Rheumatology 2007;46:154–160
Advance Access publication 17 June 2006
doi:10.1093/rheumatology/kel190

# Classification of Non-Bacterial Osteitis

## Retrospective study of clinical, immunological and genetic aspects in 89 patients

A. Jansson*,[1], E. D. Renner*,[1,2], J. Ramser[3,6], A. Mayer[1], M. Haban[3], A. Meindl[3,6], V. Grote[1], J. Diebold[4], V. Jansson[5], K. Schneider[1] and B. H. Belohradsky[1]

***Objective*. To define non-bacterial osteitis (NBO) as a clinical entity possibly associated with autoimmune manifestations. Patients with sterile osteitis were analysed to develop diagnostic criteria.**

***Methods*. A total of 89 patients with non-bacterial inflammatory bone lesions were observed for a median of 49 months. History, diagnostic imaging, laboratory and histological data were obtained. Mutation analysis in the genes *PSTPIP1* and *PSTPIP2* was performed.**

***Results*. Patients had an onset of disease at a median age of 10 yrs [interquartile range (IQR) 7.5–12] and suffered a median period of 21 (IQR 9–52) months with a median of three foci per patient. Twenty percent of all the patients demonstrated associated autoimmune disorders, particularly of the skin and bowel. The majority of bone lesions were located in the vertebrae and metaphyses. Slight-to-moderate elevation of inflammation values were found in all the patients and antinuclear antibodies were elevated in 30%. Non-steroidal anti-inflammatory drugs (NSAIDs) were effective in 85% of the patients. HLA-B27 and Human Leukocyte Antigen-DR (HLA-DR)-classification did not differ from the general population. Autoimmune diseases in 40% of all the families, multiply affected family members, linkage to 18q21 and mouse models strongly indicate a genetic basis for NBO. We observed three different courses of disease regarding the duration of complaints, rate of complications and associated autoimmune manifestations leading to a new classification of NBO.**

***Conclusions*. Clinical analysis of our cohort leads us to define NBO as a distinct disease entity with three clinical presentations: acute NBO, chronic recurrent multifocal osteomyclitis or persistent chronic NBO. Diagnostic criteria were proposed to differentiate NBO from diseases with similar clinical presentation.**

KEY WORDS: Non-bacterial osteitis (NBO), Chronic recurrent multifocal osteomyelitis (CRMO), SAPHO syndrome, Complications, Therapy, Classification, Diagnostic criteria, Genetic results.

## Introduction

Non-bacterial bone inflammations with or without associated diseases were described at all ages and at all sites of the skeleton [1–7]. Histological investigations showed non-specific inflammation, fibrotic and/or hyperostotic regeneration [1]. Bacteriological investigations of the bone lesions, however, remained negative [1, 8] and no infectious agent was to be found [1, 7, 9–11]. A number of terms [4, 12, 13] are used to describe diseases with non-bacterial osteitis (NBO) including the SAPHO (synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) syndrome, pustulotic arthro-osteitis, CRMO (*C*hronic Recurrent Multifocal Osteomyelitis), chronic sclerosing osteomyelitis, lympho-plasmacellular osteomyelitis and others.

SAPHO syndrome and CRMO present with osteitis as a common feature. CRMO was regarded to be the paediatric subset of SAPHO syndrome [4, 14]. Recently, however, adults with CRMO [15] and children with SAPHO syndrome [5, 16, 17] were described. In fact, CRMO and SAPHO syndrome share several features: osteitis (sterile bone lesions with non-specific signs of inflammation), unifocal or multifocal presentation, pustulosis, hyperostosis and a good general state of health without spiking fevers, organomegaly, weight loss or fatigue.

Several clinicians [3, 4, 18, 19] assume a common pathway for the different diseases associated with osteitis looking at clinical, radiological and histological findings.

Supporting the hypothesis of a single pathogenetic pathway for 'primary' sterile osteitis, we defined a cohort due to the isolated sterile bone lesions without any other underlying disorders. Clinical, immunological and genetic findings of 89 juvenile and adult patients with osteitis and without arthritis at first presentation were analysed. Diagnostic criteria were established for two main purposes:

- Distinguishing NBO from other disease entities with similar clinical presentation.
- To diagnose patients with osteitis alone.

## Subjects and methods

### *Subjects*

We retrospectively evaluated 89 patients with sterile bone inflammation, who had been diagnosed at or referred to the

[1]Dr v. Haunersches Kinderspital, Ludwig–Maximilians University, Munich, Germany, [2]Department of Pediatrics, University of Washington, Seattle, WA, USA, [3]Institute of Human Genetics, [4]Institute of Pathology, [5]Department of Orthopaedics, Grosshadern, Ludwig–Maximilians–University and [6]Department of Gynaecology and Obstetrics at the Technical University, Munich, Germany.

Submitted 15 December 2005; revised version accepted 25 April 2006.

Correspondence to: A. Jansson, MD, Dr v. Haunersches Kinderspital, Ludwig–Maximilians University, Lindwurmstr. 4, D-80337 Munich, Germany. E-mail: Annette.Jansson@med.uni-muenchen.de

*Annette Jansson and Ellen D. Renner contributed equally to this work.

University Children's Hospital, Munich between 1977 and 2005. Patients were from various ethnic backgrounds: 75 German, four Serbo-Croatian, three Turkish, one American, one South-American, one Guinean and one English. In three families, a parent was of French descent and in one family, of Italian descent.

All patients presented with at least one radiologically verified osteomyelitic and/or sclerotic bone focus. Patients were followed up for a period of 18 months to 28 yrs (median: 49 months).

