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Original article

The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry

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Abstract

Objectives. Chronic non-bacterial osteomyelitis (CNO) or chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disorder characterized by sterile bone osteolytic lesions. The aim of this study was to evaluate the demographic data and clinical, instrumental and therapeutic features at baseline in a large series of CNO/CRMO patients enrolled in the Eurofever registry.

Methods. A web-based registry collected retrospective data on patients affected by CRMO/CNO. Both paediatric and adult centres were involved.

Results. Complete baseline information on 486 patients was available (176 male, 310 female). The mean age of onset was 9.9 years. Adult onset (>18 years of age) was observed in 31 (6.3%) patients. The mean time from disease onset to final diagnosis was 1 year (range 0–15). MRI was performed at baseline in 426 patients (88%), revealing a mean number of 4.1 lesions. More frequent manifestations not directly related to bone involvement were myalgia (12%), mucocutaneous manifestations (5% acne, 5% palmoplantar pustulosis, 4% psoriasis, 3% papulopustular lesions, 2% urticarial rash) and gastrointestinal symptoms (8%). A total of 361 patients have been treated with NSAIDs, 112 with glucocorticoids, 61 with bisphosphonates, 58 with MTX, 47 with SSZ, 26 with anti-TNF and 4 with anakinra, with a variable response.

Conclusion. This is the largest reported case series of CNO patients, showing that the range of associated clinical manifestations is rather heterogeneous. The study confirms that the disease usually presents with an early teenage onset, but it may also occur in adults, even in the absence of mucocutaneous manifestations.

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Key words: autoinflammatory diseases, bisphosphonates, bone inflammation, chronic non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, magnetic resonance imaging, palmoplantar pustulosis, registry, SAPHO, treatment

Rheumatology key messages

- Chronic non-bacterial osteomyelitis showed a heterogeneous range of clinical manifestations.
- Chronic non-bacterial osteomyelitis usually presents with an early teenage onset but may occur in adults.
- Treatment of chronic non-bacterial osteomyelitis with NSAIDs or disease-modifying agents was favourable in the majority of patients.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) in children has been recognized as a disease entity for the last 45 years [1]. Since then its definition has varied significantly, but seems to have become more consistent with chronic non-bacterial osteomyelitis (CNO) describing the inflammation of bone regardless of the number of lesions [2] and CRMO being the chronic and/or recurrent and particularly multifocal form with a more severe course [3]. Recently, primarily based on the clinical course of the disease and the lack of detectable autoantigens/autoantibodies, CNO/CRMO has been subsumed under chronic autoinflammatory bone disorders [4–6]. Deviations in IL-1 and IL-10 biology [7] support the theory of autoinflammation. Thus a constitutive activation of the immune system seems to contribute to chronic bone inflammation followed by bone erosions and hyperostosis [8, 9]. Clinically, patients complain about bone and also joint pain, sometimes quite debilitating, especially if spinal lesions are present. Additional inflammatory conditions predominantly affecting the skin (acne, palmoplantar pustulosis, psoriasis) and the gut (Crohn disease, ulcerative colitis) are frequent [4, 10, 11]. Affection of tissues other than bone has been described and reviewed [12]. Patients severely affected by several significant bone lesions (CRMO) have been shown to have a higher prevalence of concomitant arthritis or psoriasis [13, 14]. CRMO is considered to be the paediatric form of the adult SAPHO syndrome [15, 16]. Histologically, bone lesions in CNO as well as SAPHO reveal acute and chronic inflammatory as well as reparative bone features like hyperostosis [8, 9, 17–20].

In contrast to antibiotics, treatment with NSAIDs has been reported to be quite effective in the initial therapy in the majority of patients [8, 9, 21–24]. Glucocorticoids [24, 25], SSZ [4], IFN-α [26], bisphosphonates [27–29] and TNF neutralizing agents [12, 30] have been used in the treatment of either chronic or acute relapsing cases. Even though informative observations of the long-term outcome of larger cohorts of affected children exist in different countries/centres [2, 13, 14, 31–37], prospective and controlled evaluations of therapeutic strategies are still very limited [38] and, to our knowledge, do not include long-term follow-up. For now, further insights into the pathogenesis and treatment strategies of CNO may be gathered by very large international cohorts as long as controlled trials or prospectively followed treatment-controlled cohorts are not available. In this regard, CNO has been included in the follow-up Eurofever international registry of autoinflammatory diseases [39].

