Calcitonin treatment for intersternocostoclavicular ossification: clinical experience in two cases

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Abstract

Intersternocostoclavicular ossification is a benign arthro-osteitis of the upper anterior chest of unknown cause. Two patients with acute exacerbation of this disorder were successfully treated with intramuscular injections of an eel calcitonin analogue (40 units three times a week). Besides symptomatic relief of local pain and swelling, serial scintigrams showed quantitative improvement in radiophosphonate uptake. The rapid alleviation of pain implies that the hormone has a central analgesic effect, in addition to its direct influence on bone cells and anti-inflammatory action. In one patient the disease was associated with palmoplantar pustulosis, which was cured with oral colchicine, whereas the other patient did not have such skin lesions. Despite a hypothetical link between palmoplantar pustulosis and intersternocostoclavicular ossification, colchicine had no beneficial impact on the bone pain. Salmon calcitonin delivered by nasal spray was tried for the second patient but failed, probably because of insufficient drug delivery.

The initial favourable results described here warrant future use of calcitonin injection on a larger number of patients with intersternocostoclavicular ossification.

Intersternocostoclavicular ossification^{1,2} is a benign orthopaedic disorder of the upper anterior chest wall. Known also as sternocostoclavicular hyperostosis,³ it is characterised by inflammatory ossification of the joints and hyperostosis of the surrounding bones. Judging from the common association of this ossification with palmoplantar pustulosis,^{4,5} the 'focal infection' mechanism postulated in palmoplantar pustulosis^{6,7} might also play a part in the pathogenesis of this joint disease. Antibiotics, however, are usually ineffective on the joint symptoms—namely, focal pain, swelling, and restriction of motion.² The pathophysiology of intersternocostoclavicular ossification is still to be clarified, and no specific treatment has yet been established for this disorder. Usually, non-steroidal anti-inflammatory agents are prescribed, but these provide little relief for severely affected patients. We report two patients in the exacerbation phase of typical intersternocostoclavicular ossification who were successfully treated with intramuscular injections of a calcitonin analogue. The preparation used was a synthetic eel calcitonin with a slight chemical modification, which made it more stable than

the natural form, while retaining its potent bioactivity.⁸

Case reports

CASE 1

The patient, a 45 year old man, had a history of severe head injury sustained in a traffic accident about 20 years previously, from which he recovered. For five years he had had mild but persistent pain in his shoulders and the back of his neck, which increased in December 1986 causing sleep loss and restricted motion. When he visited our clinic the skin on the upper anterior chest was reddish with localised heat. There was also slight swelling and severe percussion pain in the region. During the previous year he had noticed pustules on his palms, which had caused neither pain nor itching, and similar lesions on the soles of his feet were found on physical examination. The radiograph and radiophosphonate scintiscan (figs 1 and 2) were characteristic of intersternocostoclavicular ossification,^{2,9,10} and he was admitted to hospital. Laboratory data suggested chronic active inflammation together with mild liver dysfunction. Isoenzyme analysis of alkaline phosphatase showed increases of both skeletal and hepatic components. A bone biopsy specimen taken at the medial portion of the left clavicle showed non-suppurative chronic inflammation of bone marrow with prominent periosteal hyperostosis, thus confirming the diagnosis histopathologically.^{2,5} At the same time the results of a microscopic study of the skin biopsy specimen were compatible with palmoplantar pustulosis.

After two days' treatment with a synthetic eel calcitonin analogue (Elcatonin) in a dose of 40 units intramuscularly three times a week the localised bone pain and soft tissue swelling rapidly subsided and serum alkaline phosphatase levels were lowered (table 1). The severity of pain was estimated by the frequency of doses of analgesic drugs needed to alleviate it. Additionally, a quantitative assessment of the therapeutic response was made by serial bone scans as described for Paget's disease,¹¹ with some modifications. Briefly, two fixed regions of interest were set, one in an affected bone (in this case the left clavicle) and the other in the mandible as an internal reference (fig 2), and the ratio of uptake per pixel in these two regions was calculated. From a previous basic evaluation of the reproducibility a change in this uptake ratio of more than 20% was deemed significant. In this patient more than 50% reduction was seen after the first month of treatment with calcitonin

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Figure 1 Bone x ray film of the upper chest in patient 1. Prominent, symmetrical hyperostosis and swelling were evident in bilateral first ribs and medial halves of the clavicles.