Patients were divided by clinical presentation:

(i) Group 1 consisted of 17 patients with complaints lasting not longer than 6 months and presenting with at least one bone lesion. This group was defined as having acute non-bacterial osteitis (ANBO).
(ii) Group 2 consisted of 33 patients with persistent complaints (without remissions) lasting longer than 6 months, and presenting with at least one bone lesion. These patients were defined as having chronic non-bacterial osteitis (CNBO).
(iii) Group 3 consisted of 39 patients with multiple bone lesions, or one bone lesion plus palmoplantar pustulosis (PPP), and recurrent flares with remissions. These patients were defined as having CRMO.

### *Clinical evaluation*

We obtained a complete history, reviewed medical records and performed at least one physical examination for each patient. All patients were investigated by a single rheumatologist (A.J.). Fifty-three patients had not been seen in the last 6 months before data analysis and were clinically updated by phone using a standardized questionnaire, which addressed complaints since the last visit, associated diseases and current medication. Investigation of clinical criteria focused on the most common features seen in our patients and reports in the literature.

X-rays performed at the University Children's Hospital, Munich or elsewhere were evaluated by a single radiologist with long-term experience in bone disorders (K.S.).

Laboratory values including complete and differential blood count, levels of serum immunoglobulins, immunoglobulin G (IgG) subclasses, C-reactive protein (CRP), antinuclear antibodies (ANA), HLA-typing, HLA-B27 detection and serum tumour necrotis factor-$\alpha$ (TNF-$\alpha$), were assessed during flares. HE (haematoxylin–eosin) stained histological preparations were all evaluated by a single pathologist (J.D.).

### *Genetic studies*

Mutation screening in the genes *PSTPIP1* and *PSTPIP2* was performed in genomic DNA in 10 CRMO patients presenting with multiple, symmetrical bone foci, several relapses, hyperostosis and PPP. Coding sequences of *PSTPIP1* (Gen bank: NM_003978) and *PSTPIP2* (Gen bank: NM_024430) were amplified in a standard 25 $\mu$l polymerase chain reaction (PCR) reaction based on genomic DNA. PCR primers are available upon request. PCR products were purified on QIAquick columns (Qiagen), sequenced using Big Dye terminator chemistry (Applied Biosystems) and analysed with an automated ABI 3100 DNA sequencer (Applied Biosystems).

The study was approved by the Ethics Committee of the medical faculty of the Ludwig–Maximilians University, Munich (Germany). Written consent was obtained from all the patients.

### *Statistical analysis*

Clinical and laboratory data were analysed in Microsoft Excel and Stata 8.2 (StataCorp, Texas, USA). Average values were given in medians with interquartile ranges (IQR, 25–75th percentile). Differences between groups were tested for categorical data by Fisher's exact chi-square test and for continuous data by the Kruskal–Wallis rank test.

## Results

### *Clinical presentation*

Local pain of the bone was the leading symptom. Patients presented in a good state of health. Sixty-five percent ($n = 58$) of all the patients were female (clinical and laboratory data are summarized in Table 1). In 87% ($n = 77$), disease onset was before 18 yrs of life, ranging from 33 months to 54 yrs of age, with a median of 10 (IQR 8–12) yrs. Seventeen patients (19%) showed no more than one bone focus. Thirty-five patients (39%) initially presented with one bone lesion. Seventeen (49%) of these 35 patients developed additional [1–6] bone foci during the course of the disease. Fifty-four patients (61%) presented with at least two (range 2–14) bone foci. All together, 321 foci were detected over time, resulting in a median of 3.0 (IQR 2–5) per patient. Symmetrical afflictions were observed in 20 patients with multifocal disease (Fig. 1), of whom 15 were classified as CRMO patients. The course of the disease lasted a median of 21 months (IQR 8–52). Fifty patients (56%) were free of complaints after a median of 29 months. More than one member was affected with NBO in 6% of the families. These family relationships were: father and son, monozygotic twin sisters, two pairs of sisters, and, in one family, two sisters and their father. Multiply affected family members were observed in all the subgroups of NBO (Table 1).

### *Associated diseases*

In 31% of the patients, associated diseases were present (Table 1). Typical psoriatic afflictions of the skin and/or nails were found in four patients. PPP before ($n = 6$) or during ($n = 12$) an acute attack was found in all the groups (Fig. 2).

Chronic bowel disease occurred before or during bone involvement in six patients; two patients were affected by Crohn's disease, three patients by ulcerative colitis and one patient by coeliac disease. Associated autoimmune diseases were most frequently seen in CRMO patients (Table 2). Magnetic resonance imaging (MRI) revealed arthritis with minor synovial exudation in five patients. Their bone foci were located next to the sternoclavicular ($n = 2$), hip ($n = 2$) and ileosacral ($n = 1$) joints. None of these five patients developed clinical arthritis. Family history was positive for autoimmune diseases in 39%.

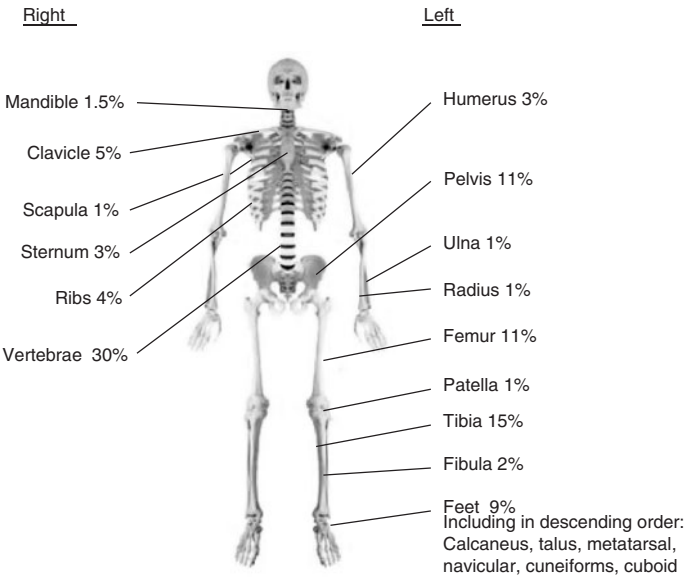


FIG. 1. Bone involvement in 89 patients with NBO; bone lesions located on the patient's left side occurred bilaterally, symmetrically in at least one patient.

