 4 (TLR4), mitogen-activated protein kinase (MAPK) and inflammasome signalling, leads to an imbalance between pro- (IL-1, IL-6, TNF- α , IL-20) and anti-inflammatory (IL-10, IL-19) cytokine expression from monocytes, resulting in

bone inflammation and osteolysis (6). The existence of monogenic autoinflammatory diseases with osteomyelitis as main clinical feature, reports of CNO occurring in twins and siblings and the association of CNO with other inflammatory diseases like psoriasis and inflammatory bowel disease (IBD) in first degree relatives suggest a genetic predisposition (7, 8).

The incidence of CNO is less than 1/100.000 children/year (3, 9). It primarily affects children and adolescents but it can persist in adulthood or present later in life. The average age at onset of symptoms is 10 years (2-5). Systemic symptoms including fever, malaise, weight loss and fatigue can be found in 1/3 of CNO patients. Extra-skeletal manifestations; arthritis, palmoplantar pustulosis, psoriasis vulgaris, IBD, Takayasu arteritis and renal disease are associated in 10 to 30% of patients (3, 4, 8, 10). CNO can be complicated by vertebral compression fractures, kyphosis and leg length discrepancy when it is not recognized early or treated adequately.

Diagnosis of CNO is challenging and made by excluding alternatives in the differential diagnosis including malignancy (primary bone tumours and leukaemia/lymphoma), Langerhans cell histiocytosis, juvenile idiopathic arthritis, metabolic disorders (including hypophosphatasia) and infection. Laboratory investigations, imaging studies and histology can be useful for diagnosis and monitoring of the disease (3, 4, 9, 11).

Treatment of CNO patients has been mostly empiric. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often the first-line treatment. Corticosteroids, bisphosphonates, tumour necrosis factor-alpha (TNF- α) blocking agents and methotrexate are reported as second-line treatment with variable success (3, 12-14).

The aim of this study was to evaluate demographic and clinical characteristics, magnetic resonance imaging (MRI) findings and therapeutic features in paediatric patients with CNO at two tertiary centres in Belgium. Radiological data were reviewed in detail to detect specific signs that can distinguish CNO from other diseases such as infection, benign bone lesions and malignancies. We correlated clinical symptomatic lesions with inflammatory signs on imaging.

Methods

A retrospective review of medical records of 30 paediatric patients diagnosed with CNO between January 1, 1996 and December 31, 2017 at the paediatric rheumatology departments of the University Hospitals of Leuven and Ghent. The study was approved by the Supervisory Committee on Medical ethics of the "Master of medicine (Leuven)" programme and the Ethics Committee UZ Ghent.

The diagnosis of CNO was defined as the presence of unifocal or multifocal bone inflammatory lesions with radiological and/or histopathological characteristics compatible with this diagnosis, having excluded infectious, oncological or other inflammatory diseases. A clinical bone lesion was defined as an area of bone pain reported by the patients.

Clinical characteristics such as age, sex, age at onset of symptoms, personal and family history, treatments with their effectiveness and side effects and sequelae were registered. Remission was defined as the absence of pain and resolution of inflammatory syndrome for at least 6 months.

Laboratory evaluations, imaging and histology from bone biopsy were collected. On MRI, lesions were defined as areas of bone marrow edema, which implicates an abnormal hyperintensity on short tau inversion recovery (STIR) images or/and abnormal hypointensity on T1-weighted images and/or areas of contrast enhancement. Lesions were evaluated for location, periosteal reaction and association with joint or/and soft tissue involvement. On radiographic images, lesions were classified according to their density (osteolytic, sclerotic or mixed) with or without periosteal reaction, hyperostosis, cortical expansion or ill-defined margins. Imaging data were compared to clinical findings.

Results

Demographic data and clinical characteristics

A total of 30 patients were enrolled in the study. 73% (n=22) were female and 27% (n=8) were male, with a gender ratio of 2.8:1. Mean age at onset of symptoms was 10.3 years (range 5.8-16.3) and mean age at diagnosis was 11.7 years (range 5.9-16.9) with a mean diagnostic delay of 17 months (range 0.5-64).

Most patients (29/30) presented with bone pain, worsening at night. 22/30 (73%) reported loss of function and 7 (23%) reported morning stiffness. Systemic features such as fever (temperature $\geq 38.5^{\circ}\text{C}$) and weight loss were present, respectively in 3 (10%) and 7 (23%) patients. 14 of all patients (47%) reported fatigue and 15 patients (50%) mentioned cessation of sports participation. In 8 patients (27%) onset of the pain was provoked by trauma, viral infection or stress.

