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# Clinical outcome in children with chronic recurrent multifocal osteomyelitis

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**Objective.** To determine the clinical outcome of children with chronic recurrent multifocal osteomyelitis (CRMO).
**Methods.** We retrospectively reviewed clinical, biological and radiological data of children with CRMO at five French paediatric centres. Outcome data were obtained through review of hospital charts and questionnaires sent to all patients to assess disease activity and educational and vocational achievement.
**Results.** Forty patients were assessed (34 females and 6 males) with a median age at diagnosis of 11.5 yrs (range 2–17). Median number of initial bony lesions was 2 at onset, and 3.5 over disease course. Median time since diagnosis was 3.5 yrs (range 0.5–15) and median duration of active disease 2.7 yrs (range 0.5–13.5). Nine (22.5%) patients had psychological or physical sequelae. Twenty-nine children (72.5%) responded to the questionnaire. Twenty-six had no physical disability as judged by the HAQ 0–1, two had moderate disability (HAQ: 1–2) and one had severe disability (HAQ: 2–3). Seventeen patients (58.6%) had active disease at follow-up (after 6 months to 15 yrs since diagnosis) and continued to have pain (median value of visual analogue scale: 10/100). CRMO had interfered with patient's education in two cases.
**Conclusions.** Clinical outcome of children with CRMO is generally good, but a sizeable proportion of patients have active disease at follow-up, and a minority of patients can have a severe and prolonged disease course despite intensive treatments. Further studies are required to determine predictive factors for severe disease.

**Key words:** Chronic recurrent multifocal osteomyelitis, Children, Outcome.

## Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is a non-infectious inflammatory bone disease of unknown aetiology, first reported by Giedion *et al.* in 1972 [1]. The disease causes multifocal lytic bone lesions with swelling and pain. It could be associated with the other symptoms of SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) [2], or with sacroiliitis, psoriasis [3] and IBD [4]. The course of the disease is characterized by periodic exacerbations and remissions but long-term outcome remains unclear. Most of the studies in the literature are case reports or short series [3, 5–8]. Huber *et al.* [9] determined the long-term clinical outcome of 23 patients with CRMO. Most subjects had no disease activity or sequelae but 25% of patients had persistent disease.

The aim of our study was to determine clinical outcome of children with CRMO.

## Patients and methods

We retrospectively reviewed clinical, biological and radiological data of children with CRMO diagnosed before 1 January 2007 and followed up at five French paediatrics centres (Hôpitaux Saint-Vincent-de-Paul, Cochin, Necker, Robert Debré, Paris and Hôpital Edouard Herriot, Lyon, France). The diagnosis of CRMO was made based on multifocal bony lesions in the absence of infectious origin, typical X-ray pattern (osteolysis with sclerosis) and high uptake on technetium bone scan (which was performed in 34 out of 40 cases), chronic evolution and age <18 yrs at diagnosis; in 28 cases, a bone biopsy with microbial investigation was performed and excluded an infectious origin. A chronic non-bacterial osteitis was diagnosed when there was only one bony lesion during the course of the disease. A patient was defined as responder to treatment if there was absence of pain and improvement in inflammatory markers.

Questionnaires were sent to assess disease activity and educational and vocational achievement. Disease activity was defined as the presence of pain or use of medical treatment. Pain was evaluated using a visual analogue scale of 0–100. Patients were asked to indicate if they had received treatment, and to specify the drug. Global impact of the disease was determined with another visual analogue scale graduated from 0 to 100. Physical function was assessed using the HAQ including eight domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activity. The final score ranged from 0 (no disability) to 3 (severe disability). Educational achievement was evaluated by the highest educational level reached and vocational achievement by asking about employment. Oral consent was obtained from the parents and, when possible, the patients, as recommended in France. In accordance with the French rules, no ethical committee agreement was needed before sending the questionnaire to the patient or the parents.