Table 1. Clinical and laboratory data of the 89 patients with NBO. Comparison of the three subgroups

| | ANBO $n=17$ | CRMO $n=39$ | CNBO $n=33$ | Total $n=89$ |
|---|---|---|---|---|
| Clinical manifestation | | | | |
| Median of onset in years of age | 10 (IQR 8–11) | 9 (IQR 8–10.5) | 11 (IQR 7–15) | 10 (IQR 8–12) |
| Median number of bone foci | 2 (IQR 1–4) | 4 (IQR 3–6) | 3 (IQR 2–3) | 3 (IQR 2–5) |
| Median duration of complaints in months | 4 (IQR 3–6) | 29 (IQR 18–67) | 21 (IQR 14–43) | 21 (IQR 8–52) |
| Female gender | 9/17 (53%) | 28/39 (72%) | 22/33 (67%) | 58/89 (65%) |
| Patients without complaints in the last 18 months | 17/17 (100%) | 19/39 (49%) | 14/33 (42%) | 50/89 (56%) |
| Unifocal presentation | 5/17 (29%) | 3/39 (8%) | 9/33 (27%) | 17/89 (19%) |
| Symmetrical bone lesions | 3/17 (18%) | 15/39 (38%) | 2/33 (6%) | 20/89 (22%) |
| Vertebral manifestation | 4/17 (23%) | 19/39 (49%) | 10/33 (30%) | 33/89 (37%) |
| Sternal and/or clavicular manifestation | 6/17 (35%) | 15/39 (38%) | 11/33 (33%) | 32/89 (36%) |
| Pelvic manifestation | 0/17 (0%) | 10/39 (26%) | 06/33 (18%) | 16/89 (18%) |
| Complications | | | | |
| Resistant complaints | 0/17 (0%) | 7/39 (18%) | 5/33 (15%) | 12/89 (13%) |
| Pathological fractures | 1/17 (6%) | 19/39 (49%) | 6/33 (18%) | 26/89 (29%) |
| Vertebral fractures derived from pathological fractures | 1/17 (6%) | 17/39 (44%) | 3/33 (9%) | 21/89 (24%) |
| Hyperostosis | 2/17 (12%) | 11/39 (28%) | 4/33 (12%) | 17/89 (19%) |
| Associated autoimmune diseases | | | | |
| PPP | 3/17 (18%) | 12/39 (31%) | 3/33 (9%) | 18/89 (20%) |
| Inflammatory bowel disease | 1/17 (6%) | 3/39 (8%) | 2/33 (6%) | 6/89 (7%) |
| Psoriasis | 0/17 (0%) | 3/39 (8%) | 1/33 (3%) | 4/89 (4%) |
| Diseases in primary or secondary relatives | | | | |
| NBO | 5/17 (29%) | 3/39 (8%) | 3/33 (9%) | 11/89 (12%) |
| Psoriasis | 5/17 (29%) | 11/39 (28%) | 2/33 (6%) | 18/89 (20%) |
| Chronic arthritis | 0/17 (0%) | 7/39 (18%) | 7/33 (21%) | 14/89 (16%) |
| Inflammatory bowel disease | 1/17 (6%) | 5/39 (13%) | 0/33 (0%) | 6/89 (7%) |
| PPP | 1/17 (6%) | 1/39 (3%) | 0/33 (0%) | 2/89 (2%) |
| Others: Alopecia areata, spondylitis ankylosans, Hashimoto thyreoiditis, overlap syndrome, sarcoidosis | 0/17 (0%) | 5/39 (13%) | 1/33 (3%) | 6/89 (7%) |
| Inflammation serum values | | | | |
| ESR >15/30 | 14/17 (82%) | 33/39 (85%) | 26/33 (79%) | 73/89 (82%) |
| CRP >0.5 mg/dl | 10/17 (59%) | 31/39 (79%) | 21/33 (64%) | 62/89 (70%) |
| CRP >5 mg/dl | 4/17 (24%) | 6/39 (15%) | 3/33 (9%) | 13/89 (15%) |
| TNF-$\alpha$ >25 pg/ml | 11/11 (100%) | 19/29 (66%) | 13/25 (52%) | 43/65 (66%) |
| Elevated total serum IgG | 3/15 (20%) | 7/38 (18%) | 3/33 (9%) | 13/86 (15%) |
| Elevated serum IgG1 | 3/11 (27%) | 6/34 (18%) | 3/27 (11%) | 12/72 (17%) |
| Elevated serum IgG2 | 3/11 (27%) | 9/34 (26%) | 8/27 (30%) | 20/72 (28%) |
| Elevated serum IgG3 | 1/11 (9%) | 0/34 (0%) | 4/27 (15%) | 5/72 (7%) |
| Serum IgD >100 IU/ml | 2/11 (18%) | 4/33 (12%) | 2/27 (7%) | 8/68 (12%) |
| ANA $\geq$1:120 U/ml | 4/15 (27%) | 14/36 (39%) | 9/31 (29%) | 27/82 (33%) |
| Histological findings of bone biopsies | | | | |
| Chronic inflammation: | | | | |
| Mild (= few lymphocytes <50% of marrow cavities) | 0/4 (0%) | 12/21 (57%) | 8/11 (73%) | 20/36 (56%) |
| Moderate (= scattered lymphocytes >50% of marrow cavities) | 2/4 (50%) | 6/21 (29%) | 2/11 (18%) | 10/36 (28%) |
| Severe (= dense lymphoid and plasma cell infiltrates >50% of marrow cavities) | 2/4 (50%) | 3/21 (14%) | 1/11 (9%) | 6/36 (17%) |
| Fibrosis of the marrow cavity: | | | | |
| None | 0/4 (0%) | 4/21 (19%) | 0/11 (0%) | 4/36 (11%) |
| Mild (= small increase in marrow fibroblasts) | 1/4 (25%) | 8/21 (38%) | 7/11 (64%) | 16/36 (44%) |
| Moderate (= dense collagenous fibres with newly formed capillaries) | 1/4 (25%) | 4/21 (19%) | 3/11 (27%) | 8/36 (22%) |
| Severe (= intermediate changes) | 2/4 (50%) | 5/21 (24%) | 1/11 (9%) | 8/36 (22%) |
| Purulent inflammation (= aggregates of neutrophilic granulocytes) | 2/4 (50%) | 6/21 (29%) | 0/11 (0%) | 8/36 (22%) |

