FAMILIAL IDIOPATHIC HYPERPHOSPHATASIA

A STUDY OF TWO YOUNG SIBLINGS TREATED WITH PORCINE CALCITONIN

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A study of two siblings with a severe infantile form of familial idiopathic hyperphosphatasia is reported. A girl aged one year was followed for two years while receiving intermittent treatment with porcine calcitonin. This induced a clinical remission, a reduction of both the high serum level of alkaline phosphatase and the raised urinary excretion of hydroxyproline, and a remarkable improvement in bone structure as seen radiologically. Her sister aged two months received porcine calcitonin for three weeks, during which clinical improvement, no change in the serum level of alkaline phosphatase and a marked decrease of the excretion of hydroxyproline were recorded.

A rare disorder of bone in childhood has been reported in the literature under different names. Its main features are progressive skeletal deformity with generalised conversion of long bones to coarsely trabeculated radiolucent widened bone, coxa vara, protusio acetabuli and diaphysal bowing, and high levels of both serum alkaline phosphatase and urinary excretion of hydroxyproline. *Chronic idiopathic or familial hyperphosphatasia*, the term coined by Caffey in 1961, has gained wide acceptance although there is general agreement that the raised serum phosphatase is only secondary to the bone disorder. Other proposed names are *Osteitis deformans in children* (Choremis *et al.* 1958), *Hyperostosis corticalis* (Swoboda 1958), *Osteochalasia desmalis familiaris* (Fanconi *et al.* 1964) and *Familial osteoectasia* (Bakwin *et al.* 1964).

In 1973 Caffey reviewed fourteen patients described in the English literature with this type of bone dysplasia (Choremis *et al.* 1958; Swoboda 1958; Marshall 1962; Bakwin *et al.* 1964; Fanconi *et al.* 1964; Eyring and Eisenberg 1968; Thompson *et al.* 1969; and Wagner and Solomon 1969). Two further cases have been reported since (Woodhouse *et al.* 1972; Desai *et al.* 1973).

Although the disease is not immediately life-threatening, the prognosis would seem to be poor in severely affected patients. The oldest patient described in the literature was nineteen (Case 2 of Thompson *et al.*). Sodium fluoride appears to have little effect (Eyring and Eisenberg 1968), but it has been reported that the administration of human calcitonin reduced the bone turnover and improved the radiological appearances in a boy with a mild form of the disease (Woodhouse *et al.* 1972; Doyle *et al.* 1974).

This report describes two sisters of Caucasian racial stock with the severe infantile form of hyperphosphatasia. Porcine calcitonin was administered to both and the responses are described.

CASE REPORTS

Case 1—A girl born in San Juan, 1,100 kilometres from Buenos Aires, was twelve months old when first admitted to the Children's Hospital in June 1971. The pregnancy and delivery had been normal and her birth weight was 2.9 kilograms. At one month of age, swelling and contracture of both legs and arms were noted. At three months radiographs were taken and a provisional diagnosis of infantile cortical hyperostosis was made locally. Prednisone (2 milligrams per kilogram of body weight daily) was then given for fifteen days. Vitamin D 600,000 international units was also given at three months, followed by the administration of vitamins D, A and C over the next three months. The child continued to have intermittent episodes of tender swelling of the limbs, each lasting about two weeks, during which she was pyrexial and very irritable.

Family history—Consanguinity was denied by the parents. Both they and their five-year-old son were in good health. In all three of them radiographs of bone and the serum calcium, phosphate and alkaline phosphatase were normal. A maternal great-uncle was said to have polydactyly and kyphosis. **Clinical findings**—On admission the height was 64 centimetres and weight 6.8 kilograms. These figures were below the 5th percentile. The circumference of the head was 43 centimetres (25th percentile). The skeletal deformities included craniotabes, bilateral coxa vara and outward bowing of the left femur. Movement of all four limbs was painful. Laboratory tests gave normal values for haemoglobin, blood urea nitrogen, serum glucose, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphate, total proteins, albumin and globulins, and liver function. The urinary findings were within normal limits for calcium, phosphate and alpha-aminonitrogen. The serum alkaline phosphatase, however, ranged between 70 and 90 Bodansky units (normal range 2 to 7 units).