On physical examination, there was pain on palpation in 22 patients (73%), bone and periarticular swelling in 20 patients (67%) and restricted range of motion in 14 (47%). 5 Patients (17%) had associated arthritis. Clinical characteristics are summarized in table 1.

Mean number of clinical lesions per patient was 1.7 (range 1-7) at onset and 6.0 (range 1-19) over the course of the disease. Twenty patients (67%) presented with a unifocal disease at onset, although during follow-up 15 of them evolved to a multifocal disease. Lesions were asymmetric in 24/30 patients (80%). In total, 180 clinical lesions were reported. Most frequently involved were the knee (18%), followed by the spine and pelvis (13%), proximal femur (9%), ankle (7%), clavicle, humerus, distal tibia and sternoclavicular joint (each 5%). Number and distribution of lesions are described in table 2.

Table 2. Number and distribution of lesions

	CLINICAL		RADIOLOGY	
	(n)	(%)	(n)	(%)
Clavicle	9	5%	13	8%
Shoulder	6	3%	5	3%
Humerus	9	5%	11	6%
Radius	3	2%	0	0%
Ulna	0	0%	0	0%
Elbow	5	3%	2	1%
Wrist	4	2%	0	0%
Hand	0	0%	0	0%
Pelvis	23	13%	28	16%
<i>Sacroiliac joint</i>	<i>12</i>	<i>7%</i>	<i>13</i>	<i>8%</i>
<i>Ileum</i>	<i>6</i>	<i>3%</i>	<i>9</i>	<i>5%</i>
<i>Pubis</i>	<i>5</i>	<i>3%</i>	<i>6</i>	<i>3%</i>
Hip	4	2%	7	4%
Femur	16	9%	22	13%
Knee	33	18%	23	13%
<i>Distal femur</i>	<i>11</i>	<i>6%</i>	<i>13</i>	<i>8%</i>
<i>Knee</i>	<i>9</i>	<i>5%</i>	<i>0</i>	<i>0%</i>
<i>Proximal tibia</i>	<i>13</i>	<i>7%</i>	<i>10</i>	<i>6%</i>
Tibia	9	5%	10	6%
Fibula	4	2%	5	3%
Ankle	12	7%	7	4%
Metatarsals	3	2%	1	1%
Spine	23	13%	23	13%
<i>Cervical</i>	<i>3</i>	<i>2%</i>	<i>2</i>	<i>1%</i>
<i>Thoracic</i>	<i>10</i>	<i>6%</i>	<i>10</i>	<i>6%</i>
<i>Lumbar</i>	<i>5</i>	<i>3%</i>	<i>4</i>	<i>2%</i>
<i>Sacral</i>	<i>5</i>	<i>3%</i>	<i>7</i>	<i>4%</i>

Scapula	3	2%	1	1%
Ribs	4	2%	3	2%
Sternum	9	5%	10	6%
Mandible	1	1%	1	1%

Half of the patients had extraosseous manifestations: 6 patients (20%) had aphthous oral ulcers, five patients (17%) had severe acne, 4 (13%) psoriasis and 4 (13%) eczema. Two patients (7%) had Crohn's disease and one patient (3%) developed malign hypertension caused by Takayasu arthritis. One patient (3%) was diagnosed with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome.

None of the patients had a family history of CNO. However, other CNO-related diseases were found in patients family members, like rheumatic disease (bechterew's, rheumatoid arthritis in 12/30 or 40%), psoriasis (in 7/30 or 23%) and IBD (in 5/30 or 17%).

Laboratory investigations

Inflammation with elevated C-reactive protein (CRP) concentrations (range 0.4-112 mg/L) and *erythrocyte sedimentation* rate (ESR) (range 12-101 mm/h) was noted in 18 patients (60%) and 26 patients (87%) respectively. Human leukocyte antigen-B27 (HLA-B27) was detected in 2 of 7 tested patients (29%), one patient had associated arthritis and the other involvement of sacroiliac joint. Antinuclear antibodies and rheumatoid factor were found in none of the tested patients (20 and 13 respectively).

Blood cultures were performed in 17/30 patients (57%) and synovial fluid was analysed in 4 (13%). Both tests remained sterile in all patients. A bone biopsy was performed in 16 patients (53%), showing a mononuclear cell infiltration, mainly plasmocytes in most patients, which is a typical finding for severe chronic inflammation. In none of the cases there was a suspicion of malignancy.

