Chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible: standard of care

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Chapter 4

Conservative treatment of children with chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible

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SUMMARY

Introduction: Chronic diffuse sclerosing osteomyelitis (DSO) of the mandible is a rare disease of unknown aetiology. It has been suggested that overuse of the masticatory muscles, tendoperiostitis (TP), is a contributing factor for DSO. Therefore, we tested this hypothesis by treating consecutive children with conservative therapy.

Material and methods: All patients were treated with conservative therapy, comprising occlusal splint therapy, physiotherapy, and/or disease counselling. Pain intensity on a visual analogue scale (VAS) and pain frequency in number of days per 3 months were recorded before the start of treatment, and at 3, 6, and 12 months after treatment initiation.

Results: Eleven children (seven girls, four boys, mean age: 11.55 ± 1.97 years) were included in this study. Six patients showed a decrease in pain intensity and pain frequency over time and they continued with conservative therapy. For the remaining five patients, bisphosphonate administration was initiated because of persistent severe pain – one after 3 months of conservative therapy, and the other four after 1 year of conservative therapy.

Conclusion: The pain complaints of patients with DSO/TP decreased with conservative therapy, and 55% did not require additional therapy. This suggests that DSO/TP of the mandible is precipitated by muscle overuse.

INTRODUCTION

Chronic diffuse sclerosing osteomyelitis (DSO) of the mandible is a rare disease accompanied by high morbidity.[1] Its characteristics include recurrent pain and swelling of the mandible, often accompanied by trismus, progressive mandibular deformity, and hypaesthesia of the mental nerve.[1,2] Depending on the stage of the disease, radiographs typically show mixed sclerosis and osteolysis, or diffuse sclerosis with subperiosteal bone formation.[2-8] During the active disease phase, bone scintigraphy shows an increased uptake of the radiopharmaceutical at the site of the increased bone turnover.[2-5] Histological examination usually shows reactive bone with subperiosteal new bone formation, remodelling of cortical bone, and an increase of subcortical bone volume. Only focal chronic inflammatory responses have been shown, with no sign of infection with micro-organisms.[1,2,9,10]

The exact underlying pathophysiological mechanism of DSO remains unclear. It has been suggested that it is due to an endogenic bacterial infection or an immunological overshoot. Others suggest that DSO is part of a syndrome, for example chronic recurrent multifocal osteomyelitis (CRMO) or synovitis, acne, pustulosis, hyperostosis, or osteitis (SAPHO) syndrome.[1,7,11-14] Finally, it has been posited that hyperactivity of the masseter and/or digastric muscle, also known as chronic tendoperiostitis (TP), is an aetiological factor.[9,15,16]

Because of the unknown pathophysiological mechanism, treatment can be challenging. Reported treatment options include longterm analgesic medication, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, corticosteroids, hyperbaric oxygenation, and surgical interventions, such as decortication and segmental resection of the mandible.[1,2,5,6,17-27] More recently, promising results with bisphosphonate therapy have also been published.[5,6,20,21,23-28]

We hypothesize that chronic tendoperiostitis serves as a possible aetiological factor for DSO in children and that conservative treatment with physiotherapy, occlusal splint therapy, and/or disease counselling will reduce complaints of DSO/TP of the mandible.

MATERIAL AND METHODS

This retrospective study reviewed the clinical records and radiographs of consecutive children who were diagnosed with DSO of the mandible between June 2006 and January 2016 in the Department of Oral and Maxillofacial Surgery and the Centre of Special Dental Care, Leiden University Medical Centre (LUMC), the Netherlands. The diagnosis of DSO was confirmed in our hospital on the basis of medical history, clinical symptoms, radiological examination, and, if present, histological and culture results from biopsy or surgery material. The latter were performed to exclude alternative disorders, such as malignancy or bacterial osteomyelitis.

All bisphosphonate-naïve children under 18 years old who were diagnosed with DSO were included in this study. Patients who did not follow the treatment protocol were excluded from this study.