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The child left the hospital without any specific treatment and was readmitted at eighteen months of age. The symptoms and signs were essentially the same. An open biopsy on the shaft of the left tibia was performed (see later). Calcium retention after a standard intravenous infusion was 90 per cent. The patient was again discharged without any treatment and readmitted at the age of two years and three months. The intermittent episodes of tender swelling of the limbs had persisted and now also affected the fingers. All movements were very limited. The girl was able to crawl and to stand with help but could not walk.

Radiological findings—At one year there was a general diminution of bone density and coarse trabeculation. The clavicles, ribs and long bones of the limbs were wider than normal, with cortical bone poorly outlined. The vertebral bodies were faintly seen and widely separated. The cranium was enlarged. At eighteen months marked deformity and enlargement of the transverse diameters of the long bones were seen, especially in the femora and humeri. There was a marked subperiosteal deposition of bone on the shafts, and within them areas of coarse trabeculation alternated with areas rather like cysts. The distal end of each ulna was angulated. By two years and three months the films recorded a progressive skeletal deterioration with the long bones

showing marked expansion, indistinct outlines, a very thin cortex and bowing (Fig. 1). Resorption clefts were present in several bones. The proximal ossification centres of the femora and humeri were absent.

Bone histology—The tibial biopsy showed an extremely thin cortex and an abnormal appearance of the spongiosa. Microscopically a marked alteration of structure was observed. The cortex was formed of trabeculae of immature (woven) bone and covered by periosteum with a highly cellular osteogenic layer (Fig. 3). The few trabeculae of mature bone observed had no Haversian systems. Most of the trabeculae of the cortex and spongiosa were covered by layers of active hypertrophic osteoblasts alternating with foci of evident osteoclastic resorption, but bone formation was predominant (Figs. 4 and 5). The bone marrow was in great part fibrous, loose and very vascular but active centrally. Histochemical study of alkaline phosphatase by Gomori's method showed intense activity in the osteoblastic cells on the bone surfaces, less intense in the marrow cells (pre-osteoblasts) and osteocytes (Fig. 6). The general histological picture indicated a very rapid turnover, similar to that observed in Paget's disease; indeed occasional sketches of "mosaic structures" were found. However, due to the fast turnover, few trabeculae of mature bone with a pagetoid structure were detectable.

FIG. 1

FIG. 2

Case 1. Figure 1—A radiograph of the left arm taken before treatment at two years and three months. Figure 2—A radiograph taken after one year of treatment with calcitonin.

FIG. 3

FIG. 4

Case 1. Figure 3—A photomicrograph at low magnification from the tibial biopsy at the age of two years, showing at **a** the cellular osteogenic layer of the periosteum and at **b** the thin cortex reduced to a few trabeculae of newly-formed immature bone surrounded by active osteoblasts. The marrow is fibrous, loose and vascular. Some trabeculae of laminar bone are covered by rows of active osteoblasts alternating with osteoclasts, and show sketches of "mosaic structure" very similar to that observed in Paget's disease. (Haematoxylin and eosin, $\times 20$.) Figure 4—A photomicrograph of a field in Figure 3 showing a mature cancellous bone trabecula with sketches of "mosaic structure" at **a**, surrounded by osteoblasts alternating with osteoclasts. (Haematoxylin and eosin, $\times 200$.)

In some aspects the appearances were very similar to those seen in osteogenesis imperfecta, but the evident alternation of osteoblastic and osteoclastic activity does not exist in this process in which the outstanding features are the production of immature bone and its failure to mature.

Treatment with calcitonin—In view of the progressive deterioration of the skeleton and the evidence of excessive bone resorption it was thought that calcitonin might be of benefit. This treatment was started in September 1972, in a daily dose of 10 MRC units of porcine calcitonin given subcutaneously, together with an oral dose of 500 milligrams of calcium in the form of gluconate and carbonate (Calcium Sandoz). A week later the dose of calcitonin was increased to 20 units, and this was continued for six months up to March 1973 (Table 1).

After a break of four months the treatment was resumed in July 1973 at 40 MRC units daily and maintained up till December 1973. The last control was performed after nine months without specific therapy, in September 1974.

The patient was kept in hospital during the first two months of treatment by calcitonin administration, and then readmitted for one week every two months. On each admission the patient was given a gelatin-free diet and all urine was collected. Frequent estimations were made of serum calcium, phosphate and alkaline phosphatase, and of urinary calcium, sodium, phosphate, total hydroxyproline and creatinine.

