Chronic non-bacterial osteomyelitis: a retrospective international study on clinical manifestations and response to treatment

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Abstract

Objective

Chronic non-bacterial osteomyelitis (CNO) is a rare non-infectious bone inflammatory disorder; when multifocal, it is referred to as Chronic Recurrent Multifocal Osteomyelitis (CRMO). This study evaluates the demographic, clinical and radiological characteristics of a multi-centre cohort of patients with CNO/CRMO.

Methods

Demographic and clinical data of patients with an established diagnosis of CNO/CRMO followed at paediatric rheumatology centres across Europe (Italy, France, Slovenia) and India were retrospectively collected.

Results

There were no demographic differences across countries, but time to diagnosis was significantly longer in India (p=0.041). Pain was almost invariably present at disease onset; functional impairment was more frequent among Italian and Slovenian patients (p=0.001). The number of sites of bone involvement was similar between genders and countries, with long bone metaphises being the most common site. Raised acute phase reactants, detected in >50% of patients, were not associated with clinical manifestations or response to treatment. Comorbidities, evinced in 37% of patients, were equally distributed between genders and nationalities. Imaging approach was similar across countries, without any association between radiological findings and clinical manifestations. NSAIDs were almost invariably used as first-line treatment, but response rate was significantly lower in Italy (p=0.02). Methotrexate was used in 28% of case, with an overall rate of response of 82%. Health conditions and rate of permanent deformities were similar across different countries.

Conclusion

The differences in clinical presentation, radiological features and response to treatment described in this multinational cohort of CNO/CRMO might provide novel insights into this still elusive disease.

Key words

chronic non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, bone inflammation, osteomyelitis, children

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Received on March 16, 2020; accepted in revised form on May 18, 2020.

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Competing interests: none declared.

Introduction

Chronic non-bacterial osteomyelitis (CNO) is a rare non-infectious inflammatory disorder that affects primarily the bone. It is characterised by single or multifocal lytic lesions, usually with a recurrent pattern. The multifocal form is also known as CRMO (Chronic Recurrent Multifocal Osteomyelitis) and is considered the most severe subtype of CNO (1, 2). Since the first description by Giedon *et al*. in 1972 (3), many cases have been reported in medical literature, especially from Europe, North America and Australia, therefore an ethnicity role in the disease onset has been suspected (4-6). This aspect, however, has not been confirmed. A recent study, conducted in Chile, describes the first 19 cases in South America, showing a longer diagnostic delay compared to European reports (more than 1 year), suggesting a lower awareness of the disease (7). The same issue is highlighted in a series of 6 cases from India, with a median diagnostic delay of 3.5 years (range 2–13 years) (8). Moreover, in spite of a possible genetic predisposition of CNO, as demonstrated in familiar monogenic disorders with non-infectious osteomyelitis as Majeed syndrome (CRMO with dyserythropoietic anaemia) (9), deficiency of interleukin-1 receptor antagonist syndrome (DIRA) (10), and pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA) (11), no specific gene mutations in the sporadic form have been reported so far. CNO may belong to the vast family of autoinflammatory disorders, with a disregulation in the balance between pro-inflammatory and immune regolatory cytokine pathways of the osteoclast activation and differentiation, thus leading to bone damage (12-14). As a matter of fact, CNO is frequently associated with other inflammatory conditions, predominantly affecting the skin and the gut, including psoriasis, pustulosis palmaris et plantaris, pyoderma gangrenosum, severe acne, Sweet syndrome and inflammatory bowel disease; some cases also have as commorbidities idiopathic arthritis, sacroiliitis, entesitis and vasculitis (15-19). Synovitis, Acne, Pustolosis, Hyperostosis, Osteitis (SAPHO) syndrome is an inflammatory bone disease with dermatologic manifestations, mainly diagnosed in adults, considered to be part of the same spectrum of CNO (20, 21).

With regard to the clinical presentation, few differences between series from Western and emerging countries have been reported. A female prevalence has been shown in European cohorts of patients, while young boys are more likely to be affected in Latin American and Indian series (4, 5, 7, 8). Conversely, the mean age at onset is comparable throughout all the studies, around 10-11 years. No substancial differences in sites of bone involvement have been found, especially the metaphysis of long bones (7, 8, 22), while the number of affected sites at diagnosis tends to be slightly increased in emerging countries (6, 7, 22).