Table 2. Proposed major and minor diagnostic criteria of NBO

| Major diagnostic criteria | Minor diagnostic criteria |
|---|---|
| 1. Radiologically proven osteolytic/-sclerotic bone lesion | A. Normal blood count and good general state of health |
| 2. Multifocal bone lesions | B. CRP and ESR mildly-to-moderately elevated |
| 3. PPP or psoriasis | C. Observation time longer than 6 months |
| 4. Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis | D. Hyperostosis |
| | E. Associated with other autoimmune diseases apart from PPP or psoriasis |
| | F. Grade I or II relatives with autoimmune or autoinflammatory disease, or with NBO |

NBO is confirmed by two major criteria or one major and three minor criteria.

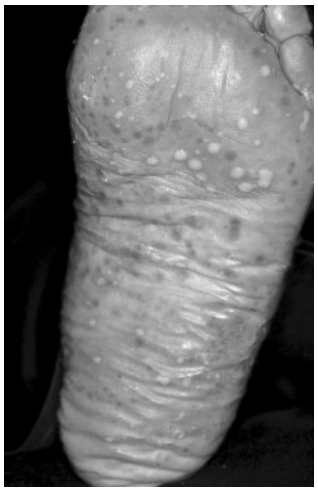

FIG. 2. Severe palmoplantar pustulosis in an adult patient with NBO.


FIG. 4. MRI of severe bone destruction at the 5th thoracic vertebra in a 22-year-old female with NBO.

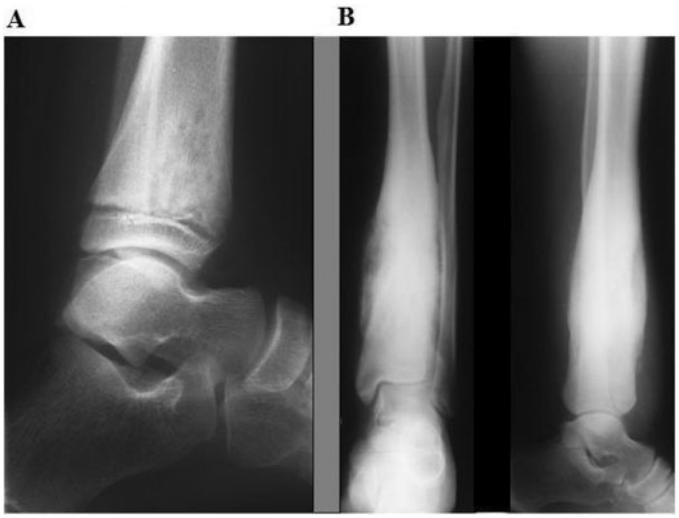


FIG. 3. Profound hyperostosis in a boy with NBO. (**A**) Osteolytic changes in the distal, left tibial metaphysis with appositional bone growth into marginal zones at 9 yrs of age. (**B**) Massive hyperostosis of left distal tibia after multiple relapses at 15 yrs of age.

### *Complications*

Forty-six percent of all the patients developed complications consisting of therapy-resistant complaints, functionally or cosmetically relevant hyperostosis (Fig. 3A and B) and pathological bone fractures (Table 1). Pathological bone fractures were the most frequent complications in 28% of all the patients, presenting in 76% (16 out of 21 patients) as vertebral fractures (Fig. 4) as well as vertebra plana. Nearly half (46%) of the patients with vertebral fractures consequently developed a scoliosis $>10^{\circ}$. Pathological bone fractures also occurred in the acetabulum ($n=1$), clavicle ($n=1$), cuboid ($n=1$), femur ($n=1$) and tibia ($n=1$).

### *Imaging*

Conventional X-rays were performed in 88 (99%) patients. Most bone lesions (31%) were localized in the metaphyses close to the growth plates (Fig. 3A). Thirty patients (34%) developed moderate-to-severe sclerosis as a long-term complication. Sixteen patients (18%) demonstrated a complete radiological recovery.

Periostal reaction was always seen in the 16 lesions of the sternal part of the clavicula. Involved vertebrae revealed osteolytic or sclerotic areas in the marginal zone similar to the findings seen in Scheuermann's disease.

Eighty of 89 (90%) patients with NBO underwent skeletal scintigraphy. In three of our patients, scintigraphy revealed no positive uptake during an acute attack while histological examination of the bone specimens determined non-specific inflammation. An additional 53 painless bone lesions were detected by skeletal scintigraphy performed during the first manifestation in 23 patients. Twenty of these silent foci involved the vertebrae.

MRI was performed in 72 (81%) patients. As described before [20–22], lesions of vertebrae, ribs, pelvis and in the smaller bones of the hands and feet were recorded more accurately by an MRI. MRI discovered additional, clinically non-detectable, inflammatory effusions in the region of osteitic foci, which we considered to be reactive. In 22 (25%) patients, a computer tomography (CT) scan was performed for a more detailed evaluation, which consequently revealed additional bone destruction in four patients.

### *Histology*

Biopsy was performed in 52 patients. Thirty-six biopsies were re-evaluated showing signs of non-specific inflammation (Fig. 5, Table 1). Histology revealed no significant differences between patients with ANBO, CNBO or CRMO with regard to chronic inflammation and fibrosis of the marrow. No purulent inflammation was seen in CNBO.