Imaging

Conventional X-ray was performed in all patients, whole-body MRI in 18/30 patients (60%) and targeted MRI in 27/30 (90%). 172 radiological lesions were identified during the follow-up with an average of 5.7 lesions per child (range 1-20). In our cohort conventional radiographs showed osteolytic (36%), sclerotic (24%) or mixed (40%) lesions. In most cases CRMO showed a typical pattern of bone involvement on MRI: multifocal, hyperintense lesions on STIR images at the metaphysis and epiphysis adjacent to growth plates of tubular bones. Symptomatic and asymptomatic lesions can show the same abnormalities on MRI, for example only bone marrow edema, although, we found that lesions with a periosteal component are mostly symptomatic. The most common sites were the pelvis (16%), the knee (13%: distal femur 8% and proximal tibia 6%), the spine (13%), proximal femur (13%), clavicle (8%),

humerus, tibia and sternum (each 6%). There were no CNO lesions found in the skull, ulna, radius or hand. Number and distribution of lesions are described in table 2.

Combining clinics with imaging

Five patients had a clinical unifocal course of their CNO, in 4 of them imaging confirmed the unifocal lesion (localizations: clavicle, distal femur, pelvis, sternoclavicular joint). One patient with a clinical unifocal sacral location had an additional, subclinical lesion at the acromion on total body MRI. On the other hand, 2 patients in our cohort had unifocal involvement on imaging but reported multiple clinically symptomatic sites. Of the 180 clinical painful bone lesions, 131 were confirmed on imaging. For 49 anamnestic painful localizations, no correlation was found on MRI imaging, as they were likely caused by other etiologies such as muscular pain. There were 41 subclinical lesions (edema on imaging but clinically asymptomatic). (Figure 1).

Treatment

In terms of treatment all patients received NSAIDs (n= 30), 15 bisphosphonates (pamidronate), 6 methotrexate, 1 azathioprine, 6 corticosteroids, 4 etanercept and 1 tocilizumab. (Figure 2).

NSAIDs were used as first-line therapy. In 47% of patients, NSAIDs were sufficient to obtain long-lasting remission. Corticosteroids were given due to associated arthritis (n = 3), new facial lesions in patient with SAPHO (n = 1), Crohn's disease (n = 1) and as bridging therapy with methotrexate in a patient who developed new lesions under therapy with pamidronate (n = 1).

15 patients (50%) received pamidronate (mean of 3.8 cycles, range 1-10 cycles). 11 of the 16 patients with vertebral involvement, were treated with pamidronate (68%). In 3 patients, pamidronate was combined with disease modifying antirheumatic drugs (DMARDs) from the start. 9/12 patients (75%) receiving pamidronate without DMARDs, could reduce the NSAIDs during treatment with pamidronate and regain their physical activity.

In our study, 7 patients (23%) were treated with a DMARD. 1 Patient with Crohn's disease was treated with azathioprine the 6 remaining patients received methotrexate. During treatment with a DMARD, corticosteroids and NSAIDs could be stopped in 3 out of 7 patients. In the 4 remaining patients (1 with SAPHO, 3 with associated arthritis), methotrexate was insufficient to control the disease and add-on with a TNF- α blocker (etanercept) was necessary. Etanercept resulted in clinical and biochemical remission in 3/4 patients. One patient had ongoing inflammation despite receiving all above mentioned therapies and was finally switched to tocilizumab in combination with methotrexate with success as long as tocilizumab was given every 4 weeks.

In 18/30 patients (60%) physical therapy was necessary to improve range of motion and regain normal mobility.

Outcome

7/30 (23%) patients had a vertebral compression fracture. One patient needed spine surgery. 5 patients (17%) had a leg length discrepancy. 4 patients (13%) needed psychiatric or psychologist support because of emotional stress caused by this disease. The patient with SAPHO experienced more stress because of the extensive cutaneous lesions and was hospitalised in the department of paediatric psychiatry for depression, auto mutilation and suicidal attempts.

26 patients (87%) achieved remission. The mean time to obtain remission was 37.6 months or 3.1 years (range 7-96 months). Three patients were lost from follow up.

Discussion

We present a retrospective multicentre series of paediatric CNO patients and describe their clinical presentation, imaging data, treatment and outcome. To our knowledge this is the first series from Belgium.

Mean age of onset of disease (10.3 years) and diagnosis (11.7 years) as well as the ratio of female to male patients (2.8:1) and diagnostic delay of 17 months were similar to data published in previous studies (2-5, 15). The protracted gap between onset of symptoms and diagnosis can be attributed to the absence of pathognomonic clinical and laboratory signs in diagnosing CNO, the relatively ignorance of the disease, as well as CNO being a diagnosis of exclusion. Increased attention to the disease has been seen, through which diagnostic delays have been shortened (5).