Figure 2 Chest spot image of bone scintigram in patient 1. Intense uptake of technetium-99m hydroxymethylene-diphosphonate was noted at the hyperostotic regions seen in the radiogram. Radioactivity in the right second rib and the whole sternum was also mildly increased. The numbered squares indicate regions of interest for the quantitative assessment of abnormal uptake. In this scintigram the ratio of count/pixel of a diseased bone (region 2) to that of a normal reference area (region 1) was 7.6.

analogue, though the abnormal uptake was still visually prominent in scintigraphic images. Despite these improvements, values and titres of serological markers remained high, with a relapse of palmoplantar pustulosis, which had previously been effectively treated with a corticosteroid ointment after the histological diagnosis. Injection of the calcitonin analogue was stopped after the ninth week, and oral colchicine was started at 0.5 mg twice daily, which normalised these indices and improved the skin pustules. Unfortunately, the occurrence of abdominal pain after four weeks' treatment with colchicine necessitated reduction of the dose to 0.5 mg daily, which caused increased abnormalities in laboratory data but not the dermatological lesions. Colchicine was discontinued after another 12 months, and this was associated with gradual improvement in serological values. During and after the colchicine regimen joint symptoms were well controlled with non-steroidal anti-inflammatory drugs, except for occasional episodes of minor left clavicular pain.

CASE 2

A 67 year old housewife was referred to our clinic for detailed examination of her right clavicle, in which she had had pain for 20 years. Three years previously she had undergone surgical curettage of the clavicle under the diagnosis of 'osteomyelitis', and thereafter had been treated continuously with several oral antibiotics, which had little effect. She had a past history of tonsillitis in her childhood but lacked the skin lesions of palmoplantar pustulosis. Upon presentation venous dilatation was seen in the skin overlying the left clavicle, together with a percussion pain of the upper anterior chest wall. Unlike case 1 the laboratory data (table 2) were not remarkable, and serological tests for streptococcal antigens were negative. Radiological and scintigraphic findings were typical of intersternocostoclavicular ossification as in case 1, and the diagnosis was confirmed histologically by a review of the specimen taken during a previous operation. Because of the encouraging results obtained in

Table 1 Treatment course of case 1

	1987						1988					
	23 Jan	6 Feb	25 Feb	9 Mar	23 Mar	30 Apr	20 May	12 Sep	5 Jan	29 Mar	10 May	12 Jul
Treatment												
Calcitonin analogue intramuscularly 40 U, 3 times/week	—————											
Steroid ointment (for pustules)		—————	—————									
Colchicine orally 1.0 mg/day					—————							
0.5 mg/day						—————	—————	—————				
Laboratory data												
AP* (IU/l)	303	196	176	173	158	160	155	177	175	193	159	143
CRP*†	5+	4+	3+	2+	5+	—	2+	1+	2+	—	6+	—
ESR* (mm/h)	113	110	107	93	84	43	76	30	72	22	115	46
ASLO* titre	640	480	320	480	480	240	160	120	120	ND*	80	80
ASK* titre	5120	5120	10 240	10 240	5120	2560	640	2560	5120	ND	640	640
Uptake ratio in bone scan	7.60	ND	3.14	ND	3.88	2.65	5.10	4.00	4.30	ND	ND	3.27
Pain	+++	+	—	—	—	±	—	—	±	—	±	—
Skin pustules	++	+	±	—	++	—	—	—	—	—	—	—

*AP=alkaline phosphatase, normal 28–110 IU/l; CRP=C reactive protein; ESR=erythrocyte sedimentation rate; ASLO=antistreptolysin O; ASK=antistreptokinase; ND=not done.

†CRP was measured by a precipitin test in capillary tubes.

Table 2 Treatment course of case 2

	1988		1989				1990			
	28 Apr	22 Nov	7 Mar	6 Jun	29 Aug	3 Oct	28 Nov	9 Dec	9 Feb	20 Mar
Treatment										
Oral antibiotics	[-----]									
Nasal spray of calcitonin	[-----]									
Colchicine orally	[-----]									
1.5 mg/day	[-----]									
Calcitonin analogue intramuscularly	[-----]									
40 U, twice a week	[-----]									
Laboratory data†										
AP* (IU/l)	91	91	77	95	117	131	100	90	84	109
CRP*‡	-	-	-	-	-	1+	-	ND	-	1+
ESR* (mm/h)	21	ND*	ND	ND	ND	45	25	ND	27	53
Uptake ratio in bone scan	ND	7.27	6.98	11.02	ND	14.40	6.88	ND	7.82	ND
Pain	+	+	++	+	+	++	-	-	-	-

*AP=alkaline phosphatase, normal 28–110 IU/l; CRP=C reactive protein; ESR=erythrocyte sedimentation rate; ND=not done.
†Antistreptolysin O and antistreptokinase were negative throughout the course.
‡CRP was measured by a precipitin test in capillary tubes.