CNO/CRMO is a diagnosis of exclusion: radiologic evaluation is extremely important in guiding and confirming the diagnostic process, but magnetic resonance imaging (MRI) is the gold standard radiological tool, as it is more sensitive than radiography and scintigraphy (23, 24). Usually, MRI findings are visible in T1, T2 and short tau inversion recovery (STIR) imaging as bone cortical thickening, lytic lesions with sclerosis and bone oedema, but the lesions can be seen also at very early stages (25). Whole body scan is widely used at diagnosis and to monitor disease progression, as it is able to detect also asymptomatic lesions. Biopsy is considered mandatory any time there is a clinical doubt, especially of malignancy, even if histological findings show non-specific bone inflammation (26).

There are no official treatment guidelines approved so far for CNO/CRMO, but only case reports and retrospective cohort studies (27). Non-steroidal anti-inflammatory drugs (NSAIDs) are generally used as first-line treatment, with good response in almost all patients, but variable stable remission (5, 28). In case of no response to NSAIDs, another option can be to administer oral corticosteroids (29). Second-line treatment options are represented by methotrexate, bisphosphonates (30) and tumour necrosis factor (TNF)-α inhibitors (31).

Sulfasalazine and anti-IL1 have also been used (24).

The aim of the present study is to evaluate the demographic, clinical and radiological characteristics in a series of CNO/CRMO patients followed in 3 European paediatric rheumatology centres (Italy – Milan, France – Lyon, Slovenia – Ljubljana) and in a paediatric rheumatology centre in India (Chandigarh), in order to underline the similarities and the differences between the presentations of this complex disease. Since the treatment strategies are not well standardised, we also evaluated the different therapeutic regimens used with their specific clinical responses.

Table I. Demographic data and clinical features of the included patients, subgrouped according to country of origin.

	Italy (n=50)	France (n=16)	Slovenia (n=14)	India (n=6)	Statistical significance
Gender (F (%)/M (%)	31 (62%)/ 19 (38%)	11 (69%)/5 (31%)	10 (71,5%)/4 (28.5%)	3 (50%)/3 (50%)	NS
Autoimmune disease in family	8 (16%)	7 (43.7%)	1 (7,1%)	0 (0%)	0.023
Pain	49 (98%)	15 (93.7%)	14 (100%)	6 (100%)	NS
Swelling	19 (38%)	6 (37.5%)	10 (71.4%)	6 (100%)	0.023
Functional impairment	36 (72%)	6 (37.5%)	10 (71.4%)	2 (33.3%)	0.012
Fever	12 (24%)	2 (12.5%)	0	2 (33.3%)	NS
Raised CRP	22 (44%)	4 (25%)	8 (57%)	3 (50%)	NS
Raised ESR	28 (56%)	2 (12.5%)	8 (57%)	4 (66.7%)	NS
Comorbidities	15 (30%)	6 (37.5%)	7 (50%)	4 (66.7%)	NS
Permanent deformities	3 (6%)	0	1 (7,1%)	0	NS

NS: not significant; F: female; M: male; CRP: C-reactive protein; ESR: elevated sedimentation rate. Continuous variable are expressed as median [interquartile range], categorical variables are expressed as percentages.

Methods

In this retrospective study, we included the 86 patients with a diagnosis of CNO/CRMO currently followed in paediatric rheumatologic units in Italy (Milan University Hospitals), France (Hopital Femme Mere Enfant of Lyon), Slovenia (Children Hospital, University Medical Center Ljubljana), and India (Institute of Medical Education and Research, Chandigarh).