Our study confirms that local bone pain, worsening at night is the main clinical feature of CNO (2, 3, 8). Similar to previous observations, local swelling and arthritis were not always present (3, 8). In previous studies systemic symptoms such as fever and weight loss were reported in one-third of the patients but were less frequent in our analysis (fever in 10%, weight loss in 23%) (2-5).

Some classify CNO in the group of autoinflammatory diseases, others see CNO as part of the spectrum of spondyloarthropathies (4, 14). HLA-B27 was determined in a small proportion of our cohort, not enabling us to find a correlation with HLA B27-associated spondylarthritis. CRP and/or ESR levels were elevated in previous published studies and in the same range as our findings (elevation of CRP in 60%, ESR in 87%) (4, 7). CNO can also be associated with other inflammatory diseases such as severe acne, psoriasis and IBD which was confirmed in our patient cohort (3, 4, 8). None of first- or second-degree relatives of our patients were diagnosed with CNO, which is different from previous reports (3, 4, 7).

As described in previous studies, multifocal pattern of CNO lesions was most common (4). The mean number of painful osseous lesions per patient over the course of the disease (6.0) was consistent with our imaging data (5.7) and similar to published data (4, 7, 16, 17). MRI correlates well with the clinical findings: lesions are most frequently seen in the lower limbs, the spine and pelvis, the clavicle and sternoclavicular joint and proximal humerus. High percentage of lesions in the lower limbs, is also described in other series (3, 4, 7, 18). The prevalence of vertebral involvement in our study (16/30 or 53%)

was higher than described previously, although, the reported percentages had a broad range (4-30%) (3, 16, 19). The clavicle is a typical site for CNO disease (4, 5, 11).

In our cohort, conventional radiographs showed characteristic lesions of osteolysis, sclerosis or mixed lesions. Radiographic CNO lesions are described in early stages as an osteolytic region and the sclerosis mostly occurs afterwards as part of the healing process, just like the periosteal reaction (3, 11). But radiography certainly has its limitations; it does not evaluate the entirety of the skeleton and has a very low sensitivity (11, 20). Most of our CNO patients showed a characteristic pattern of bone involvement on MRI: hyperintense geographic lesions at the metaphysis and epiphysis adjacent to growth plates of tubular bones. Currently, work-up with MRI is common and a standardized scoring tool for MRI has recently been published (21).

Imaging, MRI and/or isotopic bone scanning, is the cornerstone for detecting the multifocal pattern, location and distribution of lesions and to exclude the main differentials (9, 20). Furthermore, it also helps to determine the progression of the disease or the effect of the treatment (18). Whole-body MRI can be very useful in demonstrating subclinical lesions, which are important to diagnose CNO and thereby reducing the need for invasive diagnostic procedures. Bone biopsy is not required in the workup of CNO but can be useful in cases where the differential diagnosis with an infection or malignancy, especially in unifocal disease, is unclear (5, 9). If a biopsy is necessary, MRI helps to locate the optimal site for biopsy (11, 17, 22). There are some MRI sequences that are helpful to differentiate CNO from other diseases. STIR is water sensitive sequence with fat suppression and demonstrates fluid, bone marrow and soft tissue edema, as illustrated in figure 3. Bone marrow edema is a typical finding in CNO, in contrast to soft tissues abnormalities which are rare in CNO (3, 23). Another important MRI sequence is diffusion-weighted imaging (DWI). It uses the diffusion of water molecules to generate contrast in MRI images and can be quantitative assessed using the apparent diffusion coefficient (ADC). In this way information about the tissue cellularity can be obtained, in some malignant lesions it will result in a low ADC because of high cellular density which means a reduction of the diffusion of water molecules. On the other hand bone marrow edema gives a high ADC because of the high amount of free inter-cellular water (24). Enhancement with gadolinium can help to get a better view of the inflammatory activity of the lesions (3).

Treatment of CNO is yet to be standardized but there is general agreement that NSAIDs are the best first-line treatment. Uniform guidelines on the second-line treatment for children with CNO are scarce. In 2017 the CNO subgroup of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) published three standardized consensus treatment plans for patients with CNO with insufficient response to NSAID and/or the presence of active spinal lesions (25). Placebo-controlled trials on treatment of CNO are lacking.