The clinical response—Soon after the onset of treatment there was an increase of spontaneous activities such as sitting up

FIG. 5

FIG. 6

Figure 5—A photomicrograph showing an immature bone trabecula surrounded by osteoblasts at **a** and osteoclasts at **b**. (Haematoxylin and eosin, $\times 400$.) Figure 6—A photomicrograph showing intense alkaline phosphatase activity of numerous active osteoblasts on the surface of a newly-formed bone trabecula. (Gomori's technique, $\times 400$.)

without help, standing and taking a few steps with assistance. The limbs were no longer painful on movement, which made bathing and feeding easier. Though her appetite improved, a loss of weight of 550 grams was recorded over the first two months; this coincided with an increased urinary excretion of sodium and with a reduction of swelling of the limbs. The episodes of tenderness and swelling of the limbs almost ceased; only one episode involving the right index finger was noticed. When the treatment was interrupted the clinical improvement was largely maintained, though when the child

TABLE I

THE EFFECT OF PORCINE CALCITONIN ON THE SERUM LEVELS OF CALCIUM AND PHOSPHATE (CASE 1)

Dosage MRC u/day	Estimations	Serum calcium (mg/100 ml)		Serum phosphate (mg/100 ml)	
		Basal	2 hours	Basal	2 hours
10	7	9.4	8.2*	—	—
20	7	9.6	8.4*	5.1	3.7*
20 plus oral calcium	8	10.0	9.6	4.5	3.4*

* $P < 0.05$

was last examined in September 1974, after nine months without treatment, she had suffered several episodes of tender swelling of the limbs, lost six incisors, and developed severe bilateral loss of hearing.

The biochemical response—Initially both the fasting serum calcium and the serum phosphate levels were normal; with treatment the former did not change and the latter tended to

fall. Before treatment the serum alkaline phosphatase was markedly elevated, with an average level of 75 Bodansky units; a gradual decline was observed during the first five months of calcitonin, and again during the second course (Table II). Before treatment the total hydroxyproline excretion (THP) was very high (average 369 milligrams per 24 hours); with the administration of calcitonin there was a prompt fall. When calcitonin was discontinued for four months the excretion rose but not to the initial values. With resumption, in a dose of 40 units per day, there was a prompt diminution and then a gradual decline to about half the level before treatment began. After nine months without calcitonin the values had returned to the high initial levels.

The radiographic skeletal response—In every long bone there was a striking reduction of the external diameter (Figs. 1 and 2). Any bowing was partially corrected. The cortex was better defined and increased in thickness. The periosteal deposition of disorganised new bone was halted, but the internal architecture, though somewhat improved, was still markedly abnormal.

Micrometric measurements were made of the length (L) and transverse diameter (T) of the middle of the shaft of the second metacarpal. The length increased throughout the whole period of observation whereas the diameter tended to diminish during treatment (Fig. 7). The ratio T/L gives an appraisal of bone remodelling. Whereas the ratio for the second metacarpal normally falls slightly from the ages of two to four years, in Case 1 there was a sharp decrease shortly after the onset of calcitonin treatment.

Case 2—The sister of the girl in Case 1 was two months of age when admitted in September 1974. The pregnancy and delivery had been uneventful; the birth weight was 3.4 kilograms. At two weeks the mother had observed curvature and swelling of the forearms, with pain on movement. The

TABLE II

THE EFFECT OF PORCINE CALCITONIN (*) ON THE SERUM LEVELS OF ALKALINE PHOSPHATASE AND THE URINARY EXCRETION OF TOTAL HYDROXYPROLINE (THP) (CASE 1)

Date	Calcitonin MRC u/day	Serum alkaline phosphatase (Bodansky units)	THP mg/24 hours	THP/Creatinine mg : mg
September 1972	0	74.7 ± 6.3	369 ± 133	5.51 ± 0.47
September 1972	10	70.2 ± 6.6	234 ± 115	3.67 ± 0.97
November 1972	20	62.2 ± 7.1	254 ± 66	3.57 ± 1.01
February 1973	20	57.7 ± 5.3	224 ± 176	2.45 ± 0.53
February 1973	0	—	246 ± 25	2.93 ± 0.53
July 1973	0	76.5 ± 10.1	279 ± 96	4.36 ± 0.76
July/August 1973	40	77.0 ± 9.3	224 ± 44	3.66 ± 0.80
October 1973	40	61.2 ± 6.2	207 ± 66	3.86 ± 0.57
December 1973	40	50.2 ± 5.8	183 ± 68	3.30 ± 0.54
September 1974	0	50.3 ± 6.9	376 ± 53	5.58 ± 0.61

* Given in the following scheme:

10 MRC u/day from September 11 to 19, 1972.

20 MRC u/day from September 19, 1972, to March 15, 1973 (except for a break of one week in February 1973).

40 MRC u/day from July 30 to December 30, 1973.

Results are average ± 1 SEM (from three to eight daily observations).