Data collection and inclusion criteria

After approval of independent ethics committee, in accordance with local requirements for entering in the study, patient data were extracted from clinical records in each centre and then gathered anonimously in a database, which was ultimately extracted on October 31th, 2019. Inclusion criteria were represented by the presence of mono-, oligo- or multifocal inflammatory bone lesions, after the exclusion of all possible secondary causes such as infection, malignancy or monogenic autoinflammatory diseases associated to osteolytic lesions. Demographic and clinical data collected included gender, age at onset of symptoms, age at diagnosis and diagnostic delay, follow up duration time, presenting symptoms at onset (bone pain, swelling, functional impairment, fever), sites of involvement and number at diagnosis. Comorbidities and other inflammatory diseases in the patient and the family were also recorded. Moreover, data on serologic inflammatory markers (CRP, ESR), radiologic tools including x-rays, CT-scans, bone scintigraphy, MRI and Whole Body MRI, and histological diagnosis (when a biopsy was performed) were collected. We also analysed the image findings on MRI at diagnosis and noted if asymptomatic lesions were present on Whole Body MRI.

Different treatment strategies were recorded. Response to the drug used was assessed by clinical, laboratory and radiological features, categorised as remission in case of total resolution; partial response if improvement but no resolution in one or more aspects analysed; no response if no improvement was achieved. Current health conditions were defined as remission on therapy, remission without treatment, no remission. Permanent impairment on follow-up was also assessed.

Statistical analysis

Continuous data were expressed as median (interquartile range [IQR]) while categorical data were presented as percentages. The association between categorical variables was assessed by chi-squared or Fisher's test, as appropriate. The correlation between continuous variables was tested by Spearman's test. Potential differences in continuous variables between two or more subgroups were investigated using Mann-Whitney U-test or Kruskal-Wallis test, respectively.

Univariate ordinal logistic regression analyses were performed to investigate the relationship between gender and outcomes, response to NSAIDs and response to methotrexate. Multivariate ordinal logistic regression analyses were performed to identify the optimal sets of variables to predict outcomes (current health conditions, response to NSAIDs and response to methotrexate). All biologically and clinically relevant variables were inserted in the model; a step-down approach was then applied. Predictors were retained even when not significantly associated with the outcome variable in order to maximise the performance of the model.

Statistical analysis was performed with Minitab 19. Figures were drawn using GraphPad Prism 6. p-values <0.05 were considered statistically significant.

Results

Eighty-six subjects fulfilling the inclusion criteria were included in this study.

Patients were most commonly of female gender, especially in the European cohort: 50% in India, 62% in Italy, 71.4% in Slovenia, 68.5% in France. As reported in Table I, there were no demographic differences between patients from the different countries included in the study, with a median age at onset of symptoms ranging between 8 and 11 years of age (Fig. 1). The oldest patient with CRMO symptoms onset was from India (33 years old), the youngest in Italy and France (3 years old). Time to diagnosis was significantly longer in India than in Europe (18 *vs*. 6 months, respectively; p=0.041),

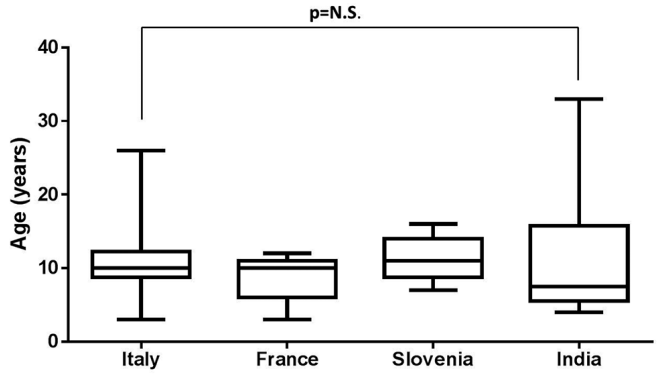

Fig. 1. Box-plots of age in patients subgrouped according to country. Whiskers indicate the 10th and the 90th percentile in each subgroup.
Median (interquartile range) age at diagnosis (years): Italy 10.6 (4.5); France 10 (5); Slovenia 11 (4.5); India 7.5 (8.25); *p*=NS