The Pearson correlation was used in a first analysis to determine as to which parameters were correlated with the duration of active disease and with the response to NSAIDs. Then a multivariate regression was used to construct a multivariate model for the duration of active disease including biological parameters (ESR, CRP, platelets, white blood cells), age at the onset, sex, initial and total number of bony lesions and response to NSAID treatment. The logistic regression was used to construct a model for the response to NSAID treatment including the same parameters.

## Results

Forty patients were evaluated (34 females and 6 males) with a median age of 10 yrs (range 1–17) at first symptoms. There was statistically no difference between the male and female patients with regard to demographic and clinical data (age at disease onset,

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TABLE 1. Bony sites affected

| Site affected | Number (%) of subjects |
|---|---|
| Distal tibia | 23 (57.5) |
| Pelvis | 13 (32.5) |
| Proximal tibia | 11 (27.5) |
| Metatarsals | 11 (27.5) |
| Vertebrae | 10 (25) |
| Proximal femur | 9 (22.5) |
| Clavicle | 8 (20) |
| Calcaneus | 8 (20) |
| Distal femur | 5 (12.5) |
| Distal fibula | 5 (12.5) |
| Sternum | 5 (12.5) |
| Distal radius | 4 (10) |
| Scapula | 4 (10) |
| Distal humerus | 3 (7.5) |
| Patella | 3 (7.5) |
| Ribs | 3 (7.5) |
| Proximal humerus | 2 (5) |
| Distal ulna | 1 (2.5) |
| Mandible | 1 (2.5) |

TABLE 2. Multivariate model for response to NSAID treatment

| | Means for non-responders | Means for responders | *P* |
|---|---|---|---|
| Age at disease onset (yrs) | 8.7 | 9.7 | NS |
| Sex ratio | 8F/1M | 25F/5M | NS |
| Initial number of lesions | 4 | 2 | **0.03** |
| Total number of lesions | 5 | 4 | NS |
| ESR (mm/1st h) | 45 | 28 | NS |
| CRP (mg/l) | 14 | 5 | NS |
| WBC (per $mm^3$) | 7600 | 8560 | NS |
| Platelet count (per $mm^3$) | 345 428 | 348 000 | NS |
| Duration of active disease (yrs) | 7.5 | 2.7 | **0.05** |

Bold values indicate $P < 0.05$. F, female; M, male; NS, not significant.

initial and total number of lesions, biological parameters, percentage of response to NSAIDs and duration of active disease). Median age at diagnosis was 11.5 yrs (range 2–17). Initial symptoms were bony pain in all patients, associated with localized swelling and arthritis secondary to local bony inflammation in four children. Three patients suffered from enthesitis, two at onset of the disease and one during the disease course. Nine patients had fever and one pustulosis plantaris. Biological evaluation at onset of the disease usually showed normal white blood cell count, haemoglobin and platelet count and slightly increased inflammatory markers with a median value of ESR of 26 mm/1st h and of CRP of 5 mg/l (ref <5 mg/l).

Median number of initial bony lesions for each patient was 2 (range 1–7) at onset and 3.5 (range 1–11) during the disease course. Fifteen patients (37.5%) had only one bone lesion at onset of the disease and four patients (10%) had a unifocal course. The sites affected are summarized in Table 1. Twenty-eight children underwent bone biopsies that showed non-specific subacute or chronic inflammation with mild fibrosis. Microbial investigations remained negative.

All patients except one were initially treated with NSAIDs. Eleven patients received antibiotics, nine corticosteroids, eight SSZ, four MTX, three intravenous bisphosphonates, two etanercept and one AZA. The efficacy of NSAIDs seemed to be linked to the initial number of bony sites (Table 2): patients who did not respond to NSAIDs had statistically more lesions at onset ($P = 0.03$). There was no significant difference of age, sex and biological parameters between the responders and non-responders to the NSAID.