FIG. 7

Case 1. Micrometric measurements of the second metacarpal bone (see text).

FIG. 8

Case 2. A radiograph of both legs taken at two months of age.

symptoms improved after another two weeks but a few days later the legs were affected. There was no pyrexia.

On admission the weight was 4.4 kilograms (between the 5th and 25th percentile) and length 56.9 centimetres (between the 50th and 75th percentile). On inspection all four limbs were widened, especially the wrists. Movement was limited and caused some pain. The blood pressure was normal. Laboratory values were normal except for serum

alkaline phosphatase of 51 to 67 Bodansky units and urinary total hydroxyproline between 158 and 395 milligrams per 24 hours. Serum calcium was 10.4 milligrams and serum phosphate 7.5 milligrams per 100 millilitres.

Radiological examination—Despite the early age, marked changes were seen, the girth of every long bone being greatly increased, the cortex extremely thin, and the internal architecture completely abnormal (Fig. 8).

TABLE III

THE EFFECT OF PORCINE CALCITONIN ON THE SERUM LEVELS OF ALKALINE PHOSPHATASE AND THE URINARY EXCRETION OF TOTAL HYDROXYPROLINE (THP) (CASE 2)

Date (1974)	Dosage	Serum alkaline phosphatase (Bodansky units)	THP mg/24 hours	THP/Creatinine mg : mg
September 20–25	0	55*	190*	5.31*
September 26	20	55	230	4.51
October 1	20	52	187	3.40
October 3	10	—	158	3.03
October 15	8	51	73	3.31

* Average of 5 estimations.

Treatment with calcitonin—This was started with 20 MRC units of porcine calcitonin daily given subcutaneously but caused an average fall of serum calcium of 2.8 milligrams per 100 millilitres after two hours. The dose was therefore reduced to 5–10 units, giving an average fall of 1.6 milligrams. The period of observation during treatment was limited to three weeks. Even so, a marked amelioration of the clinical state was observed, including a more normal appearance of the limbs, freedom of movement and relief of pain.

Biochemical response—The urinary excretion of total hydroxyproline soon fell but not the serum level of alkaline phosphatase (Table III).

DISCUSSION

The main findings in chronic idiopathic hyperphosphatasia have been well summarised by Eyring and Eisenberg (1968). A review of sixteen reported cases, however, indicates significant differences in the clinical course. The patients described by Choremis *et al.* (1958), Caffey (1961), Mitsudo (1971) and Woodhouse *et al.* (1972) had little or no diminution of height, no significant limitation of movement, no episodes of swelling and tenderness of the limbs, and increased thickness of cortical bones. On the other hand, the patients described by Swoboda (1958), Marshall (1962), Fanconi *et al.* (1964), Eyring and Eisenberg (1968), Desai *et al.* (1973), the patients in Cases 1 and 2 of Thompson *et al.* (1969) and the two patients described here had severe dwarfism, inability to walk, episodes of painful swelling of the limbs and a generalised reduction of cortical thickness.

An unusual finding in our Case 1 was the absence of ossification in the capital epiphyses of both humerus and femur, as in the patients described by Swoboda. At present it is not clear if this finding is related to the disease or is a different genetic defect.

Features common to all patients are increased fragility of bone, cranial enlargement and bowing of long bones. Moreover, the histological findings are

remarkably similar; the main feature of the disease appears to be hyperactivity of osteoblasts and osteoclasts with the failure to replace immature bone by compact Haversian bone. This leads to the subperiosteal deposition of disorganised new bone, bowing and fragility. The intrinsic cause of the disease remains unknown.

The present report supports an autosomal recessive pattern of inheritance. This is the fifth family in which multiple siblings have been affected. In all cases except one (Bakwin *et al.* 1964), the parents were normal. In two families the siblings were of both sexes.