Methods

Patients and study design

Patient characteristics were extracted from the Eurofever registry database, which has been enrolling patients since 2009 [39]. Independent ethical committee approval for entering patients into the registry was obtained in the participating countries in accordance with local requirements. The study was performed according to the principles of the Declaration of Helsinki.

The criteria for the inclusion of patients as CNO/CRMO in the registry were mono-, oligo- or multifocal inflammatory bone lesions (osteomyelitis, osteitis, osteosclerosis); duration of complaints for $>$6 weeks; exclusion of infections and malignancy and diagnosis made after 1 July 2004. Monogenic autoinflammatory diseases associated to osteolytic lesions, such as deficiency of IL-1 receptor antagonist, Majeed's syndrome or pyogenic arthritis, pyoderma gangrenosum and acne syndrome, were excluded by the study.

H.G. and M.G. validated cases with a recorded diagnosis of CNO/CRMO/SAPHO. Patients without sufficient imaging data confirming the presence of one or more inflammatory bone lesion or with incomplete clinical data were excluded from analysis. Final database extraction was done in September 2016.

Detailed epidemiological, demographic and clinical data were collected anonymously. The clinical characteristics included different organ, musculoskeletal, mucocutaneous, ocular, gastrointestinal, lymphoid, cardiac or neurological involvement. Constitutional symptoms (including fever, fatigue, malaise and mood disorders) were noted. Skin involvement was characterized as acne, psoriasis, palmoplantar pustulosis, panniculitis, apthous stomatitis, papulopustular lesions, maculopapular lesions and urticaria. Musculoskeletal manifestations were reported in the categories arthralgia, bone pain, osteitis, bone deformity, osteoporosis, osteolytic lesions, hyperostosis, monoarthritis, oligoarthritis and polyarthritis. Laboratory data primarily focusing on inflammation parameters such as ESR, CRP,

Table 1 Patients original home country

Country	Patients (*N* = 486)
Germany	190
Italy	144
Denmark	66
France	31
Spain	17
Saudi Arabia	8
Switzerland	8
Australia	5
Romania	4
Russia	3
Argentina	2
India	2
Hungary	2
Croatia	1
Lithuania	1
Netherlands	1
Japan	1
Chile	1
Greece	1

white blood cell count, serum amyloid A, IgD, IgG, IgM and IgA were reported. As stated before for the Eurofever registry, complete response denoted complete control of the clinical manifestations and normalization of laboratory parameters and imaging (except for residual asymptomatic signs on MRI). Partial response was noted in patients with persistence of some clinical manifestations or perturbation of laboratory examinations and imaging. No response/failure denoted an absence of any substantial impact on disease activity. Worsening of disease was not reported [40].

Statistical analysis

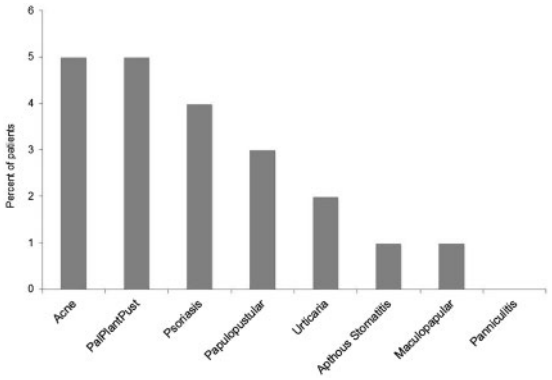
Descriptive statistics were reported as means and percentages. The patients' imaging characteristics were compared according to the presence of bone lesions in the different modalities (MRI, bone scintigraphy or conventional X-rays). Intergroup comparisons were performed with Fisher's exact or chi-square tests, as appropriate. All tests were two-sided. The threshold for statistical significance was set to $P < 0.05$. All data collection and analyses were performed using Excel software (Microsoft, Redmond, WA, USA).