In our series, NSAIDs as first-line therapy in all patients, was sufficient to obtain remission in almost half of the patients. High efficacy of NSAIDs was reported by Catalano-Pons et al. where 73% of patients were responders and the effectivity of NSAIDs appeared to be inversely associated with the number of lesions

at the onset of the disease (2). Effectivity of NSAIDs was not correlated with number of lesions in our cohort, but rather correlated with absence of associated arthritis. In a large French study, NSAIDs were also effective in 73% of patients, although effectiveness was defined as an improvement of symptoms, which does not mean the patients were in remission (4). Other studies had a lower efficacy of NSAIDs (5, 16, 26). In the different studies definition of efficacy and the described population varies, therefore results are not always comparable. The prospective use of NSAIDs has been evaluated in a single study performed in 37 CNO patients. A favourable clinical course was reported in 43% of patients taking naproxen at 6 months of follow-up; moreover, the total number of clinical detectable lesions was significantly reduced (27).

Bisphosphonates proved to be anti-inflammatory and reduce pain. They play an important role in the bone remodelling by inhibiting the osteoclast activity (12, 28, 29). The most commonly used bisphosphonate is pamidronate, but alendronate has been reported to be safe and useful as well. In our population, we saw symptomatic improvement in 9 out of 12 patients (75%) receiving more than 1 cycle pamidronate without associated DMARDs. Uniform data on dosage, duration and monitoring the effect of the bisphosphonates in CNO are lacking (28). Simm et al used bisphosphonates in children with persistent pain without spinal involvement, 4/5 patients (80%) showed a reduction of pain and an improvement of function and imaging (29). In the studies of Miettunen et al and Gleeson et al, spinal involvement was noted respectively in 2/9 and 5/7 patients, where bisphosphonates resolved the pain in respectively all 9 patients and in 6/7 of patients (12, 30). Hospach et al used bisphosphonates in patients with vertebral deformations refractory to NSAIDs, steroid and second-line therapy, with a reduction of symptoms and vertebral inflammation on MRI in all the patients (7/7) and improvement of vertebral deformities in 2 patients (28).

The most frequently used DMARDs for CNO are methotrexate and sulfasalazine (13, 16, 26). The reported success rate in inducing remission with methotrexate is variable (5, 25, 26). In our cohort the use of these conventional DMARDs was rather unsuccessful, 4 out of the 7 patients (57%) only experienced a temporary effect.

TNF- α blockade is the most frequently used biological treatment in CNO. They restore the imbalance between pro- and anti-inflammatory cytokines (13). Infliximab as well as etanercept and adalimumab are used with variable treatment responses (26, 31, 32). Disease activity seems to be better controlled with TNF- α blockers compared to conventional therapy (NSAIDs, corticosteroids and pamidronate) (33). TNF- α blockers also improve cutaneous manifestations and are therefore recommended as first choice second-line therapy in these patients (34). In our cohort, 4 patients (13%) received etanercept in combination with methotrexate, resulting in remission in 3 of them. Because of the varying results and the lack of guidelines for the use of TNF- α blockers in patients with CNO, we would recommend this therapy in refractory cases.

One of our patients received IV tocilizumab in combination with methotrexate. This patient received all of the previously described treatments without sustained remission (recurrent pain, new lesions on MRI,

systemic inflammation,...). With the combination of corticosteroids, methotrexate and IL-6 inhibition, the patient was symptom free after 3 weeks. To our knowledge, this is the first paediatric patient with CNO who receives IL-6 inhibition. Successful therapy with an IL-6 inhibition is previously reported in adult patients with persistent inflammation under the conventional therapy (35). IL-6 is known to regulate osteoclast-mediated bone erosion (36). Although the use of IL-1 inhibition is described in the treatment of CNO (32), none of our patients was treated by IL-1 inhibition.

CNO has generally a good long-term prognosis and resolves often without sequelae (3, 8, 11, 16). Physical sequelae of CNO described here are in line with other studies where incidence is varying between 20-26% (2, 4, 37). The most common long-term sequelae are vertebral compression fractures with development of spinal misalignments (3, 4, 12, 28). When the inflammatory lesions are close to the growth plate, CNO can cause a discrepancy in bone length (2, 3, 37). Early diagnosis and prompt adequate treatment are important in the prevention of long-term sequelae (9). Psychical stress and depression due to CNO is rarely mentioned in studies. 13% of our patients needed psychological support. Depression was reported in 1 patient (2.5%) by Catalano-Pons et al and Huber showed that CNO affected education in 16% of the patients (2, 37).