Attempts at medical control have been infrequent. Eyring and Eisenberg (1968) treated two severely affected siblings with sodium fluoride for eighteen months and found a moderate fall in alkaline phosphatase but no significant change in the clinical state. Woodhouse *et al.* (1972) reported a rapid response to synthetic human calcitonin in a boy aged five with repeated fractures and progressive deformities. The excretion of urinary hydroxyproline was reduced and the calcium and phosphate balances became more positive. After three months the serum alkaline phosphatase and excretion of hydroxyproline fell to about half the initial values. A progress report of the same patient by Doyle *et al.* (1974b) showed a remarkable regression of the bony abnormalities, much as in our Case 1.

Previous observations have been made of remodeling of bone induced by synthetic human calcitonin both in this disease and in Paget's disease (Doyle *et al.* 1974a and b). Our findings show that a similar result can be obtained from porcine calcitonin. Unfortunately we were unable to perform serial biopsies of bone in our two cases, mainly because of insuperable economic difficulties. Moreover, we have had no report on the state of these two girls since they were discharged at the end of 1974.

Addendum—Since this paper was submitted for publication Horwith *et al.* (1976) have reported a similar good response to human calcitonin in four children with familial idiopathic hyperphosphatasia.

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REFERENCES

- Bakwin, H., Golden, A., and Fox, S. (1964) Familial osteoectasia with macrocranium. *American Journal of Roentgenology*, **91**, 609–617.
- Caffey, J. (1961) Chronic idiopathic hyperphosphatasia. In *Pediatric X-ray Diagnosis*, pp. 1042–1044. Fourth edition. Chicago: Year Book Medical Publishers, Inc.
- Caffey, J. (1973) Familial hyperphosphatasemia with ateliosis and hypermetabolism of growing membranous bone; review of the clinical, radiographic and chemical features. *Progress in Pediatric Radiology*, **4**, 438–468.
- Choremis, C., Yannakos, D., Papadatos, C., and Baroutsou, E. (1958) Osteitis deformans (Paget's disease) in an 11-year-old boy. *Helvetica Paediatrica Acta*, **13**, 185–188.
- Desai, M. P., Joshi, N. C., and Shah, K. N. (1973) Chronic idiopathic hyperphosphatasia in an Indian child. *American Journal of Diseases of Children*, **126**, 626–628.

- Doyle, F. H., Pennock, J., Greenberg, P. B., Joplin, G. F., and MacIntyre, I. (1974a) Radiological evidence of a dose-related response to long-term treatment of Paget's disease with human calcitonin. *British Journal of Radiology*, **47**, 1-8.
- Doyle, F. H., Woodhouse, N. J. Y., Glen, A., Joplin, G. F., and MacIntyre, I. (1974b) Healing of the bones in juvenile Paget's disease treated by human calcitonin. *British Journal of Radiology*, **47**, 9-15.
- Eyring, E. J., and Eisenberg, E. (1968) Congenital hyperphosphatasia. *Journal of Bone and Joint Surgery*, **50-A**, 1099-1117.
- Fanconi, G., Moreira, G., Uehlinger, E., and Gledion, A. (1964) Osteochalasia desmialis familiaris. *Helvetica Paediatrica Acta*, **19**, 279-295.
- Horwith, M., Nunez, E. A., Krook, L., Viteri, F., Torun, B., Mena, E., Suh, S. M., Eisenberg, E., MacIntyre, I., and Whalen, J. P. (1976) Hereditary bone dysplasia with hyperphosphatasemia: response to synthetic human calcitonin. *Clinical Endocrinology*, **5**, supplement, 341s-352s.
- Marshall, W. C. (1962) A chronic progressive osteopathy with hyperphosphatasia. *Proceedings of the Royal Society of Medicine*, **55**, 238-239.
- Mitsudo, S. M. (1971) Chronic idiopathic hyperphosphatasia associated with pseudoxanthoma elasticum. *Journal of Bone and Joint Surgery*, **53-A**, 303-314.
- Swoboda, W. (1958) Hyperostosis corticalis deformans juvenilis. *Helvetica Paediatrica Acta*, **13**, 292-312.
- Thompson, R. C., Jun., Gaull, G. E., Horwitz, S. J., and Schenk, R. K. (1969) Hereditary hyperphosphatasia. *American Journal of Medicine*, **47**, 209-219.
- Wagner, J. M., and Solomon, A. (1969) Hyperostosis corticalis infantilis (Caffey's disease). *South African Medical Journal*, **43**, 754-755.
- Woodhouse, N. J. Y., Fisher, M. T., Sigurdsson, G., Joplin, G. F., and MacIntyre, I. (1972) Paget's disease in a 5-year-old: acute response to human calcitonin. *British Medical Journal*, **4**, 267-269.