### *Laboratory values*

Patients showed normal blood counts during the attack. Thirty percent of the patients had ANA levels $\geq$1:120 U/l. Specific antibody testing was carried out in cases of ANA$\geq$1:240 U/l, but no specific antibodies were verified. Serum immunoglobulin A (IgA) and immunoglobulin M (IgM) were within the normal ranges. Rheumatological investigations revealed normal values of complement components (C3 and C4) and RF for all the patients.

Compared with normal populations, HLA-B27, with an incidence of 7% (3 of 34 CRMO, 2 of 28 CNBO), was not increased. Interestingly, none of the patients with ANBO ($n=10$) was positive for HLA-B27.

Human Leukocyte Antigen-DR (HLA-DR)-typing performed in 44 patients showed no correlation.

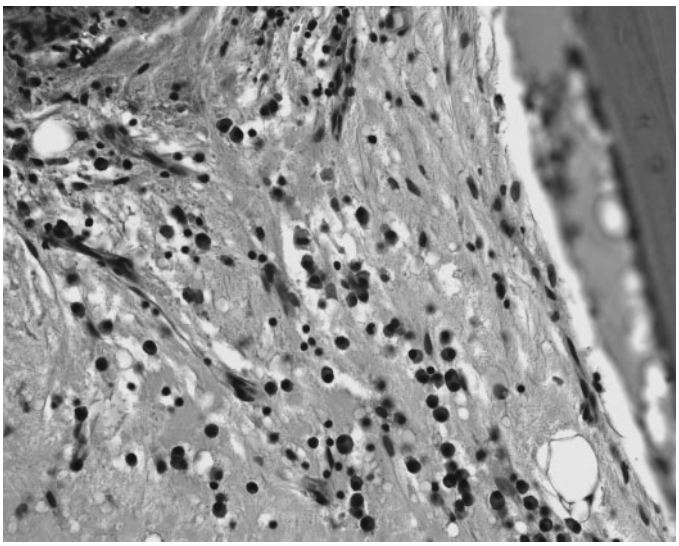

FIG. 5. Bone biopsy of a focus at the right proximal femur revealing lympho-plasmacellular infiltration and fibrosis in patient with NBO. HE (haematoxylin-eosin)-stained, 40-fold magnification.

### *Treatment*

On a suspicion of bacterial osteomyelitis, 74% ($n = 66$) of all patients had been treated with intravenous and/or oral antibiotics at the onset of the disease. Eighty-seven percent ($n = 77$) of our patients received non-steroidal anti-inflammatory drugs (NSAIDs) as a continuous or intermittent therapy (Naproxen 10, 15 mg/kg/day). Thirteen of the 77 patients were NSAID-non responders who had not experienced any pain relief after 3 months of therapy, or relapsed three or more times. Those patients received prednisolone (2 mg/kg/day orally for 5 days) or hydrocortisone (10 mg/kg/day i.v. for 3 days). Steroids led to a transient response concerning pain and inflammatory values in all the patients treated. Six patients who relapsed frequently received either methotrexate or azathioprine without any clinical benefit. Four adult patients received pamidronate. One of them showed remission for a period of 2 yrs, the second one demonstrated a relief from symptoms and the other two did not respond to pamidronate at all. Infliximab induced remissions over a period of 3 months in one patient, and another patient with severe colitis and osteitis is in complete remission for a period of 17 months.

### *Genetic findings*

Ten CRMO patients were selected for mutation screening in the genes *PSTPIP1* and *PSTPIP2*. Except for several known polymorphisms, no mutations were detected.

### *Comparison of the three groups*

Two-thirds of the CRMO and CNBO patients were female as compared with about half of the ANBO patients, revealing no statistical significance ($P = 0.156$) (Table 1). Median onset of disease did not vary between ANBO, CRMO and CNBO subsets. ANBO patients had a significantly ($P < 0.001$) shorter duration of disease (4 months) than patients with CNBO (21 months) or CRMO (29 months). The median number of bone foci was two in ANBO, three in CNBO and four in CRMO patients ($P = 0.001$). Unifocal presentation occurred more frequently ($P = 0.048$) and symmetrical bone lesions were less frequently detected in patients with ANBO and CNBO than with CRMO ($P = 0.003$) (Table 1). Pelvic manifestations were not seen in ANBO, but seen in 18% and 26% of the CNBO and CRMO patients, respectively ($P = 0.054$).

Forty-two percent of the CNBO patients, 49% of the CRMO and all the ANBO patients ($P = 0.097$) were free of complaints in the last 18 months. CRMO patients presented with 2–13 (median 4) attacks. The longest observed interval between consecutive attacks was a period of 37 months in a CRMO patient.

Pathological fractures, mainly of vertebral origin, occurred in 49% with CRMO, in 18% with CNBO and in 6% with ANBO ($P = 0.001$). Overall, CRMO was associated with the highest rate of complications and associated autoimmune diseases of patients and relatives. Serum inflammatory values did not differ except for serum-TNF-$\alpha$, which was elevated to 100% in ANBO, to 66% in CRMO and to 52% in CNBO. Histological investigations revealed chronic inflammation and fibrosis in all the groups, while no purulent inflammation was seen in CNBO.