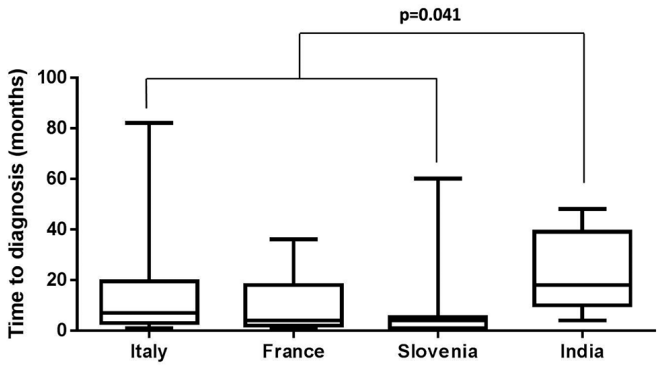

Fig. 2. Box-plots of time to diagnosis in patients subgrouped according to country. Whiskers indicate the 10th and the 90th percentile in each subgroup.
Median (interquartile range) time to diagnosis (months): Italy 7 (16); France 4 (16); Slovenia 4 (4); India 18 (29); *p*=0.011.

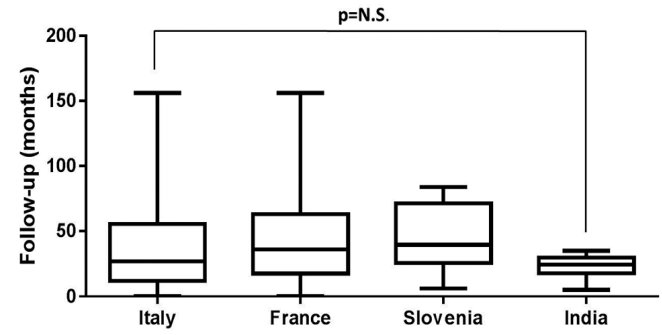

Fig. 3. Box-plots of follow-up in patients subgrouped according to country. Whiskers indicate the 10th and the 90th percentile in each subgroup.
Median (interquartile range) follow-up (months): Italy 27 (43); France 34 (27); Slovenia 39 (45); India 24 (12); *p*=NS.

Table II. Sites of bone involvement among included patients, subgrouped according to country of origin.

	Italy (n=50)	France (n=16)	Slovenia (n=14)	India (n=6)	Statistical significance
N of sites	3 (2-5)	2.5 (1-3.75)	4 (2.5-7.5)	3 (2-8)	NS
Long bones	33 (66%)	12 (75%)	10 (71.4%)	4 (66.7%)	NS
Clavicle	10 (20%)	4 (25%)	4 (28.5%)	0	NS
Sternum and ribs	6 (12%)	2 (12.5%)	4 (28.5%)	0	NS
Vertebral column	26 (52%)	1 (6.25%)	2 (14.3%)	0	0.001
Pelvis	19 (38%)	6 (37.5%)	7 (50%)	1 (16.7%)	0.012
Jaw	5 (10%)	0	0	0	NS
Hands and feet	11 (22%)	4 (25%)	6 (42.8%)	5 (83.3%)	0.003

NS: not significant.

whereas duration of follow-up was similar across national subgroups (Fig. 2 and 3, respectively).
Regarding symptoms at onset, pain was almost invariably reported by patients; the second most common clinical manifestation was functional impairment, detected in 63% of included subjects. Functional impairment was more common among Italian and Slovenian patients (χ^2=10.844, *p*=0.001). No difference in disease presentation was observed between female and male patients.
The number of sites of bone involvement was similar between genders and across different countries (Table II); no difference emerged even when patients from India were compared to European subjects (3.5 *vs*. 3, respectively). Metaphises of long bones were the most common site of involvement in all the groups. Vertebral column was more commonly involved among Italian patients (χ^2=17.275, *p*<0.001), whereas the pelvis was a more frequent site of involvement in the Slovenian group (50% of the patients). We also noted a much higher prevalence of extremities involvement (hands and feet) in the Indian group compared to the others (*p*<0.003). Five patients, all Italian, presented jaw involvement. Males displayed a higher prevalence of pelvis involvement (χ^2=7.949, *p*=0.005).
A raise in acute phase reactants was reported in less than half of patients, without any difference between males and females. ESR was raised in 43% of subjects and CRP in 40%; neither ESR nor CRP levels were associated with specific clinical manifestations or response to treatment.
Thirty-seven percent of patients presented one or multiple comorbidities, similarly distributed between genders and across European countries. In particular, osteoporosis was found in 4 subjects from Slovenia; 3 patients (2 Italian, 1 Slovenian) had a concomitant SAPHO syndrome; 3 French individuals presented psoriasis. Other comorbidities included Crohn's disease (2 Italians), autoimmune thyroiditis (2 Italians), Henoch-Schönlein purpura (1 Slovenian, 1 French) and coeliac disease (1 Slovenian, 1 Italian). Lastly, pulmonary fibrosis, ankylosing spondylitis, juvenile idiopathic arthritis were each present in a single patient (all were Italian). We also searched for autoimmune diseases in the families, evincing a prevalence of 18.6%. Indian and Slovenian patients had a lower prevalence of autoimmune diseases in their families, which approached statistical significance (χ^2=3.185, *p*=0.074).