The treatment protocol consisted of conservative treatment by the same DSO/TP-specialised gnathologist (MW) and oral and maxillofacial surgeon (RM). Conservative treatment comprised physiotherapy with habit-reversal training, myofeedback and/or relaxation therapy, occlusal splint therapy, and/or disease counselling for patients and parents.

Standard pain evaluation was performed before treatment initiation to establish baseline values, and thereafter at the 3-, 6-, and 12-month follow-up. A visual analogue scale (VAS) ranging from 0 to 10 was used and the frequency of pain complaints in number of days per 3 months was recorded. In addition, patients were asked whether they thought that their complaints were stress-related, and if they had parafunctional habits.

If patients reported insufficient response to conservative treatment after 1 year, they were treated with bisphosphonate therapy, after consultation of an endocrinologist. Patients were screened for vitamin D deficiency and markers for bone turnover (parathormone, procollagen type 1 N-terminal propeptide, β-crosslaps, 25-hydroxyvitamine D, alkaline phosphatase, and inorganic phosphate), corrected for age. Full blood count, erythrocyte sedimentation rate, C-reactive protein, and kidney function were checked as well. Subsequently, patients were treated according to protocol with intravenous doses of pamidronate 1 mg/kg with a maximum of 30 mg a day for three consecutive days. In the

case of a first course day, one 0.5 mg/kg dose was given; if no side effects were observed, the full dose was administered on days two and three.

Statistical analysis

All statistical analyses were performed using SPSS version 24.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics were performed. A generalized linear mixed model (GLMM) was used, taking the presence of repeated measurements and missing data into account, to study the effect of conservative therapy on pain intensity and pain frequency. A *p*-value <0.05 indicated statistical significance.

RESULTS

Fourteen children with DSO of the mandible were identified. Three children were excluded from the analysis because two of them were not treated by our gnathologist and one had already received bisphosphonate therapy. Therefore, 11 children – seven girls and four boys aged 8-15 years, mean age 11.55 ± 1.97 years – were included. In six patients (55%), DSO was located in the left mandible. The children were referred from other hospitals with a mean period from start of symptoms until the first visit at our clinic of 24.5 ± 21.6 months; range 3-68 months. All patients had been treated with a broad range of treatment options – medical and surgical – including NSAIDs, antibiotics, corticosteroids, and decortication, but not with bisphosphonates (Table 1). These treatments had not been effective in inducing long-term remission of the disease, and therefore the patients were referred to our clinic.

The available radiographs included at least one panoramic radiograph for each patient. In addition, a computed tomography (CT) scan was performed in ten patients, and a magnetic resonance imaging (MRI) scan in four patients. Bone scintigraphy was performed in eight patients. Histological and culture findings from biopsy or surgery material was available in eight patients.

All the patients presented with persistent temporomandibular dysfunction symptoms and all had parafunctional habits. During the clinical examination, all patients showed swelling of the mandible, ten children showed signs of bruxism and painful palpation of the masseter muscle, and in six children trismus was found.

All patients were started in analgesics and NSAIDs at baseline, or the use of these agents was emphasized. During follow-up, all patients showed wear facets in their occlusal splints, as a sign of parafunctional habits and as a sign of compliance. Six patients reported a possible connection between exacerbations and stress (Table 1).

Table 1
Patient characteristics in eleven cases of chronic diffuse sclerosing osteomyelitis (DSO) of the mandible

