HYPOPARATHYROIDISM, HYPEROSTOSIS, NORMOPHOSPHATAEMIA AND THYROCALCITONIN. A POSSIBLE CASE OF HYPERTHYROCALCITONINISM

By
Jan A. Fischer, Ulrich Binswanger and Manuel Frey-Wettstein

ABSTRACT

A patient with idiopathic hypoparathyroidism, diffuse hyperostosis, hypocalcaemia and normophosphataemia is reported. The normal renal response to an injection of parathyroid extract rules out a resistance of the kidney to the parathyroid hormone (PTH). A normal phosphate excretion and a decreased tubular phosphate reabsorption have not been observed in the absence of PTH. They are probably the result of a normal or increased PTH secretion.

A calcium infusion test produces a significantly smaller decrease in the phosphate excretion as compared to normal controls and this can be interpreted as a moderate inhibition of the PTH secretion in the presence of an excess of thyrocalcitonin (TCT). The main signs in our patient, i.e. the hyperostosis, the decreased area of bone resorption, the absence of osteoclasts, and the hypocalcaemia can be demonstrated in the rat treated with TCT. We conclude that our patient probably has an increased TCT secretion in the presence of a normal or increased PTH secretion.

The diffuse hyperostosis has been reported in a third of the patients with idiopathic hypoparathyroidism and pseudohypoparathyroidism. We are tempted to believe that a long standing increased secretion of TCT has a marked effect on calcium uptake in bone, in addition to its inhibitory effect on bone resorption. In contrast, PTH primarily increases bone resorption with only a small effect on bone formation.

In this paper a patient is described with what is believed to be a fully developed syndrome related to an overproduction of thyrocalcitonin.
Thyrocalcitonin (TCT), which has been highly purified from the thyroid (Hirsch et al. 1964; Baghdiantz et al. 1964; Tenenhouse et al. 1965), lowers the serum calcium and inorganic phosphorus concentrations in man (Foster et al. 1966 a; Milhaud & Job 1966), and is present in the human thyroid (Milhaud et al. 1965 b).

TCT inhibits bone resorption (Aliapoulios et al. 1966 a) and increases the phosphate excretion through the kidney in the rat (Robinson et al. 1966).

Soon after Copp & Cameron (1961) introduced the hypocalcaemic principle, idiopathic hypoparathyroidism was related to an overproduction of TCT by Frame et al. (1962). A decreased secretion of parathyroid hormone (PTH), or an end organ resistance in bone, or in the kidney, or in both, was not ruled out. We think that our patient, whose main signs are a diffuse hyperostosis, a decreased area of bone resorption, a total absence of osteoclasts, cataracts, hypocalcaemia, normophosphataemia and a normal renal response to parathyroid extract, has idiopathic hypoparathyroidism with no evidence of a decreased parathyroid hormone secretion, but considerable evidence of an increased TCT secretion.

CASE HISTORY

We have no knowledge of the parents of our patient. His nine brothers and one sister could not be seen by us, but they do not suffer from tetany.

Our patient was born in 1926. He complained of tetany involving both arms and legs occurring on occasions since he was six years old. He never presented any symptoms of malabsorption or signs of kidney disease, nor had he had any thyroid operation. He was always euthyroid. Except for a low normal intelligence, with difficulties at school, and an inability to master a profession, he was never seriously ill. He never complained of bone pains, nor did he suffer from fractures.

He already presented the full picture of his disease in 1956, when he was seen at our hospital for the first time. He did not receive any therapy until 1957.

Physical examination revealed a then 31 year old white male patient, 167 cm in height, who weighed 78 kg. Chvostek and Trousseau signs were positive. His face was round and his fingers were clumsy. He had cataracts of both eyes, which were removed in 1960.

INVESTIGATIONS

Laboratory data were as follows, with a normal calcium and phosphate content in the diet (no non-absorbable alkali) in 1957: 13 calcium levels ranged from 6.4 to 8.0 mg/100 ml, with a mean value of 7.3 mg/100 ml. Serum protein levels were 7.0 and 7.3 g/100 ml. The pH in the arterial blood was 7.40. 12 serum inorganic phosphorus levels ranged from 3.2 to 4.4 mg/100 ml, with a mean
value of 3.7 mg/100 ml. 12 alkaline phosphatase levels ranged from 2.6 to 3.9 Bodansky units with a mean value of 3.3 Bodansky units (normal, 2–4 Bodansky units).