case 1 calcitonin treatment was considered. In an attempt to obviate the pain of intramuscular injection a nasal spray of synthetic salmon calcitonin (SMC-20-051) was used in doses of 200 units daily for eight months, with virtually no significant analgesic effect. There was even a transient worsening of the bone pain with increase of serum alkaline phosphatase and C reactive protein. Oral colchicine 0.5 mg three times daily was prescribed for the next three months, again with no significant relief. When intramuscular calcitonin analogue was started at 40 units twice a week an analgesic effect took place from day 4, with improvement of the uptake ratio on bone scan and normalisation of laboratory indices. The venous dilatation of local skin gradually disappeared. The pain recurred during a holiday period when the hospital was closed and injections were not available for two weeks, but disappeared promptly after resumption. In the eighth week of the regimen gastrointestinal symptoms of epigastralgia, decreased appetite, and soft stool emerged but were controlled with an H2 receptor blocking agent and other stomach drugs. After a total of 16 weeks the calcitonin analogue was discontinued with no relapse of joint symptoms. At the time of this report the patient remains well without drugs.

Discussion

To our knowledge this is the first report of the treatment of intersternocostoclavicular ossification with calcitonin. Although the pain in this disease usually waxes and wanes even without any treatment, incidental spontaneous remission could not explain the prompt improvement of symptoms seen in both patients after calcitonin injections, or the worsening again when calcitonin was unavailable early in the treatment course of case 2.

This therapeutic trial was first conceived owing to the report of favourable effects of human calcitonin in Tietze's disease,¹² a benign condition with costochondral pain and swelling. As in Tietze's disease, bone pain in intersternocostoclavicular ossification was alleviated early in the course of treatment. This supports the

idea of a central analgesic effect of the peptide^{13 14} working together with its anti-inflammatory effects.¹⁵ Moreover, the noted quantitative improvement in bone scintigraphy may reflect termination of joint calcification and hyperostosis. At first sight this may seem contradictory to the restoration by calcitonin of decreased bone mass in osteoporosis.^{16 17} But the hormone might indirectly suppress new bone formation by osteoblasts through its well known inhibitory influence on osteoclasts,^{18 19} as the activity of those two types of cell is coupled.²⁰

Having noted the close association between intersternocostoclavicular ossification and palmoplantar pustulosis, Sonozaki and colleagues proposed the term pustulotic arthro-osteitis (PAO),⁴ suggesting a common cause for these two conditions. They analysed clinical features of accumulated cases and suggested that pustulotic arthro-osteitis was a seronegative spondyloarthritis.⁵ There are a significant minority of patients with intersternocostoclavicular ossification without palmoplantar pustulosis, however, as in case 2, whose symptoms and radiographic features are indistinguishable from those of patients with palmoplantar pustulosis. Interestingly, patient 2 did not have raised titres of antistreptolysin O and antistreptokinase, whereas patient 1 (with palmoplantar pustulosis) did, suggesting that other factors besides focal infection may play a part in the pathogenesis of intersternocostoclavicular ossification, at least in cases without palmoplantar pustulosis. In fact, the raised titres of these antistreptococcal antibodies in patient 1 might have simply reflected an anamnestic response to chronic inflammation, either in his liver, skin, or bone and joint. In any case our experience in these two cases showed that injection of calcitonin analogue produced symptomatic relief in the acutely exacerbated clinical situations regardless of the associated skin disease. Thus the hormone must have exerted its effects by mechanisms not directly related to the putative common cause—namely, focal infection.

The failure of treatment by calcitonin nasal spray in case 2 might have been due to

insufficient drug delivery. When the patient was examined in an otolaryngology clinic she was found to have chronic sinusitis, which might have led to reduced absorption of the hormone through nasal mucosa. Furthermore, if a spray were used in the future for patients without mucosal problems it would be necessary to determine the size of the nasal dose required to exert effects equivalent to those of the agent given intramuscularly.

Theoretically colchicine might have suppressed the inflammation of bones and joints, as in gout,²¹ but it was found not to reduce the pain of intersternocostoclavicular ossification. On the other hand, the drug has been used successfully for palmoplantar pustulosis,²² presumably owing to its inhibitory effects on leucocytes. In case 1, it certainly cured the skin lesion and lowered the inflammatory indices and titres of antistreptococcal antibodies.

Long term calcitonin treatment can be hindered by a so called 'escape' phenomenon,^{23 24} though this was not found in our cases. As the severity of symptoms in intersternocostoclavicular ossification is known to fluctuate naturally, however, an escape could be avoided by using calcitonin injections only during the waxing phase. Clinically, this would mean trying to discontinue the hormone after several months of the regimen, just as was done in the two cases reported here. After a period without calcitonin the responsiveness of target organs should be restored, and if symptoms reoccur they could be quelled again with the same regimen.

To conclude, our initial encouraging results warrant further use of calcitonin injections in cases of acute aggravation of intersternocostoclavicular ossification. In due course accumulated clinical data from a larger number of patients should help to clarify both the pathogenesis of the disease and the mechanism of action of the drug.

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