Patient	Gender	Age*	Location of DSO	Time from start of symptoms until first visit to our institute	Previous treatment	Treatment in our institute	Stress	Para-functional habits
1	F	11	Right mandible	7 months	a, n, os	a, n, ft, os, c	+	+
2	M	10	Right mandible	1 year, 10 months	a, n, ab, d	a, n, ft, os, c	?	+
3	F	13	Left mandible	2 years	a, ab, d	a, n, ft, os, c	+	+
4	M	10	Left mandible	8 months	n, ab, d	a, ft, os, c	?	+
5	F	15	Right mandible	5 years, 8 months	a, n, ab	a, n, ft, os, c	?	+
6	F	13	Left mandible	1 year, 11 months	a	a, n, ft, os, c	+	+
7	F	10	Right mandible	10 months	a, n, ab	a, n, cs, ft, os, c, b	+	+
8	F	8	Left mandible	1 year, 1 month	a, ab	a, n, ft, os, c, b	?	+
9	M	12	Right mandible	2 years, 6 months	a, cs, os	a, n, cs, ft, os, c, b	?	+
10	F	13	Left mandible	3 months	a, n	a, ft, os, c, b	+	+
11	M	12	Left mandible	5 years, 1 month	a, ab	a, n, ft, os, c, b	+	+

F = female, M = male, + = yes, ? = unknown, a = analgesics, n = NSAID, ab = antibiotics, cs = corticosteroids, os = occlusal splint, d = decortication, ft = physiotherapy, c = counselling, b = bisphosphonates
*Age at first visit.

Six of the 11 children showed a subjective decrease in pain intensity (mean pre-treatment VAS score of 8.2 versus a mean VAS score after treatment of 2.8), although this difference was not significant ($p = 0.092$). There was also a significant decrease in pain frequency – mean of 6 days per 3 months after treatment compared with a mean of 30 days per 3 months pre-treatment ($p < 0.001$) (Figure 1A and B – orange line). Therefore, they continued to receive conservative therapy. In all of these six patients, other symptoms, such as swelling of the cheek and trismus, decreased too. They showed improvement,