Table III. Treatments and response rates to different treatments.

	Italy (n=50)	France (n=16)	Slovenia (n=14)	India (n=6)	Statistical significance
NSAIDs, n (%)	39 (78%)	14 (87.5%)	14 (100%)	6 (100%)	0.012
Remission, n (%)	12 (30.8%)	13 (93%)	9 (64.3%)	2 (33.3%)	
Partial remission, n (%)	7 (17.9%)	1 (7%)	3 (21.4%)	2 (33.3%)	
Methotrexate, n (%)	17 (34%)	3 (18.7%)	2 (14.3%)	2 (33.3%)	NS
Remission, n (%)	9 (52.9%)	3 (100%)	2 (100%)	2 (100%)	
Partial remission, n (%)	4 (23.5%)	0	0	0	
Sulphasalazine, n (%)	4 (8%)	0	0	1 (16.7%)	NE
Remission, n (%)	1 (25%)			1 (100%)	
Partial remission, n (%)	1 (25%)			0	
Steroids, n (%)	10 (20%)	3 (18.7%)	1 (7.1%)	1 (16.7%)	NE
Remission, n (%)	5 (50%)	3 (100%)	1 (100%)	1 (100%)	
Partial remission, n (%)	3 (30%)	0	0	0	
Biologics, n (%)	11 (22%)	6 (37.5%)	2 (14.3%)	0	NE
Remission, n (%)	5 (45.4%)	2 (33.3%)	1 (50%)		
Partial remission, n (%)	4 (36.4%)	2 (33.3%)	1 (50%)		
Neridronate, n (%)	15 (30%)	0	0	0	NE
Remission, n (%)	8 (53.3%)				
Partial remission, n (%)	4 (26.7%)				
Pamidronate, n (%)	11 (22%)	1 (6.2%)	6 (42.8%)	2 (33.3%)	NE
Remission, n (%)	5	0	4	2	
Partial remission, n (%)	4	1	0	0	

NS: not significant; NE: not evaluated.

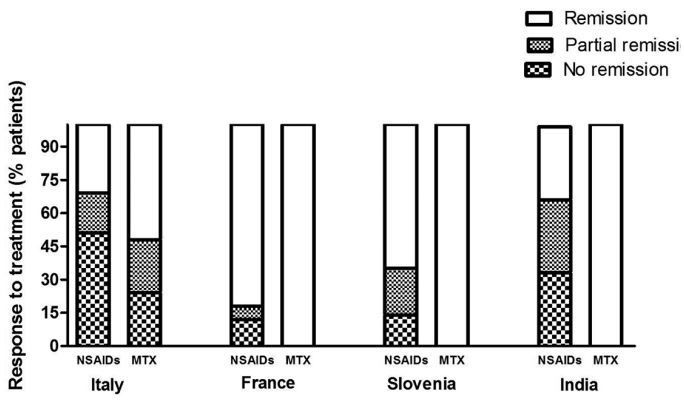

Fig. 4. The response to treatment (%) with methotrexate (MTX) and non-steroidal anti-inflammatory drugs (NSAIDs) in patients subgrouped according to country.