There are a few limitations to our study. First, our patients were recruited in 2 tertiary care centres. Presumably, most severely affected patients were sorted out, so selection bias is possible. Furthermore, it was a retrospective study, whereby data were missing and clinical and radiologic follow-up were not standardised. Due to rarity of the disease, our population was rather small, so it is essential to be careful to generalize our results. Because of lack of uniform treatment practice in both participating centres, patients outcomes are difficult to compare.

However, the study reflects on clinical manifestations, as well as diagnostic investigations, treatment and prognosis of CNO. In addition, the use of an IL-6 inhibitor in combination with methotrexate was described in this article for the first time in a paediatric population.

Conclusion

Clinical manifestations, laboratory and radiological investigations, treatment and prognosis were described in 30 patients with CNO. Bone pain is the leading symptom in this population. A typical pattern of bone involvement can be found on MRI, through which CNO can be differentiated from other diseases and demonstrates subclinical lesions. NSAIDs are first choice in the treatment of CNO. However, guidelines and consensus about the second-line treatment are still missing. Successful use of IL-6 inhibition was described in one patient resistant to first and second-line treatment. Further studies on treatment strategies and pathogenesis are warranted.

Abbreviations

CNO – Chronic Non-Bacterial Osteomyelitis

CRMO – Chronic recurrent multifocal osteomyelitis

MRI – magnetic resonance imaging

NSAIDs – Nonsteroidal anti-inflammatory drugs

IBD – inflammatory bowel disease

TNF – tumour necrosis factor-alpha

IL – interleukin

STIR – short tau inversion recovery

CRP – C-reactive protein

ESR – *erythrocyte sedimentation* rate

HLA-B27 – human leukocyte antigen B27

DMARDs – disease modifying antirheumatic drugs

WBC – white blood cells

SAPHO – synovitis, acne, pustulosis, hyperostosis and osteitis

ADC – apparent diffusion coefficient

DWI – diffusion-weighted imaging

CARRA - Childhood Arthritis and Rheumatology Research Alliance

Declarations

Ethics approval and consent to participate

UZ Leuven: "The Supervisory Committee on Medical ethics of the "Master in de geneeskunde (Leuven)" programme has reviewed your master's thesis project proposal "Retrospectief onderzoek van CRMO bij kinderen" and advises in its favour. This means that the committee has acknowledged that your project, as described in the protocol, is scientifically relevant and in line with prevailing ethical standards. This favourable advice does not entail the committee's responsibility for the planned project, however. You remain solely responsible. If you intend to publish your master's thesis, this e-mail may be used as proof of the committee's consent."

UZ Ghent: "The above mentioned documents have been reviewed by the ethics committee. A positive advice was given for his protocol on 23/03/2018."

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available (contains patients information).

Competing interests

No financial support.

Funding

No funding.

Authors' contributions

SK analysed and interpreted all patient data regarding clinical presentation, imaging, treatment and outcome from UZ Leuven and UZ Ghent. She compared clinics with imaging. She drafted the initial manuscript and deeply revised the final version of the manuscript.

IVW analysed and interpreted all patient data regarding clinical presentation, imaging, treatment and outcome from UZ Leuven.

DC interpreted all patient data regarding imaging from UZ Leuven.

CW conceptualized and designed the case collection and deeply revised the final version of the manuscript for important intellectual content.

NN analysed and interpreted all patient data regarding imaging from UZ Leuven and UZ Ghent and critically reviewed the article.

NH analysed and interpreted all patient data regarding imaging from UZ Ghent and critically reviewed the article.

JD conceptualized and designed the case collection and deeply revised the final version of the manuscript for important intellectual content.

LDS conceptualized and designed the case collection, contributed on the writing and deeply revised the final version of the manuscript for important intellectual content.

All authors read and approved the final manuscript.