Results

Demographic data and clinical characteristics

Through September 2016, 486 patients had been enrolled from 19 countries (see Table 1). Of these, 310 were female and 176 were male, mainly of Caucasian origin ($n = 460$), as well as 8 of Arab descent, 2 Hispanic, 3 Asian and 3 African American. A total of 455 were children and adolescents with disease onset (appearance of the first clinical manifestations) at a mean age of 9.9 years (range 1–17.7) and a mean age at diagnosis of 10.9 years (range 1.4–17.7). Thirty-one patients were adults [mean age of onset 33 years (range 19.0–62.4), mean age at diagnosis 40 years (range 19.4–68.1)]. The course of disease was described as continuous in 42%, recurrent in 52% and continuous and recurrent in 5% of patients. All patients reported musculoskeletal problems; 19% reported mucocutaneous manifestations, 8% gastrointestinal, 3% lymphoid (hepatosplenomegaly, enlargement of lymph nodes), 2% ocular and 1% cardiac manifestations (pericarditis). Of the mucocutaneous manifestations, 5% of patients had acne, 4% psoriasis, 5% palmoplantar pustulosis, 3% papulopustular lesions, 1% maculopapular lesions, 2% urticaria and 1% an apthous stomatitis. Of the 486 patients, 14 were reported to have a CNO-affected relative (2.8%) (Fig. 1).

Fig. 1 Inflammatory mucocutaneous manifestations associated with chronic non-bacterial osteomyelitis



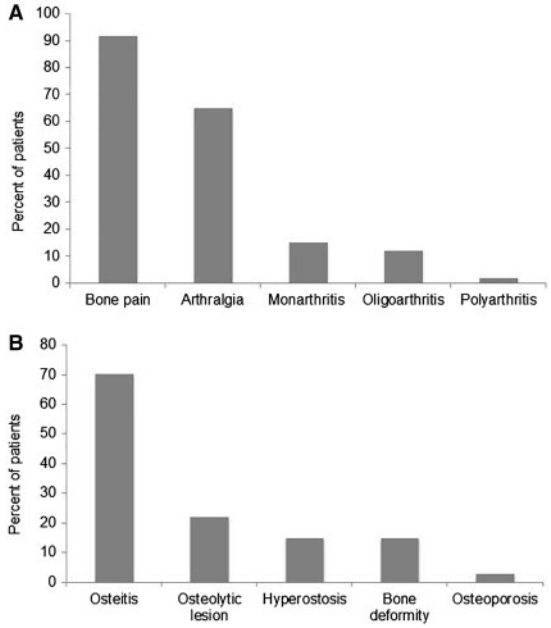
Mucocutaneous manifestations were reported in 88 patients. Relative frequencies of a total of 486 patients are given. Palplanpust: palmoplantar pustulosis.

Laboratory analysis revealed elevated ESR (above the local normal range, physicians' estimation) in 59% of patients, elevated CRP in 49%, elevated white blood cell count in 14% and elevated serum amyloid A in 12%. No relevant elevation was noted for IgD, IgG, IgA or IgM. HLA-B27 was present in 7.9% of 163 tested individuals and 38% of 222 tested patients were reported to have elevated ANA titres.

Imaging studies

Patients were diagnosed with CNO/CRMO on the basis of clinical signs of osteomyelitis (bone pain 92%, joint pain/arthralgia 65%, bone deformity 15%) and diagnostic imaging procedures including primarily regional X-rays of the clinically overt lesions in 302 patients, technetium bone scan in 318, MRI in 426 (66% regional MRI, 34% whole body MRI) and CT in 48. Imaging led to the diagnosis of osteitis in 327 patients (70%), osteoporosis in 14 (3%), osteolytic lesions in 105 (22%) and hyperostosis in 68 (15%) (Fig. 2). The number of bone lesions per individual patient is depicted in Fig. 3. Unifocal CNO was depicted by MRI, scintigraphy or X-ray in 124, 74 and 95 patients, respectively. Thus CRMO (more than one lesion) could be noted in 71, 77 and 69% of patients, respectively. The mean number of the detected lesions by different imaging

Fig. 2 Inflammatory musculoskeletal manifestations associated with chronic non-bacterial osteomyelitis



Musculoskeletal manifestations were reported in 486 patients. Relative frequencies of (**A**) clinical and (**B**) imaging features of patients are given.

techniques were MRI 4.1, scintigraphy 3.5 and X-ray 1.9 lesions per person (S.D. 4.12, 3.2 and 1.3, respectively). Thus MRI revealed more lesions per person than the other two modalities (Fig. 3). Overall, 37% of patients displayed metaphyseal, 23% epiphyseal, 15% diaphyseal, 25% pelvic, 23% vertebral, 10% chest, 15% tarsal, 3% carpal, 3% cranial and 19% clavicle lesions.