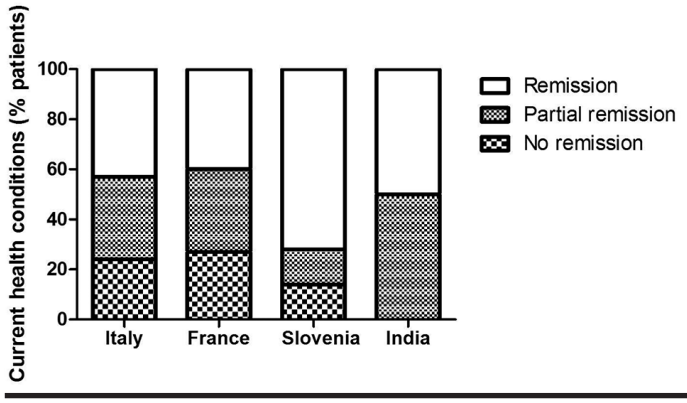

Fig. 5. Current health conditions (%) in patients sub-grouped according to country.

With regard to radiologic evaluation, there were no differences in imaging approach across countries. No association emerged between radiological findings and country or clinical manifestations. Plain x-rays were performed as first diagnostic imaging in almost all (92%) patients, and were positive for osteolytic lesions in 64 cases. CT scans were performed in 72% of all patients, with evidence of the lesion in 32 cases (52%). MRI was performed as the first or second diagnostic tool in 84/86 patients. The whole body technique was performed in 84/86 patients, allowing the recognition of asymptomatic lesions in 40 patients (47%). Skeletal scintigraphy was performed in 63 patients, and was positive in 50. MRI was performed, and repeated after treatment, in almost all patients, except for the French group where it was repeated only in one case. The most frequent radiologic findings on MRI were soft tissue oedema (74%), bone marrow oedema (86%), osteolytic lesions (67%), bone sclerosis (30%), hyperostosis (13%), and joint involvement (23%). Bone biopsy was performed in 65% of cases, and confirmed the presence of a non-specific inflammation.

Drugs used and rates of response across different countries are detailed in Table III and Figure 4. NSAIDs were used as first-line treatment in almost all patients (86%). The rate of non-response to NSAIDs was significantly lower among Italian patients (χ^2=9.904, p=0.02). No difference in the rate of response was described between genders. Methotrexate was used in 28% of patients. The overall rate of complete response was 66%, while it was partial in 17% and 17% had no response. Sulphasalazine was used in only 5% of patients. None of these patients had Crohn's disease and/or pelvis involvement. At least one cycle of corticosteroids was used in 15 patients, with a good response in 9/15 patients (60%). Biologic treatments were used in 19 patients (22%) with a good response in 42% of them, partial response in 37% and no response in 21%. It is important to note that biologics were not available in India, so it impossible to compare this to European cohorts. As for bisphosphonates, 20 patients underwent treatment with pamidronate and 15 with neridronate. In only one case pamidronate was used first with a partial response; thereafter a combination of neridronate and methotrexate allowed a stable remission. A good response was found in about half (55%) of patients receiving bisphosphonates, while the remaining had either partial (25%) or no response (20%).

Health conditions, at the time of data collection, were similar across differ-

ent countries (Fig. 5), as well as the rate of permanent deformities.

At multivariate logistic regression analysis, age at onset, the country of origin, and diagnostic delay were all predictive of response to NSAIDs. Patients presenting local swelling were less prone to respond to NSAIDs, whereas a history of fever approached statistical significance (Table IVA). Age at onset was the only variable to be significantly associated with response to methotrexate; again, a trend towards statistical significance emerged for a history of fever (Table IVB). However, a history of fever and the response to NSAIDs were found to significantly predict current health status (p=0.026 and p=0.001, respectively; Table IVC).

Table IV. Ordinal multivariate logistic regression models.

