Prevalence of cranial involvement in a cohort of Italian patients with chronic non-bacterial osteomyelitis

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Abstract

Objective

Chronic non-bacterial osteomyelitis (CNO) is a non-infectious inflammatory disease characterised by uni- or multi-focal bone lytic lesions. CNO mainly affects metaphysis of long bones, pelvis and shoulder girdle. Neurocranium lesions are extremely rare. The objective of the study is to describe the prevalence and clinical manifestations of CNO patients with neurocranium involvement in an Italian cohort of CNO patients.

Methods

This is a retrospective study. Medical records of patients with CNO admitted to eight paediatric rheumatology centres were reviewed.

Results

Among 86 patients with CNO enrolled in the study, three of them were female and presented neurocranium involvement – multifocal lesions. Two out of the 3 patients were completely asymptomatic for cranial involvement, while one of the 3 complained of cranial bossing. Cranial involvement was detected with bone scintigraphy and then confirmed by magnetic resonance imaging and/or computed tomography. Two patients presented fever and two with skin manifestations. Laboratory inflammatory markers were increased in two of them. All patients underwent bone biopsy confirming the diagnosis. They all received NSAIDs. Two patients received corticosteroids and then methotrexate and achieved clinical remission, while one patient received pamidronate.

Conclusion

This is the first report of neurocranium involvement in a cohort of patients affected by CNO. In our cohort no patient showed significant signs attributable to cranial involvement.

Key words

chronic non-bacterial osteomyelitis, skull involvement, neurocranium

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Introduction

Chronic non-bacterial osteomyelitis (CNO) is a skeletal autoinflammatory disorder that primarily affects children and adolescents and is characterised by the presence of sterile bone lesions (1). Symptoms include pain, local swelling and warmth. Systemic features such as fever, skin rash, inflammatory bowel disease and arthritis may be present (2). CNO mainly affects metaphysis of long bones, pelvis, shoulder girdle and, less commonly, spine and mandible. Bone lesions usually occur at any skeletal site except the skull (3). To date, only few manuscripts reporting single case reports with the skull involvement among CNO patients have been published (4-7). For the first time we report the prevalence and the clinical features of patients with skull lesions among an Italian cohort of CNO patients.

Material and methods

This is an observational, retrospective, multicentric study. According to Italian law, Research Ethical Board (REB) approval is not requested, only a notification, which was provided to the local REB. We retrospectively reviewed the medical records of patients with CNO from eight paediatric rheumatology centres in Italy: IRCSS Burlo Garofolo, Trieste; Spedali Civili, Brescia; ASST Grande Ospedale Metropolitano Niguarda-Milano; Anna Meyer Children's Hospital, Florence; Bambino Gesù Childen's Hospital, Rome; G. Di Cristina Childen's Hospital, Palermo; Antonio Perrino Hospital, Brindisi and Gianna Gaslini Hospital, Genoa. We enrolled patients diagnosed with CNO between January 2012 and December 2017. The diagnosis was made on the basis of clinical and histologic features. Demographic details recorded were: gender, age of onset of symptoms, age and year of diagnosis. Other information collected regarded presenting symptoms, number and locations of bone lesions, diagnostic imaging, laboratory data with particular attention to inflammatory markers, histological findings, response to treatments, and the presence of other inflammatory symptoms. Data, entered into a customised and anonymised database, were evaluated taking into particular consideration patients with skull involvement.

Results

Our population consisted of 86 patients, 31 males and 55 females, mean age at onset 9.4 years (SD ± 3.3); only 11 of them presented a monofocal involvement at onset while 75 patients already presented a multifocal disease. Fifty-eight patients underwent scintigraphy, forty-six MRI, thirty both scintigraphy and magnetic resonance imaging (MRI). Thirteen patients (11 female and 2 male) had skull lesions, 10 had mandible lesions and 3 (3.5% of all patients) involving the neurocranium. The clinical and demographic characteristics of these three patients are reported in Table I.

The three patients were females, age at onset was 2 for one patient and 12 for two. They all presented a multifocal disease at onset (12, 20 and 13 lesions active at onset, respectively), 2 of them did not show any symptom related to skull involvement (headache, vomiting, visual impairment or focal neurological involvement), while one patient reported a history of transient and recurrent swelling of frontal bossing, tender on palpation but without any other signs of inflammation. Cranial findings were detected with bone scintigraphy and in all cases with whole body MRI. One patient (the one with local signs) presented only one lesion located in the frontal bone (Fig. 1), the other two patients had two lesions each in frontal and temporal bones.