Median age at last follow-up was 14.5 yrs (range 6.5–27). Median time since diagnosis was 3.5 yrs (range 0.5–15) and median duration of active disease 2.7 yrs (range 0.5–13.5). The duration of active disease was linked to the initial number of localizations ($P < 0.001$) and the total number of localizations ($P < 0.001$) and inversely correlated with the age at onset ($P < 0.001$) in a multivariate regression analysis. ESR at onset was correlated with the duration of active disease (Pearson correlation, $P = 0.04$) in a linear regression analysis, but not in a multivariate regression model (Table 3). The other biological parameters (CRP, white blood cell count, haemoglobin and platelets) were not associated with a prolonged evolution of the disease.

TABLE 3. Pearson correlation for duration of active disease

| | Pearson correlation coefficient | *P* |
|---|---|---|
| Age at disease onset (yrs) | −0.385 | **0.01** |
| Sex | 0.04 | 0.8 |
| Initial number of localizations | **0.246** | **0.02** |
| Total number of localizations | **0.262** | **0.01** |
| NSAID response | **0.53** | 0 |
| WBC (per $mm^3$) | −0.004 | 0.9 |
| Platelet count (per $mm^3$) | 0.146 | 0.4 |
| ESR (mm/$1^{st}$ h) | **0.337** | **0.04** |
| CRP (mg/l) | 0.166 | 0.34 |

Bold values indicate $P < 0.05$.

Eight patients (20%) had physical sequelae, including leg length discrepancies in three patients, bony overgrowth of the clavicle in one patient, generalized growth failure in three patients (ranging from −1 to −2 S.D.) and vertebral compression fracture due to corticosteroids in one child. One patient suffered from depression linked to the disease. Associated features were psoriasis in two patients, pustulosis in one and Takayasu arteritis in one. Twenty-nine children (72.5%) responded to the questionnaire. Twenty-six had no physical disability (HAQ: 0–1), two had moderate disability (HAQ: 1–2) and one had severe disability (HAQ: 2–3). Seventeen patients (58.6%) had active disease at last follow-up (after 6 months to 15 yrs since diagnosis) and still suffered from pain (median value of visual analogue scale: 10/100), all requiring analgesics. Fifteen (51.7%) patients considered that CRMO had some global repercussion on their life (median value of visual analogue scale: 10/100). CRMO had interfered with the patient's education in two cases, who failed to obtain a degree because of hospitalization and pain. The first patient was a 9-yr-old boy at the beginning of the disease, with a duration of the disease of 7.5 yrs. He received successively antibiotics, NSAID, corticosteroids, intravenous bisphosphonates and etanercept. He suffered from overgrowth of the mandible and generalized growth failure of −1.5 S.D. The second patient was a 7-yr-old girl at the beginning of the disease, with a duration of the disease of 15 yrs. She was treated successively with NSAIDs, SSZ, corticosteroids, MTX and AZA. She suffered from generalized growth failure of −2 S.D. No other patient thought that CRMO had affected their ability to obtain a degree or a job.

## Discussion

In our study as reported in the literature [2, 7], 85% of the cases of CRMO occurred in females with a median age at onset of the disease of 10 yrs [2, 3]. An association with SAPHO syndrome or psoriasis has been reported in up to 23% of the cases [3], but was rare in our study, affecting only three patients. Initial symptoms were bone pain in all patients and fever in only nine patients. Inflammatory markers were increased in 65% of the patients in one series [10], and in 68% of our cases. Median number of total bony lesions was 3.5, in agreement with what is described in the literature [3, 9]. Lower limbs were mostly affected, usually with lesions of the metaphysis as in previous reports [5, 6, 8, 9].

Involvement of the clavicle has classically been described [11], but was found in only 20% of our patients, as reported in other studies [7, 9]. Bone biopsy was only performed when diagnosis was uncertain and showed non-specific chronic inflammation, as described by Girschick *et al.* [8].