A. Multivariate logistic regression model to predict response to non-steroidal anti-inflammatory drugs.

Predictors	Coef	SE Coef	Z	*p*	OR	95% CI
Age at onset	0.176789	0.0900668	1.96	0.050	1.19	1.00-1.42
Swelling	-1.32372	0.609266	-2.17	0.030	0.27	0.08-0.88
Raised CRP	-0.647945	0.582088	-1.11	0.266	0.52	0.17-1.64
Country	-0.943775	0.374732	-2.52	0.012	0.39	0.19-0.81
Diagnostic delay	0.0394482	0.0196695	2.01	0.045	1.04	1.00-1.08
Fever	1.35558	0.711496	1.91	0.057	3.88	0.96-15.64

B. Multivariate logistic regression model to predict response to methotrexate.

Predictors	Coef	SE Coef	Z	*p*	OR	95% CI
Fever	2.54000	1.31081	1.94	0.053	12.68	0.97-165.53
Age at onset	0.244727	0.117116	2.09	0.037	1.28	1.02-1.61

C. Multivariate logistic regression model to predict current health conditions.

Predictors	Coef	SE Coef	Z	*p*	OR	95% CI
Fever	1.29954	0.584218	2.22	0.026	3.67	1.17-11.53
Response to NSAIDs	-0.947707	0.291394	-3.25	0.001	0.39	0.22-0.69
Comorbidities	-0.497579	0.511752	-0.97	0.331	0.61	0.22-1.66

Discussion

The present study describes a multifaced cohort of patients from 4 different countries, showing similarities and differences in clinical characteristics, diagnostic approach and treatment strategies, in order to gain further insights about this still underecognised disease (5, 7, 8). In our study the largest group of patients is from Europe, in particular from Italy (50 patients), while the smallest is from India (only 6 patients), in spite of the total number of inhabitants of the two regions. We also found that time to diagnosis was significantly longer in the Indian group compared to the others.

As documented in previous studies (5, 6), we noted a female prevalence, especially in the European cohort of patients. There was no gender predilection in the Indian group, but this is probably due to the small sample and should be better addressed in further studies.

Mean age at onset of the disease is comparable in all groups, supporting what has been already found in other reports (5, 6). Only 4 patients (4.65%) had symptoms onset after 16 years, confirming the peculiar paediatric onset for CNO/CRMO (5).

The disease can present with a range of clinical manifestations, but typically is characterised by an insidious onset of local bone pain, possibly associated with swelling and warmth of the area and eventually also inflammation of the adjacent joint. There might be an abrupt onset, with fever and elevated inflammation signs, even if it is less frequent (22). Our study confirmed previous reports, with all the patients complaining of pain as the first symptom. The second most common clinical manifestation was functional impairment, especially among Italian and Slovenian patients, while local swelling and adjacent joint involvement were less frequently reported. Systemic signs of inflammation were detected in less than half of our patients, without any difference between males and females: fever was reported in 16 patients; raised acute phase reactants (ESR and CRP) in 43% and 40% of subjects, respectively; neither ESR nor CRP were associated with specific clinical manifestations or response to treatment. Moreover, no difference in disease presentation was observed between female and male patients.

The most common sites of involvement reported in the literature are the metaphyseal areas of lower extremities, the pelvis and the spine; some sites such as clavicle, mandible and sternum are almost pathognomonic for the disease (15, 22). These data are also confirmed in our report, with the metaphises of long bones as the most common sites of involvement in all groups. Vertebral column was significantly more involved among Italian patients, whereas the pelvis in the Slovenian group. We also noted that males in general displayed a higher prevalence of pelvis involvement. In the Indian group there was a much higher prevalence of extremities involvement compared to the others, while no involvement of clavicle, mandible and sternum, which were anyway more infrequent also in the European groups. Indeed, in the whole cohort, mandible lesions were detected in 6% of patients, a lower rate compared to a recent report on 86 Italian patients (32). The disease presented with a multifocal pattern and we did not find any difference in the number of sites of involvement at diagnosis between our groups.

CNO/CRMO is considered an autoinflammatory disease and is frequently associated with other inflammatory conditions such as juvenile idiopathic arthritis, sacroiliitis, psoriasis, pustulosis palmaris et plantaris, pyoderma gangrenosum, severe acne, Sweet syndrome, inflammatory bowel disease and vasculitis (12-19). There is also evidence that CNO/CRMO might be part of the same spectrum of SAPHO syndrome, from which it differs for the most common paediatric onset and probably for the sites of bone inflammation (20, 21). In our study, 37% of patients presented one or multiple comor-

bidities, similarly distributed between genders and across European countries. No autoimmune disease was found in Indian patients instead, suggesting a possible different genetic background or a lack of informations.