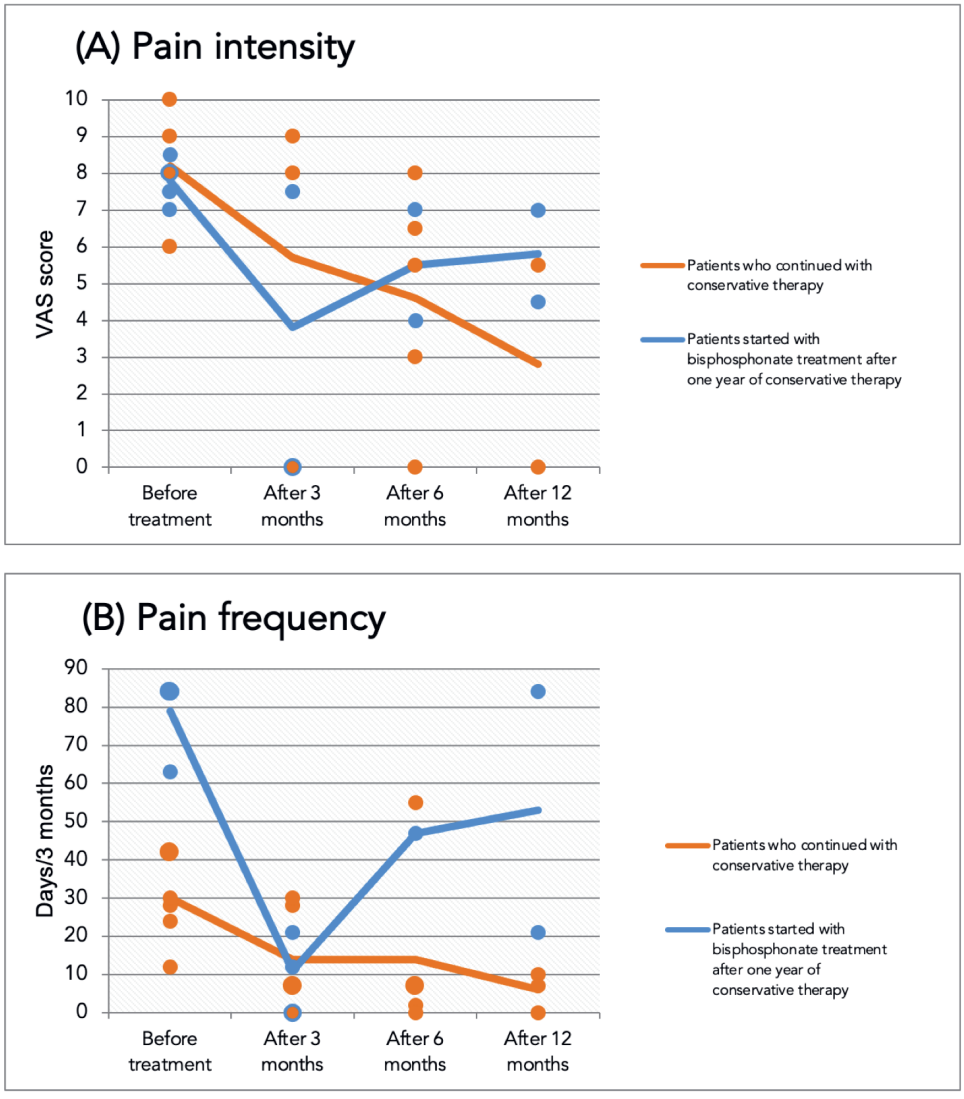

Figure 1. Influence of conservative therapy on pain intensity and pain frequency in children with DSO, during the first year of treatment. During this treatment period ten of the 11 patients only received conservative treatment. The orange line represents patients who continued to receive only conservative treatment. The blue line represents patients who started with bisphosphonate treatment due to recurring symptoms. (A) Mean pain intensity according to VAS score over time. (B) Mean pain frequency in days per 3 months over time. Both graphs are missing data from patient 9. (VAS = visual analogue scale).

with a normal anatomy and symmetry, and without subperiosteal bone formation, on the panoramic radiographs taken after one year of conservative therapy. Normalisation of the mandible was even observed in one patient (Figure 2).