Acknowledgements

None

References

1. Giedion A, Holthusen W, Masel LF, Vischer D. Subacute and chronic symmetrical osteomyelitis. *Ann Radiol (Paris)*. 1972;15(3):329-42.
2. Catalano-Pons C, Comte A, Wipff J, Quartier P, Faye A, Gendrel D, et al. Clinical outcome in children with chronic recurrent multifocal osteomyelitis. *Rheumatology (Oxford)*. 2008;47(9):1397-9.
3. Costa-Reis P, Sullivan KE. Chronic Recurrent Multifocal Osteomyelitis. *J Clin Immunol*. 2013;33(6):1043-56.
4. Wipff J, Costantino F, Lemelle I, Pajot C, Duquesne A, Lorrot M, et al. A large national cohort of French patients with chronic recurrent multifocal osteitis. *Arthritis Rheumatol*. 2015;67(4):1128-37.
5. Roderick MR, Shah R, Rogers V, Finn A, Ramanan AV. Chronic recurrent multifocal osteomyelitis (CRMO) - advancing the diagnosis. *Pediatr Rheumatol Online J*. 2016;14(1):47.
6. Hofmann SR, Kapplusch F, Mäbert K, Hedrich CM. The molecular pathophysiology of chronic non-bacterial osteomyelitis (cno) - a systematic review. *Mol Cell Pediatr*. 2017;4(1):7.
7. Jansson A, Renner ED, Ramser J, Mayer A, Haban M, Meindl A, et al. Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. *Rheumatology (Oxford)*. 2007;46(1):154-60.
8. Ferguson PJ, Sandu M. Current understanding of the pathogenesis and management of chronic recurrent multifocal osteomyelitis. *Curr Rheumatol Rep*. 2012;14(2):130-41.
9. Schnabel A, Range U, Hahn G, Siepmann T, Berner R, Hedrich CM. Unexpectedly high incidences of chronic non-bacterial as compared to bacterial osteomyelitis in children. *Rheumatol Int*. 2016;36(12):1737-45.
10. Pastore S, Ferrara G, Monasta L, Meini A, Cattalini M, Martino S, et al. Chronic nonbacterial osteomyelitis may be associated with renal disease and bisphosphonates are a good option for the majority of patients. *Acta Paediatr*. 2016;105(7):e328-33.
11. Falip C, Alison M, Boutry N, Job-Deslandre C, Cotten A, Azoulay R, et al. Chronic recurrent multifocal osteomyelitis (crmo): a longitudinal case series review. *Pediatr Radiol*. 2013;43(3):355-75.
12. Gleeson H, Wiltshire E, Briody J, Hall J, Chaitow J, Sillence D, et al. Childhood chronic recurrent multifocal osteomyelitis: pamidronate therapy decreases pain and improves vertebral shape. *J Rheumatol*. 2008;35(4):707-12.
13. Hofmann SR, Schnabel A, Rosen-Wolff A, Morbach H, Girschick HJ, Hedrich CM. Chronic nonbacterial osteomyelitis: pathophysiological concepts and current treatment strategies. *J Rheumatol*.

2016;43(11):1956-64.

14. Hedrich CM, Morbach H, Reiser C, Girschick HJ. New insights into adult and paediatric chronic non-bacterial osteomyelitis cno. *Curr Rheumatol Rep*. 2020;22(9):52.
15. Kaiser D, Bolt I, Hofer M, Relly C, Berthet G, Bolz D, et al. Chronic nonbacterial osteomyelitis in children: a retrospective multicenter study. *Pediatr Rheumatol Online J*. 2015;13:25.
16. Walsh P, Manners PJ, Vercoe J, Burgner D, Murray KJ. Chronic recurrent multifocal osteomyelitis in children: nine years' experience at a statewide tertiary paediatric rheumatology referral centre. *Rheumatology (Oxford)*. 2015;54(9):1688-91.
17. von Kalle T, Heim N, Hospach T, Langendorfer M, Winkler P, Stuber T. Typical patterns of bone involvement in whole-body mri of patients with chronic recurrent multifocal osteomyelitis (crmo). *Rofo*. 2013;185(7):655-61.
18. Ferrari J, Pilkington C. Chronic recurrent multifocal osteomyelitis: the prevalence of lower-limb and foot involvement. *J Am Podiatr Med Assoc*. 2014;104(6):583-7.
19. Khanna G, Sato TSP, Ferguson P. Imaging of chronic recurrent multifocal osteomyelitis. *Radiographics*. 2009;29(4):1159-78.
20. Voit AM, Arnoldi AP, Douis H, Bleisteiner F, Jansson MK, Reiser MF, et al. Whole-body magnetic resonance imaging in chronic recurrent multifocal osteomyelitis: clinical longterm assessment may underestimate activity. *J Rheumatol*. 2015;42(8):1455-62.
21. Zhao Y, Sato TS, Nielsen SM, Beer M, Huang M, Iyer RS, et al. Development of a scoring tool for chronic nonbacterial osteomyelitis magnetic resonance imaging and evaluation of its interrater reliability. *J Rheumatol*. 2020;47(5):739-47.
22. Fritz J, Tzaribatchev N, Claussen CD, Carrino JA, Horger MS. Chronic recurrent multifocal osteomyelitis: comparison of whole-body mr imaging with radiography and correlation with clinical and laboratory data. *Radiology*. 2009;252(3):842-51.
23. Sato T, Watal P, Ferguson PJ. Imaging mimics of chronic recurrent multifocal osteomyelitis: avoiding pitfalls in a diagnosis of exclusion. *Pediatr Radiol*. 2020;50(1):124-36.
24. Leclair N, Thormer G, Sorge I, Ritter L, Schuster V, Hirsch FW. Whole-body diffusion-weighted imaging in chronic recurrent multifocal osteomyelitis in children. *PloS One*. 2016;11(1).
25. Zhao Y, Wu EY, Oliver MS, Cooper AM, Basiaga ML, Vora SS, et al. Consensus treatment plans for chronic nonbacterial osteomyelitis refractory to nonsteroidal antiinflammatory drugs and/or with active spinal lesions. *Arthritis Care Res (Hoboken)*. 2018;70(8):1228-37.

