Hypohyperparathyroidism: a model for renal osteodystrophy?

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Summary

A child who presented with features of renal osteodystrophy but with normal renal function is described. Improvement occurred both on large doses of vitamin D and small doses of $1, \alpha$ -hydroxy-vitamin D_3 ($1, \alpha$ -OHD $_3$). Investigations suggested that the primary defect was an impaired renal response to parathyroid hormone. The relationship between renal osteodystrophy, abnormalities of vitamin D metabolism and hypohyperparathyroidism is discussed and an alternative hypothesis for the development of renal bone disease suggested.

Introduction

The mechanism of development of renal osteodystrophy has been the subject of controversy for many years. Owing to this condition's resemblance to nutritional rickets, vitamin D was initially considered to be the major factor involved. Albright and Reifenstein (1948) discounted this theory claiming that parathyroid hypertrophy was the dominant feature. In 1968, Stanbury suggested that a defect in the metabolism of vitamin D was present in chronic renal failure. This was later shown to be a deficiency in $1, \alpha$ -hydroxylase activity in the kidney resulting in low serum levels of $1, 25$ dihydroxy-vitamin D_3 ($1, 25(\text{OH})_2 D_3$) in chronic renal failure (Mawer *et al.*, 1973). There is also a high circulating level of immunoreactive parathyroid hormone (PTH) in renal failure, the origin of which is multifactorial (Papapoulos *et al.*, 1977).

The investigation of the pathogenesis of renal bone disease is complicated by several of the features of uraemia including acidosis, inadequate nutrition and the effects of dialysis. A clinical model for renal osteodystrophy without the additional features of uraemia has not yet been described. The resemblance between a patient with hypohyperparathyroidism and patients with renal osteodystrophy suggests a unifying hypothesis for the pathogenesis of the major components of renal bone disease.

Case report

The patient was the first child of a non-consan-

guineous marriage in which there was no family history of renal or bone disease. She first presented at the age of 2 years with non-febrile convulsions. No biochemical investigations were performed and she was commenced on phenobarbitone despite a normal EEG.

Eighteen months later she was readmitted to hospital complaining of pain in her legs when walking. Radiographs of the knees and wrists showed widening of the metaphyseal regions with cortical erosions present in both radius and ulna, findings compatible with renal rickets (Fig. 1). Creatinine clearance corrected for surface area was normal and no aminoaciduria was detected.

On admission, tetanic spasms were observed. The serum calcium was low at 1.4 mmol/l (corrected for serum albumin) while serum phosphate (2.2 mmol/l) and alkaline phosphatase (476 i.u./l) values were elevated above expected levels. A dietary history revealed adequate intakes of calcium and vitamin D and investigations for malabsorption, including a jejunal biopsy, were all normal. Daily urinary excretion of both calcium (2.25 mmol) and phosphate (15.5 mmol) was low.

In December 1966, at the age of 4 years, treatment was commenced with 5000 units of calciferol daily but progressive increases in dosage to 75 000 units daily were required to restore the serum Ca concentration to normal. For the following 4 years biochemical values remained within normal limits for her age, her growth chart closely followed the 50th centile and the radiological appearances returned to normal. Phenobarbitone therapy was discontinued in March 1970. In May 1973, the dose of vitamin D was reduced to 50 000 units daily and treatment discontinued in May 1974.

Four months later, serum Ca concentrations again fell below the normal range and the serum alkaline phosphatase rose from 183 to 330 i.u./l. During 1975 the serum Ca fell further to below 2.0 mmol/l and the phosphate rose to 2.8 mmol/l. By August 1976, sub-periosteal bone resorption was again evident (Fig. 2(a)). Serum 25 hydroxyvitamin D_3 (25 OHD $_3$) concentrations were persistently elevated with

FIG. 1. X-ray wrists, November, 1966, showing widened metaphyseal regions with cortical erosions.

values from 38.9 to over 70 $\mu\text{g/l}$ (upper limit normal 30 $\mu\text{g/l}$) while the serum $1,25(\text{OH})_2\text{D}_3$ level was low at 19 ng/l (normal 34 ng/l). Four values for serum PTH concentration were 4 $\mu\text{g/l}$ or higher (upper limit normal 1 $\mu\text{g/l}$). Radioisotope calcium absorption was poor (Table 1). A trans-iliac bone biopsy revealed 2 to 3 seams of osteoid covering most of the trabecular bone surface (Fig. 3(a)) but cellular details were obscured owing to a technical difficulty in staining.