Sedimentation rate, 6 mm in one hour. Haemoglobin, 15.8 g/100 ml. White cell count, 6600/mm³, with a normal differential.

Kidney function: The 24-hour inorganic phosphorus clearance varied from 12 to 19 ml per minute. The calcium excretion varied from 15 to 50 mg in 24 hours. Urea, 30 mg/100ml. Specific gravity of the urine up to 1026, negative test for albumin and glucose, and nothing noteworthy in the sediment. Chromatography of the amino acids in the urine within normal limits. The Ellsworth-Howard test showed a 59 per cent increase in the phosphorus excretion. (P excretion from 2 to 4 p.m.: 20.5 mg/hour; intravenous injection of 340 USPU Lilly parathyroid extract (PTE) at 4 p.m.; P excretion from 4 to 6 p.m.: 48.4 mg/hour). Control subjects showed an increase from 40 to 152 per cent with the same extract. The diurnal variations were insignificant.

Significant radiological findings were a diffuse hyperostosis of the skull, the ribs, the vertebral bodies, the arms, the pelvis and the tibiae with coarse trabecular bone structure (Fig. 1 A and B). The hands showed subperiostal splitting in the distal phalanges (Fig. 1 C). No soft tissue calcification, no nephrocalcinosis, a possible calcification of the basal ganglia.

A surgical bone biopsy from the iliac crest revealed a coarse spongiosal structure with thick trabecules, no osteoclasts; the osteoid seams were of normal thinness (Fig. 2).

The teeth were small with small roots. A section revealed hypoplastic enamel. The dentine had apposition rings, some poorly, some normally calcified. The laminae durae were intact with normal thinness.

Thyroid: The patient was euthyroid. Basal metabolic rate, + 18 per cent. Protein-bound-iodine, 6.4 µg/100 ml. Cholesterol, 190 and 215 mg/100 ml. ¹³¹I uptake into the thyroids was within low normal limits (method of Joyet (1964)).

Our patient was subsequently treated in 1957 with small amounts of dihydrotachysterol, 2 mg per day for 22 days, when his serum calcium, which was regularly checked, only once rose to 10.5 mg/100 ml, and the therapy was discontinued. He again received 0.3–1.2 mg dihydrotachysterol per day in 1960–1961, and the serum calcium remained between 8.9 and 10.1 mg/100 ml. He had no therapy between 1961 and 1966, when he complained of dizziness, which could not be explained in a detailed vestibular and neurological examination.

Additional laboratory investigations in 1966 revealed the following results:

The serum calcium, inorganic phosphorus and alkaline phosphatases remained unchanged. 7 serum creatinine levels ranged from 0.8 to 1.1 mg/100 ml, with a mean value of 0.9 mg/100 ml. Creatinine clearances, 80 to 120 ml per minute.

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The 24-hour inorganic phosphorus clearances stayed at 13 to 23 ml per minute, with lowered tubular reabsorptions of 79, 83, 84 and 87 per cent. Phenolsulphonphthalein excretion, 73 per cent after 120 minutes (52 per cent after 35 minutes).

The Ellsworth-Howard test was repeated and showed a 250 per cent increase in the phosphate creatinine clearance ratio ($C_{p}/C_C$) after an intravenous injection of 200 USPU PTE as compared with a 45 to 880 per cent increase in normal subjects treated with the same extract (Table 1). The serum calcium remained unchanged in our patient and in the controls at 2, 4, 8, 12 and 24 hours after the injection of the PTE.

A calcium infusion test according to Kyle et al. (1962) showed a small depression of the phosphate clearance ($C_{P}$) of –11 and –33 per cent with unchanged creatinine clearances ($C_C$) (normal range –40 to –100 per cent).
**Fig. 1 B.**

Pelvis. Note the diffuse hyperostosis and the coarse trabecular bone structure.