Histologic and microbial analysis of bone biopsies

A total of 281 single bone biopsies were reported (60% of 467 patients). Histologic results were categorized as predominantly lymphocytic [$n = 88$ (31%)], granulocytic [$n = 40$ (14%)], a mixture of both [$n = 89$ (32%)] and sclerotic [$n = 64$ (23%)], in addition to inconclusive results [$n = 58$ (21%)]. Microbial analysis was done in 215 of 281 biopsies (77%); however, results were not reported in the registry. Mycobacterial analysis was done in 112 biopsies (40%). Eubacterial PCR amplifying ribosomal RNA of eubacteria was done in 90 probes (32%) and specific mycobacterial PCR (*Mycoplasma hominis*) was reported in 40 patients (14%).

Arthritis

Based on clinical and/or imaging studies, arthritis was described as monoarthritis in 72 patients (15%), oligoarthritis (two to four joints affected) in 54 patients (12%) and polyarthritis (five or more joints affected) in 10 patients (2%). Data on the regional relation of arthritis to the bone lesion were not available. Overall, 29% of patients were reported to be affected by arthritis (Fig. 2).

Efficacy of therapy

Since there is no established definition of response to therapy in CNO, it was up to the reporting physician to categorize the patients' therapeutic response as remission, partial response, no response and worsening of disease. It was not possible to define the particular effect of therapy with regards to concomitant or parallel medication, duration and intensity of medication. The Eurofever working group is well aware of this particular limitation of the registry, thus a follow-up registry addressing these questions has recently been implemented. Overall no worsening of disease was reported. Of 486 patients, 74% ($n = 361$) received NSAIDs, 23% ($n = 112$) glucocorticoids, 9.6% ($n = 47$) SSZ, 12% ($n = 58$) MTX, 0.8% ($n = 4$) anakinra, 1.8% ($n = 9$) infliximab, 3.5% ($n = 17$) etanercept, 1.6% ($n = 8$) adalimumab and 12.5% ($n = 61$) bisphosphonates. Response to CNO-relevant mediation is summarized in Fig. 4.

Thirty-nine percent of patients treated with NSAIDs displayed a remission under medication, 52% displayed a partial response and 9% were classified as non-responders.

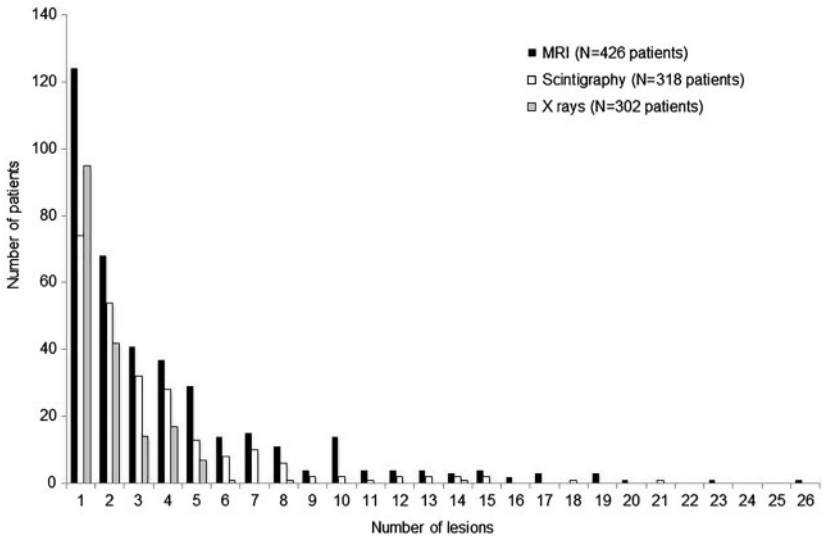
Among second-line treatments, a complete response was found in 37% of patients in the glucocorticoid group, 38% in the SSZ group, 22% in the MTX group, 41% in the etanercept group and 51% in the bisphosphonate group. Partial response was noted in 54% of patients in the glucocorticoid group, 49% in the SSZ group, 50% in the MTX group, 29% in the etanercept group and 46% in the bisphosphonate group. No response was noted in 8% of patients in the glucocorticoid group, 13% in the SSZ group, 28% in the MTX group, 29% in the etanercept group and 3% in the bisphosphonate group.