### *Clinical criteria*

Applying our proposed clinical criteria (Table 2), all the patients met at least one major plus three minor criteria. Fourteen (82%) patients with ANBO, 21 (64%) patients with CNBO and 14 (36%) patients with CRMO met one to two major and up to four minor criteria. Four major and at least three minor criteria were found in one ANBO, one CNBO and five CRMO patients. The four major criteria were detected with the following frequencies: (i) osteolytic/-sclerotic bone lesions in 85%; (ii) multifocal disease in 81%; (iii) PPP in 20% of all the patients; and (iv) the fourth major criteria, 'sterile bone biopsy with signs of inflammation and/or fibrosis or sclerosis', was present in 94% of the 52 patients who underwent biopsy. Re-evaluation of biopsy specimens was possible in 36 patients and revealed presence of major criteria in all the 36 patients. The six minor criteria were: (i) normal blood count with good general condition; (ii) and moderately elevated inflammation markers, both found in 97% of all the patients; (iii) all the patients had been observed longer than 6 months; (iv) hyperostosis occurred in 17 (19%) and (v) associated autoimmune diseases apart from PPP in 12 (13%) patients; and (vi) family members with NBO were observed in 12% of the patients out of all the 85 families. Reviewing all possible combinations of criteria, the largest group consisted of 11% of all the patients who showed osteolytic/-sclerotic bone lesions, multifocal disease with normal blood count and elevated inflammation markers during observation for more than 6 months. Major criteria, (i) and (ii), and the minor criteria, (i), (ii), and (iii), were seen to be present in 53 (60%) of all the 89 patients, although some of these 53 patients demonstrated additional criteria.

## Discussion

Guided by the CRMO mouse models [18, 23] and by our own observations [24] that sterile bone inflammation might underlie a single pathogenetic pathway, we defined a cohort with non-bacterial osteitis but with no other underlying disorders. Clinical, immunological and genetic findings of 89 juvenile and adult patients with osteitis and without arthritis at first presentation have been analysed, revealing NBO as a distinct disease entity.

Reviewing the literature and summarizing our clinical and laboratory findings, we developed clinical criteria to diagnose NBO (Table 2). Applying the proposed diagnostic criteria, we found that the fewer the criteria met, the more likely the ANBO was diagnosed; and the more criteria that were met, the more likely the CRMO was diagnosed. This classification of the patients into defined groups might help to find prognostic indicators. Prospective clinical application of the diagnostic criteria is ongoing.

Sterile bone lesions are well-known and are thoroughly described as a criteria of the SAPHO syndrome [2–4, 10, 11, 15, 18, 19] and of other similar disorders like pustulotic arthro-osteitis and CRMO [4, 6, 7, 11–13, 20, 25]. Arthritis, pustulosis, acne, hyperostosis or CRMO were proposed—amongst other conditions—as the inclusion criteria of the SAPHO syndrome [3]. However, osteitis is a common presentation in patients with the SAPHO syndrome, but is not required for the diagnosis. Features such as arthritis, psoriasis and/or severe acne seen in the SAPHO patients might not be pathopyhsiologically related.

A classification based on osteitis—including bone lesions without other SAPHO criteria—seemed more reasonable to us for promising clinical and genetic research on sterile bone lesions. According to our inclusion criteria, dermatoses and arthritis occurred less frequently in our osteitis-based cohort than seen in patients with the SAPHO syndrome [2, 4, 5]. Acne fulminans, which can be associated with NBO, is a disorder with highly elevated inflammation markers and is present predominantly in adolescent males [6, 26], suggesting a heredity factor other than that seen for NBO.

Arthritis does not seem to be associated with NBO. Only one girl, who was in addition HLA-27-positive, developed reactive arthritis 2 years after NBO remission—the only one out of our cohort suffering from 'primary' NBO in a median observation time of 49 months.

Three different clinical courses of NBO were observed in our cohort, consisting of ANBO, CRMO and CNBO. ANBO, which has not been described previously, was presented by 19% of our patients. ANBO shares more features with CRMO than with CNBO such as PPP, associated diseases and purulent inflammation, but resolves within 6 months. As ANBO patients might relapse and convert into CRMO, all our ANBO patients were recently re-evaluated, but no relapses had been reported (median complaint-free interval of ANBO was 31 months, longest interval between two relapses in CRMO in our patients was 37 months). Patients with CNBO presented with persistent pain and also showed fewer associated autoimmune diseases, as did their relatives compared with ANBO and CRMO.

More complications, especially vertebral fractures, were present in patients with classical CRMO than in CNBO. Two of our CRMO patients underwent stabilizing surgery since they were suffering from fractures of the cervical spine with imminent myelocompression. Vertebra plana and vertebral fractures have been reported previously [10, 21, 25, 27]. Some authors postulated CRMO and SAPHO as being a feature of spondylarthropathy [3, 21, 28]. Even though 30% of our patients had bone foci of the vertebrae, oligoarthritis and enthesitis, which would define juvenile spondylarthropathy, were not present [29]. In addition, our NBO patients showed no association with HLA-B27 in contrast to patients with spondylarthropathy [30].

The erythrocyte sedimentation rate (ESR), CRP and serum-TNF-$\alpha$ seemed to be the valuable laboratory parameters to detect flares in all the subgroups [2, 4, 5, 10, 11]. ANA were elevated in 30% of all the patients, and autoimmune diseases present in primary/secondary relatives in 40% of all families. Comparable data have not been described before, leading us to postulate that NBO belongs to the spectrum of autoimmune disorders. Treatment is still symptomatic, because the underlying defect of NBO still remains unknown.

NSAIDs—still the drugs of first choice—induced remission in 85% of our patients [2, 4, 7, 10, 19]. Remission was defined as no pain, decrease of elevated inflammation markers back to normal values and no radiological progression. In 13 NSAID-non-responders, steroids were effective for short-term relief. Six of our patients did not respond to azithromycin. Azithromycin was reported to be effective in patients with CRMO previously [31]. Bisphosphonates seem to induce remissions in the SAPHO syndrome [2, 4, 16, 17, 19, 32], but have not been approved for use in our cohort for the treatment of children. Pamidronate was effective in one out of four adult patients and induced partial relief in a second patient. Two of our patients were treated successfully with the TNF-inhibitor infliximab as reported previously [33–35]. Controlled therapeutic regimes are strongly needed in this disease with its severe complications affecting quality of life.