Regarding the presence of other symptoms, two patients presented cutaneous manifestations: psoriasis in one case and morphea in the other one. Low grade fever was present in two. Laboratory investigations revealed an elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in two out of three patients. Bone biopsy was performed in all three patients and was consistent with CNO diagnosis in all cases ruling out histiocytosis and other malignancies. All three patients were prescribed non-steroidal anti-inflammatory drugs (NSAIDs) as first line treatment without persistent benefit. Two patients subsequently received corticosteroids, followed by methotrex-

Table I. Clinical data of CNO patients with neurocranium involvement.

Data	Patient 1	Patient 2	Patient 3
Gender	Female	Female	Female
Age at onset, years	2	12	12
High ESR (mm/hr)* and CRP (mg/dL)°	no	yes	yes
Symptoms			
Headache	no	no	no
Low grade fever	yes	no	yes
Lesions			
n° of lesions (total)	12	20	13
n° of lesions in neurocranium	2	2	1
Location of lesions in neurocranium	frontal and temporal bones	frontal and temporal bones	frontal bone
Comorbidity	none	psoriasis	morphea, pericarditis
Therapy	NSAID^ + MTX‡+oral steroid	NSAID+pamidronate	NSAID+MTX+ oral steroid

*erythrocyte sedimentation rate; °C-reactive protein; ^non-steroidal anti-inflammatory drugs; ‡Methotrexate.

Table II. Clinical information of CNO patients. Comparison of our series *versus* literature data.

	Foley *et al*. (4)	Wedman *et al*. (5)	Watanabe *et al*. (6)	Barrani *et al*. (7)	Our series
Number of patients	1	1	1	1	3
Clinical symptoms	Orbit swelling Ptosis Blepharoptosis	Headache; Bone swelling	Occipital headache; Bone swelling	Orbital headache	Bone swelling (1/3); No clinical symptoms (2/3)
Imaging techniques	CT scan; x-ray	CT scan; MRI	CT scan; MRI	CT scan; MRI; Scintigraphy	Scintigraphy and MRI (3/3)
Multifocal involvement	Yes	Yes	Yes	Yes	Yes
Bone biopsy	Yes	Yes	Yes	Yes	Yes
Treatment	Steroids	NSAIDs	NSAIDs	NSAIDs Bisphosphonte	NSAIDs (3/3) Steroids (2/3) Methotrexate (2/3) Bisphosphonate (1/3)

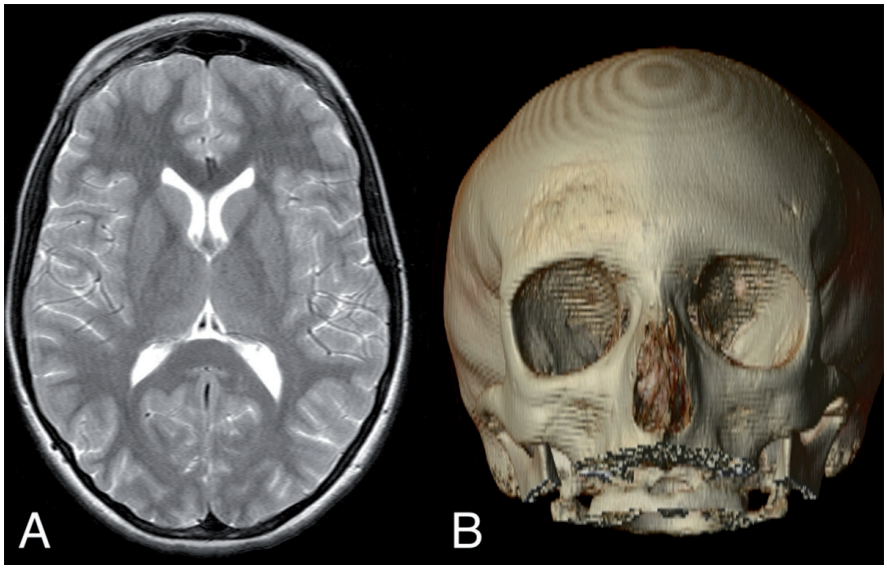

Fig. 1. 3D-CT reconstruction (**A**) and MR feature of frontal bone lesion of a CNO patient.
CT: computed tomography; MR: magnetic resonance.

ate, and achieved clinical remission. One patient was given pamidronate but had no benefit and she still presents an active disease after 3 years of follow-up. No statistical significance difference was found between the two groups of CNO patients (skull involvement *vs*. no skull involvement) in terms of clinical manifestations, number of lesions, elevation of inflammatory markers and presence of other comorbidities.