In the remission group a significant difference was noted when comparing glucocorticoids with MTX ($P = 0.046$, χ^2 test), and bisphosphonates with MTX ($P = 0.0013$, χ^2 test), suggesting a lesser therapeutic effect of MTX compared with the glucocorticoid and bisphosphonate treatment regimen. No other significant difference was noted between the groups. In the no-response group, when tested against MTX, glucocorticoids ($P = 0.0006$, χ^2 test) and bisphosphonates ($P = 0.0002$, χ^2 test), no response was reported to be significantly lower, again suggesting a lesser therapeutic effect of MTX when compared with glucocorticoids, etanercept and bisphosphonates. When tested against bisphosphonates, only etanercept and MTX were reported to be less effective statistically ($P = 0.0008$ and $P = 0.0002$, respectively, χ^2 test). Of four anakinra-treated patients, two were noted to reach remission, one had a partial response and one had no response. For infliximab ($n = 9$), the numbers were three, four and two, respectively. For adalimumab, out of eight treated patients, four were noted to reach remission and four had a partial response.

Characteristics of adult patients

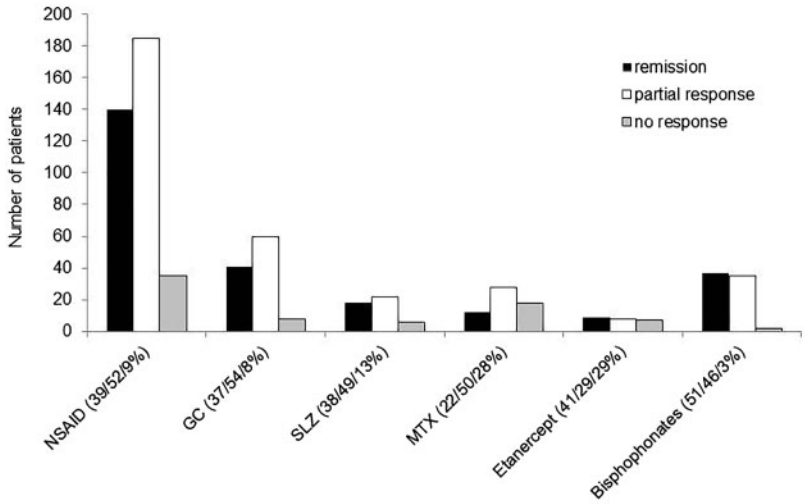
The analysis included 31 adult patients. The description of symptoms included more mucocutaneous manifestations than in children (41 *vs* 19%). This was mainly due to

Fig. 3 Number of bone lesions detected by different imaging modalities



Bone lesions were reported in 486 patients. Absolute numbers of lesions detected in patients are depicted. MRI has been shown to depict more CNO lesions than conventional X-rays or technetium bone scan.

Fig. 4 Response categories by different therapeutic modalities



Response criteria were reported in 486 patients. Remission, partial response and no response are depicted in absolute numbers of patients with regards to different treatment modalities. The percentage of patients who reached the different efficacies is given in parentheses.

more palmoplantar pustulosis cases (22 *vs* 5%). Musculoskeletal manifestations were comparable. Solely lytic bone lesions were more common in adult patients (89 *vs* 22%; $P = 7.10^{-15}$, χ^2 test). Therapeutic efficacy does seem to be less effective in adults than in children. Only 22% of adults were categorized as complete response (*vs* 37% in children; $P = 0.07$, χ^2 test) using NSAIDs. Using glucocorticoids, 15% of patients reached complete response (39% in children; $P = 0.02$, χ^2 test). However, using bisphosphonates, the same efficacy was noted in adults (62 *vs* 51%; $P = 0.5$, χ^2 test). The other medications were only noted in a few patients, thus no further analysis was done.