26. Borzutzky A, Stern S, Reiff A, Zurakowski D, Steinberg EA, Dedeoglu F, et al. Pediatric chronic nonbacterial osteomyelitis. *Pediatrics*. 2012;130(5):E1190-7.
27. Beck C, Morbach H, Beer M, Stenzel M, Tappe D, Gattenlohner S, et al. Chronic nonbacterial osteomyelitis in childhood: prospective follow-up during the first year of anti-inflammatory treatment. *Arthritis Res Ther*. 2010;12(2): R74.
28. Hospach T, Langendoerfer M, von Kalle T, Maier J, Dannecker GE. Spinal involvement in chronic recurrent multifocal osteomyelitis (CRMO) in childhood and effect of pamidronate. *Eur J Pediatr*. 2010;169(9):1105-11.
29. Simm PJ, Allen RC, Zacharin MR. Bisphosphonate treatment in chronic recurrent multifocal osteomyelitis. *J Pediatr*. 2008;152(4):571-5.
30. Miettunen PMH, Wei XC, Kaura D, Abou Reslan W, Aguirre AN, Kellner JD. Dramatic pain relief and resolution of bone inflammation following pamidronate in 9 pediatric patients with persistent chronic recurrent multifocal osteomyelitis (crmo). *Pediatr Rheumatol Online J*. 2009;7:2.
31. Wipff J, Adamsbaum C, Kahan A, Job-Deslandre C. Chronic recurrent multifocal osteomyelitis. *Joint Bone Spine*. 2011;78(6):555-60.
32. Eleftheriou D, Gerschman T, Sebire N, Woo P, Pilkington CA, Brogan PA. Biologic therapy in refractory chronic non-bacterial osteomyelitis of childhood. *Rheumatology (Oxford)*. 2010;49(8):1505-12.
33. Bustamante J, Murias S, Enriquez E, Alcobendas R, Remesal A, Inocencio J. Biological therapy in refractory chronic nonbacterial osteomyelitis. *Joint Bone Spine*. 2020:105120.
34. Moreno-Mateo F, Perea SH, Onel KB. Chronic recurrent multifocal osteomyelitis: diagnosis and treatment. *Curr Opin Pediatr*. 2021;33(1):90-6.
35. Sato H, Wada Y, Hasegawa E, Nozawa Y, Nakatsue T, Ito T, et al. Adult-onset chronic recurrent multifocal osteomyelitis with high intensity of muscles detected by magnetic resonance imaging, successfully controlled with tocilizumab. *Intern Med*. 2017;56(17):2353-60.
36. O'Brien W, Fissel BM, Maeda Y, Yan J, Ge XP, Gravallese EM, et al. RANK-independent osteoclast formation and bone erosion in inflammatory arthritis. *Arthritis Rheumatol*. 2016;68(12):2889-900.
37. Huber AM, Lam PY, Duffy CM, Yeung RSM, Ditchfield M, Laxer D, et al. Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. *J Pediatr*. 2002;141(2):198-203.

Tables

Due to technical limitations, Table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Comparison of lesions clinical and on imaging Blue: clinical painful bone lesions (symptomatic). Yellow: subclinical lesions (edema on imaging but clinically asymptomatic). Green: clinical lesions confirmed on imaging.

Figure 2

Overview of treatment VI = vertebral involvement CS = corticosteroids MTX = methotrexate AZA = azathioprine * patient with Crohn's Disease ** patient with associated arthritis *** patient with SAPHO

Figure 3

Comparison between CT imaging and MRI imaging. Left: CT image shows osteolytic region with periosteal reaction. Right: MRI image (STIR) demonstrates bone marrow edema and surrounding soft tissue edema and layers of periosteal reaction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.docx](#)