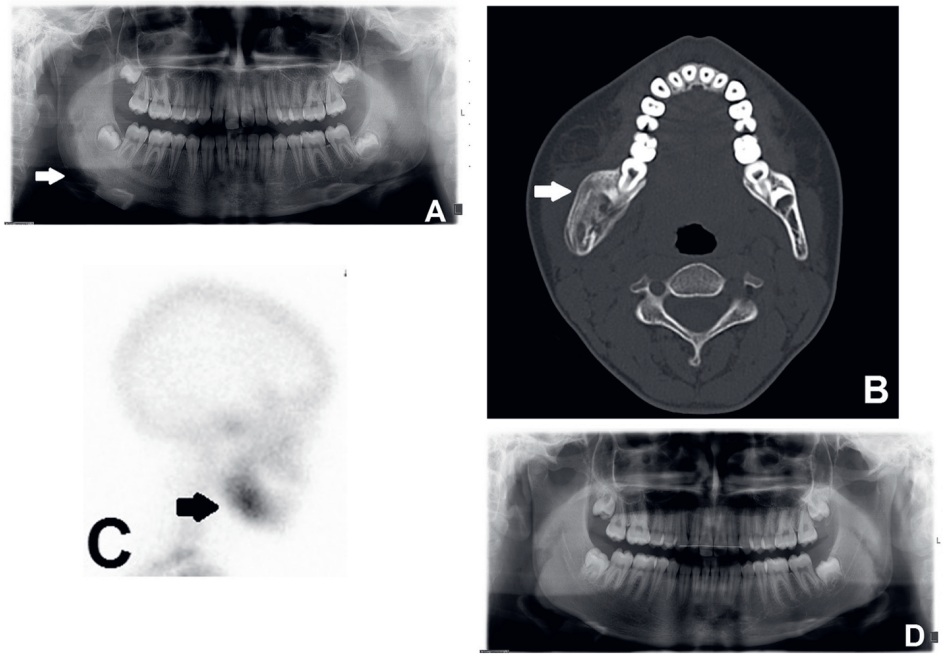

Figure 2. An 11-year-old girl on her first visit to our institute. She had been complaining of trismus, continuous swelling, and recurrent pain in her right mandible for 7 months. She exhibited parafunctional habits, such as nail biting and cheek sucking. During clinical examination, signs of bruxism and a painful right masseter muscle were found, as well as swelling of the cheek and trismus. Panoramic radiograph (A) revealed diffuse sclerosis with slight osteolysis (arrow), and CT (B) showed sclerosis and subperiosteal bone formation (arrow). Histological diagnosis of DSO had already been established in the referring hospital. Increased uptake of radiopharmaceutical in the right mandible was seen on the bone scintigraphy (C). The patient reported a VAS score of 8 and a pain frequency of 63 days per 3 months, before she was treated with conservative therapy. After 6 months she reported a VAS score of 6.5 on only 2 days in the previous 3 months. After 1 year, the girl was pain free. The panoramic X-ray (D), taken approximately 3 years after the start of conservative treatment, showed an almost normal bone architecture.

The remaining five patients did not respond completely to conservative therapy and were started on bisphosphonates. These five patients showed a decrease in pain intensity in the first 3 months of conservative therapy, but subsequently a rebound occurred (Figure 1A and B – blue line). Other symptoms, such as swelling of the cheek, improved in three

of these five children after conservative therapy. Trismus improved after conservative therapy in three of the four children who complained of trismus before treatment initiation. On the panoramic radiograph, four of the patients showed some improvement.

The mean time between the start of conservative therapy and the start of bisphosphonate treatment was 31 months, range 3-83 months. One patient started with bisphosphonates after 3 months of conservative therapy, due to intense pain and lack of improvement. Three others were treated conservatively for more than 12 months, but they were started on bisphosphonates when they suffered from a rebound, with swelling of the mandible and trismus. In two of these three children, radiographs also showed pathological changes. The fifth patient was free of pain after 3 months of conservative therapy, but started with bisphosphonates after 2 years because of a slight increase in pain and complaints of facial asymmetry, for which modelling reconstructive surgery of the mandible was planned.

Bisphosphonate therapy improved symptoms of pain and swelling of the mandible, and improved the aspect of panoramic radiographs in all of these five patients. Three patients were free of pain after one cycle of pamidronate infusion. Two patients are still regularly treated with bisphosphonates because of exacerbations. One of these patients received four courses of pamidronate infusions, and one patient received three.

The patients who received bisphosphonates had similar baseline VAS scores ($p = 0.755$) but a much higher pain frequency ($p < 0.001$) before starting conservative treatment than the patients who did not need bisphosphonates. Tables 2 and 3 show the means for each group and each time point, along with their 95% confidence intervals.

Table 2
Pain intensity over time during conservative therapy in patients with DSO

	Before start of conservative treatment	After 3 months of conservative treatment	After 6 months of conservative treatment	After 12 months of conservative treatment
Patients who resumed conservative therapy	8.2 [5.7-10.6]	5.7 [2.2-9.2]	4.6 [1.9-7.3]	2.8 [-1.5-7.0]
Patients started with bisphosphonate treatment after one year of conservative therapy	7.8 [4.7-10.8]	3.8 [-0.5-8.0]	5.5 [1.2-9.8]	5.8 [1.5-10.0]

Data represent mean visual analogue scale [95% confidence interval].

Table 3
Pain frequency over time during conservative therapy in patients with DSO

	Before start of conservative treatment	After 3 months of conservative treatment	After 6 months of conservative treatment	After 12 months of conservative treatment
Patients who resumed conservative therapy	29.7 [15.2-44.1]	514.4 [-1.5-30.3]	14.2 [-1.7-30.1]	5.7 [-14.8-26.1]
Patients started with bisphosphonate treatment after one year of conservative therapy	78.8 [61.0-96.5]	11.0 [-9.5-31.5]	47.0 [11.5-82.5]	52.5 [27.4-77.6]

Data represent mean days/3 months [95% confidence interval].