**Fig. 1 C.**

Hands. Note the subperiostal splitting in the distal phalanges and the coarse trabecular structure of the spongiosa.
Fig. 2.
Microphotograph of a bone biopsy from the iliac crest. Note the coarse spongiosal structure, the diffuse hyperostosis, the osteoid seams with normal thickness, and the total absence of osteoclasts.

Table 1.
Results of the Ellsworth-Howard Test.

<table>
<thead>
<tr>
<th>Time a.m.</th>
<th>Urinary volume ml</th>
<th>C_p ml/min</th>
<th>C_cr ml/min</th>
<th>C_p/C_cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-7</td>
<td>45</td>
<td>10.1</td>
<td>115</td>
<td>0.088</td>
</tr>
<tr>
<td>7-8</td>
<td>24</td>
<td>5.0</td>
<td>86.5</td>
<td>0.058</td>
</tr>
<tr>
<td>8-9</td>
<td>160</td>
<td>7.2</td>
<td>123</td>
<td>0.059</td>
</tr>
<tr>
<td>(average)</td>
<td></td>
<td></td>
<td></td>
<td>0.068</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.v. injection of 200 USPU Parathyroid Extract (Lilly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-10</td>
<td>700</td>
<td>20.7</td>
<td>151</td>
<td>0.14</td>
</tr>
<tr>
<td>10-11</td>
<td>270</td>
<td>25.4</td>
<td>148</td>
<td>0.17</td>
</tr>
<tr>
<td>11-12</td>
<td>80</td>
<td>19.9</td>
<td>108</td>
<td>0.18</td>
</tr>
<tr>
<td>12-13</td>
<td>140</td>
<td>19.2</td>
<td>105</td>
<td>0.18</td>
</tr>
</tbody>
</table>

1st day: 8 to 9 a.m.: C_p 15.1 ml per minute, C_cr 110 ml per minute, 9 to 10 a.m.: C_p 13.5 ml per minute, C_cr 127 ml per minute; 9 to 12 p.m.: Infusion of 15 mg calcium per kg body weight as calcium gluconate. 2nd day: 8 to 9 a.m.: C_p 13.5 ml

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per minute, $C_{Cr} \ 110 \ \text{ml per minute}; 9\text{ to }10\ \text{a.m.: } C_P \ 9.0 \ \text{ml per minute, } C_{Cr} \ 132 \ \text{ml per minute. There was an increase in the serum calcium concentration after the calcium infusion from 7.9 to 10.4 \ \text{mg/100 ml.}}$

The intestinal absorption of $^{47}\text{Ca}$ performed according to modified method of Avioli et al. (1965) was lowered in our patient but not significantly, and we consider it to be in the low normal range (Fig. 3).

Malabsorption could be ruled out with a normal xylose excretion of 7.1 g in the urine for 5 hours after an oral dose of 25 g. The fat content of the three-day stool specimen was 6.5 g and the nitrogen content was 3.0 g. An oral glucose load of 50 g revealed a fasting blood sugar of 75 mg/100 ml, which increased to 172 mg/100 ml 30 minutes after ingestion, and decreased to 156 mg/100 ml at 60 minutes, 114 mg/100 ml at 90 minutes and 73 mg/100 ml at 120 minutes.

\[\text{Fig. 3.}\]

$^{47}\text{Ca}$ retention in the plasma after an oral load. $P =$ probability of chance difference between our patient (---) and four normal controls (——). n.s. = values not significantly different.

There was a normal acid secretion in the gastric juice (64 meq. per liter free HCl after a subcutaneous injection of 0.5 mg histamine).
The radiological findings were the same in 1966 as in 1957. A quantitative evaluation of a second surgical bone biopsy according to Schenk (1966) from the iliac crest showed a decreased surface area of resorption of 1.8 per cent (normal, 3–5 per cent) and no osteoclasts. The osteoid seams were of different thickness, some of them enlarged, some of them normal. The spongiosal structure was coarse, with thick trabecules. The subperiostal bone mass was enlarged.

