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A CASE OF ALBRIGHT'S SYNDROME TREATED WITH CALCITONIN

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A 23-year-old woman with Albright's syndrome (polyostotic fibrous dysplasia of bone, precocious puberty and irregular cutaneous pigmentations) had sustained multiple fractures and was grossly disabled. Evaluation disclosed markedly raised serum alkaline phosphatases and a high urinary excretion of hydroxyproline, suggesting an accelerated bone turnover, while calcium metabolism was virtually undisturbed. During 12 months therapy with calcitonin, however, no apparent benefit was recorded and there was no evidence of any significant metabolic effects of the treatment. Initial discomfort with nausea and vomiting disappeared after dose reduction whereas diffuse bone and muscle pain, which gradually increased after a few months treatment, did not subside until after cessation of the therapy.

Key words: calcitonin; calcium metabolism; fibrous dysplasia; side effects

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Fibrous dysplasia of bone is a disorder in which an excessive proliferation of fibrous tissue disrupts the normal architecture of bone. The disorder sometimes only affects one bone but frequently engages several areas, often symmetrically, throughout the skeleton. The pathogenesis is obscure. For equally unknown reasons there is an association between the polyostotic form of the disease and various endocrinopathies, among them thyroid, parathyroid and adrenal disorders. The triad polyostotic fibrous dysplasia, precocious puberty and hyperpigmentation has become known as Albright's syndrome (Albright et al. 1938).

The progressive replacement of bone by fibrous tissue may result in severe deformities. Limited surgical corrections can be helpful but until recently no medical treatment for the bone disease has been reported.

Calcitonin is a polypeptide hormone with potent inhibitory effects on bone resorption (Hirsch & Munson 1969) and therapy with calcitonin has proven to be of considerable value in disorders characterized by an increased bone turnover, e.g. Paget's disease (Kanis et al. 1975). It has also been reported that when calcitonin was given to patients with fibrous dysplasia the serum concentrations of alkaline phosphatase decreased together with the urinary excretion of hydroxyproline (Bell et al. 1970, Morii et al. 1971). These short-term metabolic effects suggested that the pathological skeletal turnover might be affected and consequently raised the hope of some beneficial clinical value of calcitonin also in this disease. As Albright's syndrome is a rare disorder no controlled studies seem to have been performed. We have, therefore, considered it worthwhile to report our experience in a case treated with calcitonin for 1 year.

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CASE REPORT

A 3-year-old girl was diagnosed as having Albright's syndrome because of typical cutaneous pigmentations and fibrous dysplasia of both femurs. At the age of 6 she had her first fracture after a minor trauma. Since then and up to the age of 23, when the present study was undertaken, she had experienced at least 15 fractures, primarily of the arms and legs, and had been submitted to 10 corrective osteotomies. She was grossly disabled and confined to a wheel chair. Pubertas precox was experienced at the age of 9, at which time laparotomy disclosed normal postpubertal gynaecological findings as did a biopsy from one ovary. Menstruations thereafter have been slightly irregular.

At the time of admission examination disclosed marked malformations of the extremities and several irregular pigmentations. Areas of fibrous dysplasia were roentgenologically demonstrated throughout the skeleton. She had a normal routine laboratory profile including blood picture, serum electrolytes, tests of hepatic and renal function and urinalysis. Thyroid function was normal; T_4 100 nmol/l, T_3 3.0 nmol/l, TSH 4 mU/l, but there was no significant rise of the TSH levels after i.v. injection of 200 µg TRH. A thyroid scan was normal and she had a normal iodine uptake. The serum cortisol levels displayed a normal circadian rhythm and the urinary excretion of oxogenic steroids were in the lower part of the normal range. Both LH and FSH serum concentrations were normal and after injection of LRH a significant increase was demonstrated. Growth hormone concentrations were repeatedly around 3 ng/ml, without significant suppression during an intravenous glucose tolerance test, whereas a marked rise was noted following the injection of insulin. The glucose tolerance was normal (T 1/2 = 48 min) as were the serum insulin levels. The serum calcium, phosphate, parathyroid hormone and calcitonin concentrations were all normal but the serum alkaline phosphate activity was greatly increased, exclusively due to an increase in the bone phosphatases. Also the urinary hydroxyproline excretion was greatly increased (Table 1).

Therapy was initially instituted with 80 MRC units calcitonin (Miacalcic®) daily. Because of severe nausea and vomiting, appearing after a few days, the dose was reduced after 1 month to 8 MRC units, which was maintained during the following 11 months. During treatment no significant metabolic effects could be detected, serum alkaline phosphatases remained high as did the urinary excretion of hydroxyproline (Table 1). Nor was there any clinical response. She continued to develop fractures also during therapy and at the end of one year of treatment increasing discomfort with diffuse bone and muscle pain was experienced. When therapy was stopped these complaints disappeared within a week.

DISCUSSION

In this patient all the typical features of Albright's syndrome were present. The metabolic evaluation suggested an accelerated bone turnover with constantly raised serum alkaline phosphatases and a marked increase in the urinary hydroxyproline excretion. Therapy with calcitonin, however, although useful in other disorders characterized by increased bone resorption and formation (Gray & Ontjes 1975) was of no apparent clinical benefit in the present case, nor could any significant metabolic changes be detected.

Table 1. Laboratory effects of treatment with calcitonin in a case of Albright's syndrome

		Normal range	Months of treatment 0	1	12
Serum	calcium (mmol/l)	2.20–2.60	2.35	2.35	2.25
	phosphate (mmol/l)	0.76–1.44	0.80	0.80	0.80
	alkaline phosphatase (µkat/l)	0.8–4.8	26	26	25
	parathyroid hormone (ng/ml)	1.1–2.5	1.6		
Urinary	calcium (mmol/24 h)	–5	3.5	4.2	3.4
	phosphate (mmol/24 h)	–25	20	25	15
	hydroxyproline (mg/24 h)	6 –22	109	210	167
Daily dose of calcitonin (MRC units)			—	80	8

Several factors might have contributed to this picture.

It seems probable that calcitonin is less important for skeletal homeostasis than for calcium homeostasis (Potts 1969). Further, in the present case the biochemical disturbances presented are more likely to have reflected continuous bone repair and remodelling rather than resorption of mineralized bone and hence probably there is inadequate theoretical basis for therapy with calcitonin in fibrous dysplasia.

During the major part of the time the dosage of calcitonin was comparatively low, 8 MRC units per day. Although we were, in the present study, unable to determine any effects of the drug the dosage was similar to that used by others (Morii et al. 1971). Further, no metabolic effects were noted during the first treatment month with a tenfold higher dose. Thus, it is unlikely that the lack of response was due to inadequate calcitonin dosage.

The original intention to use a higher maintenance dose turned out to be impossible because of various side reactions. Nausea and vomiting, which were the initial complaints, are well known and generally temporary, as in the present case. The diffuse pain of bone and muscle, on the other hand, which appeared after several months treatment seems to be less frequent. The underlying mechanism is unknown. Since the pain persisted for several weeks during calcitonin therapy but subsided within days after cessation of the treatment a relationship with the calcitonin administration seems probable.

It has been suggested that the endocrine manifestations of Albright's syndrome are caused by a hypothalamic hypersecretion of releasing hormones (Warrick 1973). However, in the present case the basal levels of the serum pituitary hormone concentrations were not increased as would have been expected in the case of continuous hypothalamic stimulation. Furthermore, adequate pituitary responses were obtained after the administration of the corresponding releasing hormones, which also supports a normal hypothalamic-pituitary relationship.

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