DISCUSSION

This study aimed to test the hypothesis that chronic tendoperiostitis serves as a possible aetiological factor for DSO in children. Therefore, we analysed the effect of conservative therapy on complaints of pain in children with DSO/TP of the mandible. Of the 11 children with DSO/TP of the mandible enrolled in this study, more than half reacted positively to conservative treatment only, and additional therapy was not necessary. The combination of physiotherapy, occlusal splint therapy, and counselling in particular led to improvement in symptoms. Only five patients needed additional bisphosphonate therapy. Patients requiring bisphosphonate therapy exhibited a significantly higher baseline pain frequency compared with those who responded completely to conservative treatment alone. The higher pain frequency score might reflect a more severe form of DSO/TP, in which conservative treatment alone might not be sufficient. Bisphosphonate therapy has been shown to be effective, and therefore the patients who did not respond sufficiently to conservative therapy were all started on this form of second-line therapy.[5,6,20,21,23-29] The rationale on bisphosphonate use in DSO is based on its known antiresorptive, anti-inflammatory, and analgesic features. In patients with DSO, it can lead to a reduction in pain and a decrease in bone remodelling.[6,20,21,23,25-27] Various types of bisphosphonates, different dosages, and different routes of administration are reported.[5,6,20,23,25-27] More research is necessary to fine-tune the optimal bisphosphonate treatment. Bisphosphonates are associated with an acute phase reaction right after infusion, which includes fever, headache, and flu-like symptoms due to cytokine release, but is often well tolerated. Since bisphosphonates in DSO are usually effective within a couple of courses, there is no need for long-term treatment and thus side-effects associated with long-term treatment are not expected.

Early diagnosis of DSO/TP is difficult, and the disease is often misdiagnosed as an infection in the parotic gland or tumorous process, causing treatment delay.[17,21] Patients are treated with antibiotics, analgesics, corticosteroids, hyperbaric oxygen therapy, and surgical interventions.[1,2,5,6,17-27] However, these treatments do not provide long-term improvement.

The exact underlying pathophysiological mechanism of DSO remains unclear and numerous hypotheses have been suggested, including an infectious origin for DSO.[1] However, it is highly unlikely that DSO has an infectious origin, because antimicrobial treatment has not proved to be effective, cultures are always negative, and, furthermore, this does not explain the chronic recurrent nature of the disease.[9] Other, more logical hypotheses include underlying autoimmunity, or that the disease is a part of a different condition, such as SAPHO syndrome.[1,11,12,14,19] Overuse of the masticatory muscles as a contributing factor for DSO, also known as TP, has also been suggested as an aetiological factor.[9,15,16] As previously described by van Merkesteyn *et al.*[9], the following characteristics of DSO/TP support the theory of chronic tendoperiostitis; absence of infectious aetiology; recurrence after treatment with antibiotics and decortication; frequently observed parafunctional habits; and the relation of exacerbations to stress. Therefore, the hypothesis that chronic tendoperiostitis serves as a possible aetiological factor for DSO was tested in this study using a well-defined conservative treatment protocol, which showed an improvement of symptoms in children with DSO/TP of the mandible, thus confirming our hypothesis.

Our study has limitations owing to the small sample size, though this is a direct consequence of the rare nature of DSO/TP.[1,6,17,20,22,26,27] Furthermore, the retrospective nature of the study means that some data on pain intensity and pain frequency are missing.

CONCLUSION

Conservative treatment in children with DSO/TP of the mandible can result in a significant improvement of symptoms. In our study, conservative treatment was even effective in patients who already had been treated extensively elsewhere. Patients showed significant improvement, especially in pain complaints, with no need for additional treatment in 55% of patients. This supports the hypothesis that DSO/TP of the mandible is possibly initiated

and exacerbated by muscle overuse. We recommend treating patients with DSO for at least 6-12 months with conservative therapy, including analgesics and NSAIDs, before starting second-line therapies, such as bisphosphonate therapy.

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