Discussion

The present analysis of the CNO cohort in the Eurofever registry constitutes a detailed description of the clinical phenotype and the therapeutic response of the largest reported cohort of CNO patients. Predominantly the

Table 2 Selected national CNO cohorts compared with the Eurofever cohort

	Canada (Huber *et al.* [32])	German (Jansson *et al.* [41])	USA (Borzutzky *et al.* [12])	Denmark (Ziobrowska-Bech *et al.* [33])	Suisse (Kaiser *et al.* [35])	France (Wipff *et al.* [34])	UK (Roderick *et al.* [37])	Italy (Pastore *et al.* [36])	German (Dresden Schnabel *et al.* [13])	German (Würzburg Schwarz *et al.* [44])	Eurofever 2017	All (mean)
Patients, *n*	23	89	70	31	41	178	41	47	56	95	486	
Male, %	17	27	33	39	25	31	25	30	40	42	36	31.4
Female, %	83	73	67	61	75	69	75	70	60	58	64	68.6
Age at disease onset, years, mean	9	10	9.6	10.3	9.5	10.9	9	9	11.1	11.7	9.9	9.3
Delay of diagnosis, months, mean	13	21	6	17	8	17	15	?	3	11	12	12.3
Lesions, *n*, mean	4	3	3.5	3.5	NA	3.5	NA	4	6	4.4	4.1	4.3
Unifocal, %	43	19	29	29	10	7	24	15	23	16	29	22.2
Multifocal, %	57	81	71	71	90	93	76	85	77	84	71	77.8
Patients with arthritis, %	26	6	35	56	22	11	17	NA	36	25	32	26.6
Patients with skin lesions, %	30	20	20	22	17	12	10	17	18	10	19	17.7
Patients with IBD, %	13	7	5	0	0	6	0	0	11	7.5	8	5.0
NSAIDS, %	78	87	97	100	90	97	100	100	100	94	74	92.5
SSZ,%	10	0	31	0	0	12	3	9	7	37	10	10.8
Glucocorticoids, %	13	15	27	55	29	8	8	51	41	20	23	26.4
Bisphosphonates,%	0	4	0	10	12	10	54	55	14	8	13	16.4
TNF blocking agents, %	0	2	15	3	20	7	3	11	12	4	7	7.6
MTX, %	9	7	42	29	25	8	15	40	4	0	12	17.4
Antibiotics, %	89	74	42	9	49	35	54	NA	36	5	NA	38.0
Active disease, % after follow-up	22	44	39	85	78	66	NG	45	60	33	50	52.2
Follow-up, months, mean	68	29	22	56	52	48	NG	34	60	49	NG	46.4

NA: not available.

patients were reported from Germany, Italy, Denmark and France (Table 1). Thus it seems obvious that the current analysis reflects the larger cohorts reported from these countries so far in the literature [33, 34, 36, 38, 41, 42]. The cohort is certainly biased to Caucasian, European patients, which comprise 95% of the reported individuals. By arbitrarily selecting international large-sized cohorts from Canada, Germany, the USA, Denmark, Switzerland, France, the UK and Italy [13, 14, 32, 33, 35, 36, 37, 43, 44] and comparing the data with the current analysis, the description of the disease can now be based on a large data set. We found that 68% of CNO patients are female (Eurofever 64%) (Table 2). The disease is generally diagnosed at ~10 years of age (Eurofever 9.9 years). There is still an overall significant delay in diagnosis of ~1 year. The mean number of lesions has been reported to be ~4, however, the denomination of an unifocal lesion varies between the cohorts from 7 to 43%, with a mean of 22.2% (Eurofever 29%). In the Eurofever registry, MRI has been shown to depict more CNO lesions than conventional X-rays or technetium bone scan, thus confirming previous reports [45, 46].

It has been a long-standing debate whether arthritis is a feature of this disease. Overall, 26.6% of patients (range 6–56) were affected by arthritis (Eurofever 32%). It seems of relevance that there is a considerable overlap with patients diagnosed with enthesitis-related arthritis or SpA [31]. Generally it seems to be difficult to make either one of the diagnoses when bone lesions of the pelvis and sacrum are involved. Diagnostic criteria have been formulated to distinguish CNO from other bone lesions, like infections [43]. However, internationally agreed upon diagnostic criteria to distinguish PsA or enthesitis-related arthritis from CNO are not available. Since a clinical lab test or genetic analysis is also not available [7, 47], one would assume that a consensus strategy defining such criteria would have limitations. Even though there seems to be clinical overlap, the presence of HLA-B27 does not seem to be a hallmark of paediatric CNO disease; in Eurofever, HLA-B27 was present in 7.9% of 163 tested paediatric individuals. This is close to the HLA-B27 mean frequency throughout Europe. Of note, in Eurofever eight adult CNO patients were tested for HLA-B27, but none was reported positive. Skin lesions have been consistently described as features of CNO [mean 17.7% (range 10–30%); Eurofever 19%]. IBD ranged from 0 to 30% with a mean of 5% (Eurofever 8%). Again, as with arthritis as a symptom of CNO, this documents a relevant difference in the cohorts.