We also searched for autoimmune diseases in the patients' families, finding that they were present in 18% with a lower prevalence in Indian and Slovenian families.

The diagnosis is made after exclusion of other conditions, especially infections and malignancies, with the combination of clinical, radiological, and histological data. In our study, x-rays were performed as first diagnostic imaging in almost all patients, confirming the clinical suspicion of inflammatory osteolytic lesions in 64 patients. Skeletal scintigraphy was widely performed as well, usually with positive findings (79% of all scans). As reported in previous reports (25), the most frequent radiologic findings on MRI of our patients were in decreasing order soft tissue oedema, bone marrow oedema, osteolytic lesions, bone sclerosis, and hyperostosis.

Regarding treatment strategies, there are no official protocols approved so far. Usually, NSAIDs are first used, but stable remission is not always achieved (5, 28). Other options include the temporary administration of oral corticosteroids alone or combined with other drugs (28), *e.g.* sulphasalazine or methotrexate (24). Bisphosphonates and TNF-α inhibitors are very effective in the more severe forms (30, 31). In the present study, NSAIDs were used as first-line treatment in almost all patients with a good response in half of them, but not all of them reached a stable remission. The rate of non-response to NSAIDs was significantly lower among Italian patients. We did not find any difference in the rate of response between genders. Notably, in our cohort the response rate to methotrexate was as high as 66%, with 83% of patients achieving at least a partial disease remission. Evidence on the efficacy of methotrexate in CNO/CRMO patients is still scarce, due to the limited number of treated patients and the retrospective design of available studies. Moreover, the rate of response to methotrexate is highly variable across different reports, possibly due to the wide heterogeneity in terms of patients' selection and definition of remission. In a recent study on 19 CNO patients, treatment with methotrexate led to a full remission in 50% of cases; in another US-based CNO cohort, the estimated response rate to methotrexate was 91% (7, 33). In our cohorts, sulphasalazine was used in a few patients, confirming a moderate efficacy (24). At least one cycle of oral corticosteroids was used in 15 patients, with a good response in 9. All these patients underwent other treatments. Biologic treatments, especially adalimumab, were used in the patients not responding to other strategies, with a good response in almost half of them; we have to underline though that 21% of them did not respond at all. It is important to note that biologics were not available for the Indian patients, so it impossible to compare this topic to European cohorts. Bisphosphonates was another good alternative in patients not responding to NSAIDS. Infact we found a good response in more than half of cases where they were used; the rate of no response was however around 20%.

Remission was achieved in three quarters of cases, confirming the overall good prognosis of the disease with a mean follow up time of 38 months (34). However, we noted almost 6% of permanent disabilities, especially vertebral fractures, without any difference across the countries.

Limitations of our study include the fact that patients with incomplete clinical data were not excluded from analysis. In particular, we acknowledge that bone biopsy was not performed in all cases; however, all patients without histopathological analysis had highly suggestive lesions at MRI, whole body MRI and/or scintigraphy. Some patients have been lost during follow up, thus especially the evaluation of treatment response might have been partially influenced by lack of data. Moreover, not all the treatment strategies were available, especially for biologics also due to the high cost and the off label use. Lastly, despite a relatively high number of patients for such a rare disease, statistical comparisons for some clinical manifestations were hampered by lack of power. In addition, the limited number of Indian patients included in this study prevented us to draw solid conclusions about the potential impact of ethnicity on the clinical presentation or the response to treatment.

In conclusion, the present study describes the clinical and radiological characteristics of this complex autoinflammatory disease in a multinational cohort, underlying similarities and differences between countries. Further studies with a larger number of patients are needed to better confirm this report both in Europe and Asia, as well as in other continents, in order to improve the knowledge about CNO/CRMO, to elucidate the optimal therapeutic approach and to create appropriate treatment guidelines (35).

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