Family members in our cohort who were afflicted by this illness, and linkage analysis to 18q21, strongly indicate a genetic basis of NBO [24]. Recently, Wise *et al*. [36] detected a mutation in the *PSTPIP1* gene in patients with pyogenic arthritis, pyoderma gangaenosum and acne (PAPA) syndrome, defined according to pyogenic sterile arthritis, pyoderma gangrenosum and acne (OMIM #604416). Ferguson *et al*. [23] described a missense mutation in *pstpip2*, the murine orthologue of the human *PSTPIP2*, in the cmo (chronic multifocal osteomyelitis) mouse. Grosse *et al*. [37] described a T–A nucleotide exchange leading to an amino acid substitution in *pstpip2* in a mutant mouse that exhibited an autoinflammatory disorder characterized by macrophage infiltration and inflammation leading to osteolysis and necrosis of paws and ears. Though osteitis does not belong to PAPA syndrome, overlapping the symptoms of NBO and PAPA syndrome, the two mouse models [18, 23] led us to consider *PSTPIP1* and *PSTPIP2* as candidate genes for NBO. So far, no mutations were detected in 10 osteitis patients presenting with at least three major and four minor criteria and multiply affected family members of four of these patients. Although low penetrance variants in both genes cannot be excluded, the existence of missense mutations is unlikely in human NBO patients. Further investigations, however, are ongoing.

Seventy-seven of our patients have been treated with antibiotics due to diagnostic delay. Three out of 89 received chemotherapy, and nine of all underwent several biopsies and resections. Better knowledge of the disorder and the criteria may help to spare the patients such unnecessary therapeutic and diagnostic procedures [14].

On the basis of this extended work-up of 89 patients, we propose to term the different forms of osteitis of non-bacterial cause as one distinct disease called: NBO. We hypothesize that NBO, so far, is a distinct autoimmune disease of the bone which is not well-known. In this study, helpful clinical criteria to determine the diagnosis were developed. Although a genetic basis for NBO seems to exist, the underlying defect is still unknown and treatment remains symptomatic with a lack of proven therapeutic regimens. To date, patients with NBO but without other SAPHO features seem to be underdiagnosed and will most likely be detected more frequently using diagnostic criteria proposed in this article.

| *Rheumatology* | Key messages |
|---|---|
| | • NBO, an under-diagnosed autoimmune disease, may demonstrate acute, chronic recurrent or chronic persistent courses.<br>• Vertebral fractures should be considered as the most severe complication of NBO. |

## Acknowledgements

We are grateful to A. Golla for supporting genetic investigations, E.D. Albert for performing the HLA-DR phenotyping, G. Plewig for relinquishment of Fig. 2, G. Welser, B. Kammer and F. Sollinger for advice and helpful discussions, E. Ocheltree for critically reviewing the manuscript, and S. Schlieben and G. Strotmann for their medical assistance over more than 10 yrs.

We thank the patients and their parents for their participation and the clinicians for help with patient recruitment: T. Biedermann, Berlin; S. Breitner, Munich; M. Borte, Leipzig; F. Dressler, Hanover; A. Eckardt, Mainz; T. Endres, Dresden; J. Erkel, Vechta; G. Ganser, Sendenhorst; H. Girschick, Wuerzburg, Dresden; B. Graf, Suhl; S. Gross, Giessen; K.-P. Guenther, Dresden; R. Haefner, Garmisch-Partenkirchen; H. Hatz, Munich; G. Horneff, Halle; T. Hospach, Stuttgart; M. Hummler, Hildesheim; R. Keitzer, Berlin; J. and S. Killburger, Schalksmuehle; L. Kloecker, Moenchengladbach; R.M. Kuester, Bad Bramstedt; M. Mann, St. Augustin; C. Mache, Graz; R.-P. Moeritz, Mainz; A. Marques, Wetter; J. Meister, Aue; D. Meyer, Ulm; T. Niehues, Duesseldorf; R. Oberstaller, Salzburg; W. Oelkers, Hamburg; S. Peetz, Mainz; G. Plewig, Munich; K.-H. Pulcher, Hargesheim; G. Reutter, Nuremberg; C. Rock, Deggendorf; C. Schauer, Berlin; F. Schilling, Mainz; M. Schimmel, Goettingen; P. von Schoenaich, Augsburg; P. Schuetze, Dresden; H. Schulte-Wissermann, Krefeld; M. Schoentube, Berlin; C. Sengler, Berlin; S. Stolz, Cottbus; U. Tenbrink, Munich; A. Veihelmann, Munich; M. Weiss, Cologne; D. Windschall, Bamberg.

The authors have declared no conflicts of interest.