In August 1976, treatment was commenced with 2 $\mu\text{g/day}$ of $1\alpha\text{OHD}_3$. Calcium absorption 4 months later showed a marked improvement (Table 1). The serum Ca rose to the lower limit of normal within 4 months but phosphate concentrations did not return to the normal range for a further 4 months (Fig. 4). Serum concentrations of PTH also returned to normal values at 8 months. The appearances of a further bone biopsy after 4 months of treatment were normal (Fig. 3(b)) and radiological bone resorption also disappeared (Fig. 2(b)).

After 6 months of therapy 200 units of bovine PTH of known efficacy were given i.v. to measure the urinary and serum cyclic adenosine monophosphate (AMP) response. Plasma cyclic AMP values did not rise after injection (Fig. 5). Values for urinary phosphate, calcium and cyclic AMP excretion expressed as a percentage of creatinine clearance did not significantly alter (Table 2).

Discussion

The initial radiological appearances of renal rickets did not improve on doses of calciferol which heal vitamin D-deficient rickets. The phenobarbitone used to treat the convulsions (presumed to be hypocalcaemic) may have increased the requirement for vitamin D (Pierides *et al.*, 1976) but both the amount required and subsequent events confirmed the presence of vitamin D resistance.

Vitamin D resistance was described by Albright, Drake and Sulkowitch in 1937 but the term was used to include conditions such as steatorrhoea, chronic renal failure and renal tubular abnormalities. In 1961 Prader, Illig and Heierli reported the syndrome of pseudo-vitamin D deficiency and further descriptions emphasized the need for high doses of vitamin D (Soriano *et al.*, 1966; Stoop, Schraagen and Tiddens, 1967; Dent, Friedman and Watson, 1968; Fanconi and Prader, 1969; Birtwell *et al.*, 1970; Salenius, Lindholm and Tierala, 1973). Arnaud *et al.* (1970) considered the abnormality to be due to defective synthesis of 25OHD_3 but Balsan and Garabedian (1972) and Cohamin, de Luca and Yendt (1973) demonstrated resistance also to 25OHD_3 . Fraser *et al.* (1973) showed that minute doses of $1,25(\text{OH})_2\text{D}_3$ were able to improve the bone lesions and postulated that a genetic defect in 25OHD_3 - 1α Ohydroxylase activity was present.

Elevated PTH levels in pseudo-vitamin D deficiency rickets fell in response to calcium infusion (Falls *et al.*, 1968) or treatment with vitamin D (Arnaud *et al.*, 1970). Fanconi and Prader (1969) were able to find a response to exogenous PTH only when the rickets were radiologically healed. However, Rosen and Finberg (1973) found a prompt response in urinary cyclic AMP to PTH in 3 patients with pseudo-vitamin D deficiency.

Although there are some features in common between renal osteodystrophy and pseudo-vitamin D deficiency, the low serum phosphate in the latter condition makes direct comparison impossible.

Sub-periosteal bone resorption and elevated PTH concentrations confirmed the presence of hyperparathyroidism in the present patient. The radiological appearances of primary hyperparathyroidism can simulate rickets (Fretheim and Gardborg, 1965). Lack of response to exogenous PTH indicates 'end-organ resistance' described by Albright *et al.*

FIG. 2. Before (a) and after (b) 4 months' treatment with $1,\alpha\text{-OHD}_3$.

(1942) as pseudo-hypoparathyroidism. Chase, Melson and Aurbach (1969) demonstrated a marked impairment of urinary cyclic AMP excretion in response to PTH in pseudohypoparathyroidism. Although anatomical abnormalities of bone are present, most cases of pseudo-hypoparathyroidism

TABLE 1. ^{45}Ca absorption test: serum concentrations as % of oral dose

Date	1 hr	2 hr	4 hr
20/07/76 . . . Before treatment	0	0.8	1.4
06/01/77 . . . After 4 months' treatment	0.35	1.59	1.76

show neither radiological defects in bone structure nor a raised serum alkaline phosphatase suggesting that the bones are also resistant to the action of PTH.

Singleton and Teng (1962) described a patient with biochemical features of pseudo-hypoparathyroidism but without the associated somatotype abnormalities. Radiographic evidence of bone re-

sorption was present. The following year Costello and Dent (1963), describing a similar case in which radiological healing was achieved with large doses of vitamin D, named the condition hypohyperparathyroidism.