As in SAPHO syndrome, NSAIDs are usually effective with a response in up to 80% of the cases [3, 12]. The fraction of good responders has been probably overstated because inflammatory markers were usually only slightly increased and the patient's pain evaluation was rather good despite the persistence of the disease. In our study, they were used in almost all cases, with 73% responders. Corticosteroids can be used for severe relapsing cases with a very high response rate [13, 14]. In a small number of patients, improvement has been observed after treatment with SSZ, MTX, colchicine [9], IFN-$\gamma$ [15], IFN-$\alpha$ [16], bisphosphonates [17, 18] and infliximab [4, 19].

Although the early literature suggested that CRMO is a self-limiting condition without sequelae, more recent studies have found that symptoms can be prolonged. Some cases that remained active for many years have been reported [11]. In this study, median duration of active disease was 2.7 yrs with a median time since diagnosis of 3.5 yrs. More than half of the patients had active disease at follow-up, continued to have pain and considered that CRMO had global consequencies on their life. In their review of the literature, Schultz *et al.* [3] reported data similar to ours, with similar median duration from diagnosis to remission (2 yrs) and similar median time from onset of illness to last follow-up (3.5 yrs). In Huber's study, median overall duration of active disease was 5.7 yrs. More than 25% of the patients had persistent CRMO activity at the time of evaluation, a median of 12.4 yrs later [9]. In comparison with our study in which 20% of the patients had physical sequelae, only 7% of patients in Schultz *et al.*'s review [3] had long-term sequelae such as growth retardation, bone deformities, kyphosis and thoracic outlet syndrome. This may be due to a recruitment bias because all of our patients were referred to tertiary care hospitals and were therefore likely to be more severely affected. Duffy *et al.* [20] also found a high rate of orthopaedic complications at maturity in a cohort of 12 adults, including deformities in seven patients and leg-length inequality in five patients, requiring surgery in one. Huber *et al.* [9] confirmed those results with nearly half of the cohort suffering from bone deformities.

In spite of this significant morbidity associated with CRMO, only 3 patients out of 29 had moderate or severe disability when measured by the HAQ. CRMO had interfered with patients' education in only two cases, and no patient felt that CRMO had affected their ability to obtain a job. In Huber *et al.*'s [9] long-term follow-up (median time since diagnosis of 13 yrs), 78% of subjects had HAQ scores of 0, indicating no or minimal impairment of physical function; in our study with a median time since diagnosis of 3.5 yrs, an HAQ of 0 was present in 59% of the cases. In Huber *et al.*'s [9] study, impairments were seen in all domains of measurement of a quality-of-life test, but appeared more frequently in non-physical aspects of health. CRMO had affected education for seven patients out of 23 and the ability to work in three patients.

Very few studies have analysed predictive factors for persistent evolution of CRMO. Girschick *et al.* [12] showed that there was no significant difference in the duration of NSAID treatment between the unifocal and multifocal forms. In our study, we showed that young patients at the onset of the disease with a high number of bony sites seemed to be at risk for persistent disease. Moreover, a high number of bony sites at the onset was also a risk factor for a poor response to NSAIDs. Sex and biological parameters did not seem to influence the evolution or the response to the treatment. However, our group of patients is rather small and these results have to be confirmed by larger series. Despite this fact, we must underline that we were able to gather information on the majority (72.5%) of the patients, which is a high rate of response for such type of study.

In conclusion, our study suggests that clinical outcome of children with CRMO is generally good, but a sizeable proportion of patients have active disease at follow-up, and a minority of patients can have a severe and prolonged disease course despite intensive treatments. Further studies are required to confirm the risk factors for severe and persistent disease, and then to treat those patients more aggressively in order to prevent a poor long-term outcome.

## Rheumatology key messages

- Clinical outcome of children with CRMO is generally good.
- About one-fifth of the patients can have severe and prolonged disease course.
- Younger age and high number of bony sites at onset seems to be predictive of poorer outcome.

*Disclosure statement*: The authors have declared no conflicts of interest.

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