Thyroid: The patient remained euthyroid. Basal metabolic rate, +18 per cent; protein-bound iodine, 6.0 μg/100 ml; cholesterol, 280 mg/100 ml. No antibodies against his thyroid could be detected (against thyroid microsomes and thyroglobulin).

Neurological examination: Supranuclear vestibular disturbance (doubtful), audiogram with a C5 depression, electroencephalogram with a mild cerebral hyperirritability with no change between 1957 and 1966, no other pathological changes.

DISCUSSION

The most significant radiological finding in our patient was a diffuse hyperostosis, verified in a bone biopsy of the iliac crest. The bone biopsy in addition showed a decreased area of bone resorption and no osteoclasts. Our patient suffered from a persistent hypocalcaemia with normophosphataemia. The phosphate clearance was in the normal range, the tubular phosphate reabsorption decreased. The intestinal 47Ca absorption was in the low normal range. The curves represent at least two exponential slopes, which suggests that not only the intestinal calcium absorption but the rapid exchange with the extracellular fluid and probably bone were in the normal range, too (Fig. 3.). Small doses of Vitamin D brought the serum calcium only once to 10.5 mg per 100 ml, which, together with the normal kidney function, rules out Vitamin D resistant rickets and vitamin D intoxication. Osteomalacia could be ruled out by the radiological appearance of the skeleton, the coarse trabecular bone structure, the absence of pseudofractures, the normal thickness of the osteoid seams in a bone biopsy, the normal alkaline phosphatase and the normal phosphate clearance.

At first sight the picture looks like idiopathic hypoparathyroidism. However, there are a number of inconsistencies. If, as postulated, there was no circulating parathyroid hormone (PTH), we would not expect a normal serum inorganic phosphorus concentration, a normal phosphate clearance and a decreased tubular phosphate reabsorption (Kyle et al. 1958). Idiopathic and pseudohypoparathyroidism, which are closely related, and normophosphataemia are rarely found together. Bromsky et al. (1958) in a review of 90 patients with idiopathic and pseudohypoparathyroidism do not mention a serum inorganic phosphorus concentration.
concentration below 3.96 mg/100 ml. However, Frame et al. (1962) found a normal serum phosphorus, and Bell et al. (1962) a serum phosphorus of 4.4 to 4.7 mg/100 ml in two patients with »hypoparathyroidism«, who both had hyperplastic parathyroids. PTH was actually measured in high concentration in the thyroid venous plasma of two patients with pseudohypoparathyroidism by Tashjian et al. (1966). An end organ resistance to the PTH could not only be ruled out in the kidney, as evidenced in our patient, where an intravenous injection of parathyroid extract produced an increase in the phosphate excretion of the same range as that in normal subjects. In bone, too, Bell et al. (1962) showed osteitis fibrosa cystica in a biopsy taken from the iliac crest. Two more patients of Kolb & Steinbach (1962) and Costello & Dent (1963) with »hypoparathyroidism« showed radiological evidence of hyperparathyroidism in their skeleton, which was more marked than in the distal phalanges of our patient, (Fig. 1 C).

From this we conclude that our patient and probably other patients with »hypoparathyroidism« have normal if not increased PTH secretion, due to the stimulation of the parathyroid glands by a lowered serum calcium as seen in secondary hyperparathyroidism.

The calcium infusion test according to Kyle et al. (1962) showed a small decrease in phosphate clearance (-11 and -33 per cent), significantly smaller than that found in normal subjects (-40 to -100 per cent) and similar to the results of Bell et al. (1962) (-14, -31 per cent) and Haas (1966) (-25 per cent) in pseudohypoparathyroidism.

Howard et al. (1953) even reported results in the hyperparathyroid range in patients with freshly removed or infarcted parathyroid adenomas (+30, +50 per cent). The calcium infusion test were performed four to eight days after the removal of the parathyroid adenomas, when most of the circulating PTH (half life between twenty and thirty minutes (Melick et al. 1965)) has disappeared from the plasma and the remaining parathyroids had not yet regenerated. In one patient, the serum calcium had fallen from 11.2 mg/100 ml before the operation to 9.6 mg/100 ml after the operation, with a rise in the serum phosphorus from 2.7 to 4.1 mg/100 ml; in the second patient the serum calcium had fallen from 20.2 to 8.2 mg/100 ml, when the test was performed. The tests were again repeated four weeks to six months after the removal of the parathyroid adenoma and the results were normal.