In a further 5 cases (Bell, Gerard and Bartter, 1963; Allen, Millard and Nassim, 1968; Cohen and Vince, 1969; Frame *et al.*, 1972), histological examination of bone was performed before treatment. In 3 the appearances were compatible with osteitis fibrosa cystica but in the other 2 the predominant feature was an increase in osteoid. Only case 1 of Frame *et al.* (1972) failed to show radiological improvement in bone resorption on treatment with high doses of vitamin D, but in only 2 patients was the improvement confirmed by histology (Allen *et al.*, 1968; Bell *et al.*, 1963). The osteoid present in the present case was excessive both in volume and the extent of trabecular bone surface covered, while the radiological features were those of hyperparathyroidism.

FIG. 3. Iliac crest bone biopsy before (a) and after (b) 4 months' treatment with $1,\alpha\text{-OHD}_2$.

FIG. 4. Serum calcium, phosphate and PTH concentrations before and during treatment with $1,\alpha\text{-OHD}_3$.

FIG. 5. Parathyroid hormone stimulation test: plasma cyclic AMP response in patient compared with normal.

The lack of renal response to PTH in the presence of response by bone does not explain the hypocalcaemia in hypohyperparathyroidism. Ca absorption improved on therapy in 3 of the previously described patients with hypohyperparathyroidism similar to the response, in the present patient, to $1\alpha\text{OHD}_3$. PTH is recognized not to act directly on the intestine but it increases Ca absorption by stimulating the production of $1,25(\text{OH})_2\text{D}_3$ (Garabedian *et al.*, 1974; Ribovich and de Luca, 1976).

The low serum $1,25(\text{OH})_2\text{D}_3$ level in this patient could be due to either a failure of response to PTH

or a depression of synthesis secondary to raised phosphate concentrations (Tanaka and de Luca, 1973). In all 7 patients with hypohyperparathyroidism serum phosphate levels returned to normal on treatment with vitamin D or dihydrotachysterol. With $1\alpha\text{OHD}_3$ alone, serum phosphate and PTH concentrations progressively returned to the normal range preceded by a rise in serum Ca to the lower limit of normal.

$1,25(\text{OH})_2\text{D}_3$ is required by PTH for mobilization of Ca from bone (Garabedian *et al.*, 1974; Gerblich, Genuth and Haddad, 1977). Bone resorption in the present patient was less than might be expected with the concentrations of PTH similar to the resistance of bone to PTH in uraemia, attributed by Massry *et al.* (1976) to defective production of $1,25(\text{OH})_2\text{D}_3$.

Chase *et al.* (1969) concluded that the primary action of PTH on both skeletal and renal tissue was activation of adenylate cyclase AMP. Although lack of response to PTH could be explained by an abnormality in cyclic AMP synthesis, Sinha *et al.* (1976) demonstrated a normal adenylate cyclase response in the fat cells of patients with pseudohypoparathyroidism.

Features in common between hypohyperparathyroidism and renal osteodystrophy are elevated

TABLE 2. Parathyroid hormone stimulation test: urinary PO_4 , Ca and cAMP response

Time (hr)	PO_4 clearance/Ccr	Ca clearance/Ccr	cAMP excretion/Ccr
0-1	3.25	0.25	1.21
1-2	3.57	0.28	0.59
2-3	4.76	0.16	0.70
i.v. 200 i.u. $\longrightarrow$ bovine PTH			
3-3.5	7.17	0.56	1.19
3.5-4	5.8	0.17	0.54
4-5	9.22	0.27	0.93
5-6	8.05	0.22	0.79

serum phosphate, alkaline phosphatase and PTH concentrations, low serum calcium and $1,25(\text{OH})_2\text{D}_3$ concentrations, radiographic bone resorption with increased osteoid volume, absent renal and possibly impaired skeletal response to PTH and improvement with small doses of $1\alpha\text{OHD}_3$.

The pathogenesis of hypohyperparathyroidism is best explained by a defect in the renal receptor site for PTH. A common receptor site for both the effect on phosphate excretion and $1,25\text{-hydroxylase}$ activity would result in hyperphosphataemia and low serum levels of $1,25(\text{OH})_2\text{D}_3$ leading to hypocalcaemia. The resultant elevated PTH levels would have no effect on the kidney and, owing to the low $1,25(\text{OH})_2\text{D}_3$ concentrations, there would also be a relative resistance of the skeleton to PTH.

Damage to the receptor site for PTH from ischaemia, reflux nephropathy or other tubular lesions would also lead to the above features. Thus a single pathological lesion could explain the previous controversy over the development of the major features of renal osteodystrophy.

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