It appears that CNO overall does not seem to be a monogenetic disease, since a relevant familial occurrence is not prevalent. In Eurofever, only 2.8% of patients have a family history of CNO. However, it seems of interest that in some CNO cohorts a few patients with genetically inherited disease can be identified, like hypophosphatasia mimicking CNO [48] or deficiency of IL-1 receptor antagonist [49]. Thirty-eight percent of 222 tested patients in Eurofever were reported to have elevated ANA titres. With the concept of autoinflammation, this finding would be contradictory. Titre levels were reported in Eurofever and all were <1:480, predominantly 1:120 and 1:240. Thus it seems that ANA elevation reflects a bystander inflammation, suggested in part by a minor immunoglobulin elevation seen in some patients in a previous cohort [2]. However, in Eurofever only 1, 6 and 0.6% of patients were reported to have elevations of IgG, IgM or IgA. In the literature, comparable ANA presence has been documented. Jansson *et al*. [41] report up to 39% (14/36) of CRMO patients have ANA present, and in less severe CNO forms the frequency was ~28% of patients (13/46). Wipff *et al*. [34] reported 12% (9/74) of patients being positive for ANA. Schwarz *et al*. [44] also reported 12% (9/74). We performed an extensive analysis to define whether patients with ANAs present show clinical features different from those lacking ANAs. No significant difference was found with regards to ESR elevation; CRP elevation; the frequencies of palmoplantar pustulosis, psoriasis, monoarthritis, oligoarthritis or polyarthritis; the frequencies of metaphyseal, diaphaseal or epiphyseal lesions and the response rate when using NSAIDs, glucocorticoids, SSZ, MTX, etanercept or bisphosphonates. Only the mean number of lesions were different: ANA-positive patients had a mean number of 3.3 lesions and ANA-negative patients had a mean number of 4.0 lesions. Thus the presence of ANAs cannot be considered a risk factor for disease severity when considering the number of lesions. Further analysis to define the relevance of the presence of ANA is subject to further analysis and beyond the scope of the registry.

Currently, national and international consensus treat-to-target strategies to establish treatment protocols for CNO are being developed. Physicians' estimation of treatment efficacy in Eurofever may assist in the generation of such protocols. Overall, in the mentioned national cohorts, 52% of patients were affected by active disease after a follow-up of 22–68 months (Eurofever 50%) (supplementary Fig. S1, available at *Rheumatology* online). Almost all patients received NSAIDs (91%; Eurofever 74%), SSZ was used in 11% (Eurofever 10%), glucocorticoids in 26% (Eurofever 23%), bisphosphonates in 16% (Eurofever 13%), TNF blocking agents in 8% (Eurofever 7%) and MTX in 17% (Eurofever 12%). In Eurofever, response (partial response and remission together) was particularly noted with bisphosphonates, NSAIDS, glucocorticoids and SSZ (91, 91, 92 and 87%, respectively). MTX and etanercept were considered less effective, particularly when compared with glucocorticoids and bisphosphonates (71 and 71%, respectively). There is a limitation in the comparison of the depicted treatment regimen, because with the registry a prospectively controlled setting is not present. Thus treat-to-target protocols are urgently needed to identify patients' characteristics associated with a predictable positive treatment response. At the moment, such characteristics are not available. Of note, a lot of patients are treated with antibiotics at some time during the course of disease (mean 38% in the national cohorts). No data from Eurofever are available in this regard.

This international registry of CNO patients in Eurofever is the largest reported case series of CRMO/CNO patients. This study shows that the disease can present with a range of clinical manifestations. At least in the early phases of the disease, NSAIDs are the most widely used drugs, with a complete response in almost 40% of patients. Eurofever treatment efficacy using DMARDs may be the basis for treat-to-target protocols of the future.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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