The results of the calcium infusion test can be interpreted as an inhibition of the PTH secretion in the presence of an excessive production of thyrocalcitonin (TCT). Evidence for an increased phosphorus excretion in the presence of TCT has not yet been obtained in man; it has, however, been shown in the rat (Robinson et al. 1966). The normal phosphate clearance and the normal inorganic phosphate concentration cannot be explained by a lack of PTH, but by the synergistic action of PTH and TCT on the renal phosphate excretion.
TCT lowers the serum calcium in nephrectomised animals (Hirsch et al. 1964). TCT inhibits bone resorption, as shown in acute experiments in the rat, in vitro in isolated calvariae (Aliapoulios et al. 1966a), and according to kinetic studies with $^{47}$Ca (Milhaud et al. 1965a). The number of osteoclasts is decreased as shown by Gaillard (1966) in isolated radii.

The coarse trabecular bone structure and the diffuse hyperostosis in our patient look similar in the rat treated for several weeks with TCT (Foster et al. 1966b). They suggest in addition to the inhibition of bone resorption by TCT a prolonged effect on bone formation, which requires further experimental proof. It is, however, in line with observations by Wase et al. (1966) who found an increased $^{46}$Ca content of rat tibiae perfused with TCT and $^{48}$Ca, and by MacIntyre & Parsons (1966) who perfused the isolated cat's tibia and observed an increased calcium uptake in the presence of TCT. More evidence is presented in reviews by Bronsky et al. (1958) and by Courvoisier (1959) who find radiological evidence of a diffuse hyperostosis in 24 per cent of 50 patients and in 40 per cent of 62 patients with idiopathic hypoparathyroidism. Similar changes are found in 31 per cent of 40 patients with pseudohypoparathyroidism (Bronsky et al. 1958). Courvoisier (1959) and Molinoff (1957) on the contrary mention diffuse hyperostosis in only one (doubtful) of six euthyroid patients suffering from hypoparathyroidism due to the removal of the parathyroids following a thyroidectomy for up to 36 years. Diffuse hyperostosis is rarely found in hyperparathyroidism, probably because of an increased TCT secretion in the presence of a high serum calcium concentration. The rare occurrence of diffuse hyperostosis in either hyperparathyroidism or hypoparathyroidism after a thyroidectomy makes it unlikely that increased or decreased PTH secretion is the primary cause of the considerably increased calcium uptake in bone. Osteopetrosis, increased bone formation and a low serum calcium and phosphorus are, however, found in grey-lethal-mice, who have a high number of parafollicular cells in the thyroids containing TCT (Pearse 1966; Walker 1966).

Final evidence awaits the isolation of increased TCT concentrations in the plasma and the thyroids of our patient. There is some evidence in two patients of Aliapoulios et al. (1966b) and of Tashjian et al. (1966), both with pseudohypoparathyroidism, where up to a hundred times increased TCT concentrations were measured in the thyroids.

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REFERENCES

Avioli L. V., McDonald J. E., Singer R. A. & Henneman P. H.: J. clin. Invest. 44
(1965) 897.
Bronsky D., Kushner D. S., Dubin A. & Snapper I.: Medicine (Baltimore) 37
(1958) 317.
Foster G. V., Joplin G. F., MacIntyre I., Melvin K. E. W. & Slack E.: Lancet 1
(1966 a) 107.
pean symposium on calcified tissues, Amsterdam (1966) 32.
Haas H. G. In: Knochenstoffwechsel und Parathyroideaerkrankungen, Stuttgart
1966 60.
MacIntyre I. & Parsons J. A.: J. Physiol. (Lond.) 183 (1966) 31P.
(1965 a) 815.
261 (1965 b) 4513.
Molinoff S.: Les modifications de squelette dans l'hypoparathyroidisme. Thèse, Genève
(1957).
(1966) 1158.
(1965) 818.
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