## References

1. Bjorksten B, Boquist L. Histopathological aspects of chronic recurrent multifocal osteomyelitis. J Bone Joint Surg Br 1980;62:376–80.
2. Hayem G, Bouchaud-Chabot A, Benali K *et al*. SAPHO syndrome: a long-term follow-up study of 120 cases. Semin Arthritis Rheum 1999;29:159–71.
3. Benhamou CL, Chamot AM, Kahn MF. Synovitis-acne-pustulosis hyperostosis–osteomyelitis syndrome (SAPHO). A new syndrome among the spondyloarthropathies? Clin Exp Rheumatol 1988;6: 109–12.
4. Kahn MF. Current status of the SAPHO syndrome. Presse Med 1995;24:338–40.
5. Beretta-Piccoli BC, Sauvain MJ, Gal I *et al*. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome in childhood: a report of ten cases and review of the literature. Eur J Pediatr 2000;159:594–601.
6. Jansson A, Golla A, Plewig G, Meindl A, Belohradsky BH. Chronisch rezidivierende multifokale Osteomyelitis und andere nichtbakterielle Osteitiden: Klink, Diagnostik, Therapie, Prognose und genetische Untersuchungen. Deutsches Aerzteblatt 2004;101:584–89.
7. Jansson A, Golla A, Schneider K, Jansson V, Belohradsky BH. Die chronisch rezidivierende multifokale Osteomyelitis (CRMO) Übersicht und erste Befunde einer genetisch-rheumatologischen Studie. Monatsschr Kinderheilkd 2002;150:477–89.
8. Schultz C, Holterhus PM, Seidel A *et al*. Chronic recurrent multifocal osteomyelitis in children. Pediatr Infect Dis J 1999;18:1008–13.
9. Probst FP. Chronic recurrent multifocal osteomyelitis. Case report and overview as a contribution to the knowledge about the disease. Radiologe 1984;24:24–30.
10. Carr AJ, Cole WG, Roberton DM, Chow CW. Chronic multifocal osteomyelitis. J Bone Joint Surg Br 1993;75:582–91.
11. Job-Deslandre C, Krebs S, Kahan A. Chronic recurrent multifocal osteomyelitis: five-year outcomes in 14 pediatric cases. Joint Bone Spine 2001;68:245–51.
12. Dihlmann W, Hering L, Bargon GW. The acquired hyperostosis syndrome. Synthesis of 13 personal observations of sternocostoclavicular hyperostosis and 300 cases from the literature. 1. Rofo 1988;149:386–91.
13. Freyschmidt J, Sternberg A. The bullhead sign: scintigraphic pattern of sternocostoclavicular hyperostosis and pustulotic arthroosteitis. Eur Radiol 1998;8:807–12.
14. Anderson SE, Heini P, Sauvain MJ *et al*. Imaging of chronic recurrent multifocal osteomyelitis of childhood first presenting with isolated primary spinal involvement. Skeletal Radiol 2003;32:328–36.
15. Schilling F, Marker-Hermann E. Chronic recurrent multifocal osteomyelitis in association with chronic inflammatory bowel disease: enteropathic CRMO. J Rheumatol 2003;62:527–38.
16. Valls-Roc M, Sanmarti M, Salles M, Holgado S, Olive A. SAPHO syndrome and pamidronate revisited. Rheumatology 2005;44:137–8.
17. Kerrison C, Davidson JE, Cleary AG, Beresford MW. Pamidronate in the treatment of childhood SAPHO syndrome. Rheumatology 2004;43:1246–51.
18. Baltensperger M, Gratz K, Bruder E, Lebeda R, Makek M, Eyrich G. Is primary chronic osteomyelitis a uniform disease? Proposal of a classification based on a retrospective analysis of patients treated in the past 30 years. J Craniomaxillofac Surg 2004;32:43–50.
19. Earwaker JW, Cotten A. SAPHO: syndrome or concept? Imaging findings. Skeletal Radiol 2003;32:311–27.
20. Jurik AG. Chronic recurrent multifocal osteomyelitis. Semin Musculoskelet Radiol 2004;8:243–53.
21. Jurik AG, Egund N. MRI in chronic recurrent multifocal osteomyelitis. Skeletal Radiol 1997;26:230–8.
22. Jurriaans E, Singh NP, Finlay K, Friedman L. Imaging of chronic recurrent multifocal osteomyelitis. Radiol Clin North Am 2001;39:305–27.
23. Ferguson PJ, Bing X, Vasef MA *et al*. A missense mutation in pstpip2 is associated with the murine autoinflammatory disorder chronic multifocal osteomyelitis. Bone 2005 (in press).
24. Golla A, Jansson A, Ramser J *et al*. Chronic recurrent multifocal osteomyelitis (CRMO): evidence for a susceptibility gene located on chromosome 18q21.3–18q22. Eur J Hum Genet 2002;10:217–21.
25. Huber AM, Lam PY, Duffy CM *et al*. Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. J Pediatr 2002;141:198–203.
26. Iqbal M, Kolodney MS. Acne fulminans with synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome treated with infliximab. J Am Acad Dermatol 2005;52(5 Suppl 1):S118–20.
27. Duffy CM, Lam PY, Ditchfield M, Allen R, Graham HK. Chronic recurrent multifocal osteomyelitis: review of orthopaedic complications at maturity. J Pediatr Orthop 2002;22:501–5.
28. Vittecoq O, Said LA, Michot C *et al*. Evolution of chronic recurrent multifocal osteitis toward spondylarthropathy over the long term. Arthritis Rheum 2000;43:109–19.
29. Aggarval AEA. Juvenile ankylosing spondylitis—is it the same disease as adult ankylosing spondylitis? Rheumatol Int 2005;25:94–6.
30. Breban M. Genetic studies of spondylarthropathies. French Spondylarthropathy Genetic Study Group. Ann Med Interne 1998;149:142–4.
31. Schilling F, Wagner AD. Azithromycin: an anti-inflammatory effect in chronic recurrent multifocal osteomyelitis? A preliminary report. J Rheumatol 2000;59:352–3.
32. Amital H, Applbaum YH, Aamar S, Daniel N, Rubinow A. SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. Rheumatology 2004;43:658–61.
33. Wagner AD, Andresen J, Jendro MC, Hulsemann JL, Zeidler H. Sustained response to tumor necrosis factor alpha-blocking agents in two patients with SAPHO syndrome. Arthritis Rheum 2002;46:1965–8.
34. Olivieri I, Padula A, Ciancio G, Salvarani C, Niccoli L, Cantini F. Successful treatment of SAPHO syndrome with infliximab: report of two cases. Ann Rheum Dis 2002;61:375–6.
35. Carpenter E, Jackson MA, Friesen CA, Scarbrough M, Roberts CC. Crohn's-associated chronic recurrent multifocal osteomyelitis responsive to infliximab. J Pediatr 2004;144:541–4.
36. Wise CA, Gillum JD, Seidman CE *et al*. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. Hum Mol Genet 2002;11:961–9.
37. Grosse J, Chitu V, Marquardt A *et al*. Mutation of mouse MAYP/PSTPIP2 causes a macrophage autoinflammatory disease. Blood 2006 (in press).