Discussion

CNO is the most common autoinflammatory disorder affecting bone in children (3, 8). The mechanism underlying the disease is based on impaired regulation of the innate immune system, which causes uncontrolled inflammation of the bone, subsequent increased osteoclast activity, osteolysis and bone remodelling (9). Inflammation usually involves long bones near growth plates, or vertebral bodies and rarely flat bones; skull involvement is very rare and the most recent literature does not normally recognise it as a typical site of CNO involvement (10). We report for the first time the prevalence of skull involvement in CNO patients,

showing that in our cohort neurocranium localisation was present in 3.5% of cases. To our knowledge only few reports have demonstrated neurocranium involvement among CNO patients. Foley *et al*. (4) described for the first time a 9-year-old girl with a 2-month history of swelling of the left orbit, causing blepharoptosis and proptosis. CT revealed a mass in the superior left orbit that expanded orbital dimensions. Radiography showed abnormalities in parietal and frontal bones and distal right tibia. As orbital and tibial biopsies showed a non-specific chronic inflammation, she was diagnosed with non-specific chronic systemic inflammatory process, but retrospectively the presence of multiple bone lesions and the response to corticosteroids could lead to CNO diagnosis. Wedman *et al*. (5) reported the case of a 12-year-old girl with CNO affecting tibia and ribs who complained of a frontal burning headache and presented a minimal swelling above her left eyebrow. CT and MRI scans revealed spots of osteomyelitis in left frontal bone and in the left side of the sphenoid bone. The third report by Watanabe *et al*. (6) describes an 11-year-old boy with a previous diagnosis of CNO affecting right femur and sacrum, confirmed by biopsy. He later developed occipital headache and local swelling and CT showed the osteolytic lesion in the occipital bone that did not respond to NSAIDs. Finally, Barrani *et al*. (7) reported the case of a 12-year-old girl suffering from recurrent episodes of left supraorbital pain, initially treated as migraine. Then she developed hyperaemia and swelling of left periorbital area and MRI detected an inflammatory process of frontal, zygomatic and sphenoid bones. Few months later she reported pain and swelling of the left clavicle and sternal bone. Bone biopsy confirmed CNO diagnosis. A comparison between our patients and CNO patients with neurocranium involvement described in the literature is summarised in Table II.

It is interesting to underline that in our experience the skull involvement was not so rare, but it was completely asymptomatic in 2/3 patients, being diagnosed only by radiological findings, and accompanied only by local signs in the third one. This could be explained by the absence in the first two patients by soft tissue involvement along with cranial lesions. In the cases described in the literature all patients presented symptoms or signs like pain, swelling of the periorbital area or blepharoptosis that could be related to the presence of soft tissue oedema, similarly to what found in our third case. The demographic and main clinical characteristics of our cohort of patients with CNO (prevalence of females, age of onset, majority of multiple lesions instead of monofocal involvement) are in line to those reported in most recent published studies (11-14).

We underline that cranial involvement was detected in 3 patients who underwent to total body imaging, but among 86 patients, whole-body imaging (scintigraphy or MRI) was performed in only 64 patients. This means that we might have missed some patients with cranial involvement. In front of a suspicion of CNO it is mandatory to check for neurocranium involvement with whole-body imaging; it is also important to underline the importance of bone biopsy in these cases. Although some authors have proposed a clinical score in order to facilitate the clinical diagnosis avoiding an unnecessary bone biopsy (15), we think that in the presence of cranial involvement it is mandatory to perform a bone biopsy to rule out malignancy even if other bone lesions with radiologic features suggestive for inflammatory osteomyelitis are present. It is also important, in this case, to rule out the histiocytosis that can affect children and adolescents, involving typically flat bones including the skull.

In conclusion, we have described the prevalence of skull involvement among an Italian cohort of CNO patients. Our experience shows that the neurocranium involvement among CNO patients is not so rare, although it may be asymptomatic.

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