Normocalcaemic pseudohypoparathyroidism with unusual phenotype

J. M. GERTNER, S. TOMLINSON*, AND J. GONZALEZ-MACIAS†

From the Department of Human Metabolism, University College Hospital Medical School, London, and Department of Medicine, Middlesex Hospital, London

SUMMARY We describe a boy who presented at 4 years of age with radiological hyperparathyroidism, osteosclerosis, and necrosis of the femoral heads. Plasma biochemistry was normal but the parathyroid hormone (PTH) level was very high. He was deaf and had an unusual facies but did not have the phenotype of Albright's hereditary osteodystrophy. Plasma and urine cyclic AMP responses to bovine PTH were markedly subnormal. Vitamin D produced sustained hypercalcaemia and a fall in plasma phosphorus. After four hyperplastic parathyroid glands were removed he became hypocalcaemic and plasma phosphorus rose. After operation he remained unresponsive to exogenous PTH. We suggest that he had a form of pseudohypoparathyroidism without the phenotype of Albright's hereditary osteodystrophy and with some residual skeletal and renal responsiveness to PTH.

Hypoparathyroidism and states of resistance to parathyroid hormone (PTH) are among the causes of persistent hypocalcaemia in childhood. Most such patients have the round facies, short stature, and short metacarpals which constitute the phenotype of Albright's hereditary osteodystrophy. A few have a normal somatotype or even unusual tallness, as in the patient described by Costello and Dent (1963). Some patients with Albright's hereditary osteodystrophy and many of those with normal or tall body builds have radiological hyperparathyroidism. A classification of these unusual and complicated disorders has been given by Nusynowitz *et al.* (1976). We describe a boy with an unusual phenotype who showed many features of resistance to PTH and yet remained normocalcaemic for some years and who presented with the bony consequences of prolonged exposure to high levels of PTH.

Case report

A boy weighing 2.8 kg at birth, and with no significant family history, presented with failure to thrive and hypocalcaemia at age 10 weeks. The biochemical abnormalities persisted for a few months. Thereafter he was well apart from a profound

sensorineural deafness diagnosed at the age of one year. At 4½ years he was referred to the late Professor C. E. Dent because of osteosclerosis.

On examination he was of normal intelligence and stature. He was deaf and had an unusual round face (Fig. 1) with some proptosis. Plasma calcium was 2.25 mmol/l (9 mg/100 ml), magnesium 0.71 mmol/l (1.7 mg/100 ml), phosphorus 1.46 mmol/l (4.5 mg/100 ml), and alkaline phosphatase 24 KA units. Plasma urea and electrolytes were normal and haemoglobin was 11.2 g/dl. Plasma 25-hydroxyvitamin D (25-OHD) was 23 nmol/l (9 ng/ml) (normal

Fig. 1 Facial appearance of patient.

Received 23 August 1977

Present addresses: *Department of Chemical Pathology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX.

†Colegio Major Fonseca, Plaza Fonseca, Salamanca, Spain.

20–90; 8–36 ng/ml) and serum immunoreactive PTH was 7.0 ng/ml (normal up to 0.4 ng/ml at UCH). A 24-hour urine contained 0.075 mmol (3 mg/24 h) calcium, 5.1 mmol (0.16 mg/24 h) phosphorus, and 0.74 mmol (97 mg/24 h) total hydroxyproline. Faecal fat excretion was normal. Skeletal x-rays showed generalised osteosclerosis (Fig. 2) and erosions at the wrist, slight distortion of the right femoral head, and metacarpals of normal length.

Response to injected bovine PTH (bPTH) is described below (Table and Fig. 4). Because of progression of the lesion in the right femoral head and the similar appearance on the left we felt obliged

Fig. 2 X-ray of legs in patient, showing generalised increase in bone density.

to attempt to reduce the output of the parathyroid glands. He was first treated with vitamin D (2 mg/day for 5 days and 1 mg/day for another 5 days) in an attempt to suppress the parathyroids. This gave rise to sustained hypercalcaemia while plasma phosphorus fell. At this stage a second bPTH injection was given (see Table).

As medical suppression of the parathyroids had failed, a total parathyroidectomy (Mr G. Bunton) was carried out in April 1975. Four glands, all showing clear cell hyperplasia, were removed. After operation he developed severe hypocalcaemia and plasma phosphorus rose, persisting after plasma calcium was normalised with dihydrotachysterol. Alkaline phosphatase fell from 24–33 KA units preoperatively to 10–12 KA units after operation. Parathyroidectomy did not halt the progression of his hip disease and orthopaedic surgery for Perthe's disease was later carried out by Mr M. H. M. Harrison. Intravenous injections of bPTH (200 MRC units batch No 72/786 and 94% pure) were given on three occasions. Urinary cyclic AMP (cAMP) and phosphate excretion were measured each time while changes in plasma cAMP were monitored after the first and third injections. The methods used were as described by Tomlinson *et al.* (1974). The first injection (28.3.1974) was given before any treatment had been started; the second (11.1.1975) was given one month after he had received vitamin D and while he was still hypercalcaemic; and the third (8.5.1975) was given 3 weeks after total parathyroidectomy.

Results

Changes in plasma calcium and phosphorus over the period of vitamin D treatment and parathyroidectomy are shown in Fig. 3. Plasma cyclic AMP (cAMP) levels after intravenous injections of bPTH are shown in Fig. 4, which also shows the response to be expected in normal adults as no data are available for young children. Plasma cAMP response was markedly subnormal on both occasions.

Changes in urinary cAMP and phosphate excretion after the three injections of bPTH are given in the Table. The expected normal responses in

Table Urinary response to intravenous bovine PTH

Injection date	Plasma Ca (mmol/l)	Serum iPTH (pg/ml)	cAMP excretion		Phosphorus excretion	
			baseline	maximal	baseline	maximal
28 Mar. 1974	2.35	7000	1.1	1.6 (mmol/mmol creatinine)	2.9	5.6 (mmol/mmol creatinine)
11 Jan. 1975	2.98	3200	0.9	2.1 (mmol/min)	0.25	1.3 (mmol/min)
8 May 1975	2.35	Undetectable	0.51	1.54 (mmol/mmol creatinine)	0.1	0.5 (mmol/mmol creatinine)
Normal	2.23–2.53	0–400	20–200 fold rise		Variable	

Conversion: SI to traditional units Ca: 1 mmol/l $\approx$ 4 mg/100 ml).

Fig. 3 Changes in plasma biochemistry before and after total parathyroidectomy. Conversion: SI to traditional units—P: 1 mmol/l $\approx$ 3 mg/100 ml. 25-OHD: 1 nmol/l $\approx$ 0.4 ng/ml. DHT=dihydroxycholesterol.

cAMP excretion are also given. No figures for normal phosphaturic responses are quoted as these may be extremely variable.

Discussion

In 1942, Albright *et al.* described pseudohypoparathyroidism in patients who were hypocalcaemic, who had the phenotype of Albright's hereditary osteodystrophy, and who were resistant to PTH. Since then other patients with biochemical features of hypoparathyroidism and resistance to PTH have been reported (Costello and Dent 1963; Cohen and Vince, 1969; Frame and Parfitt, 1973). Many of these patients have a completely normal phenotype.

Our patient is of interest from several points of view. Firstly, the unusual facies and sensorineural deafness are anomalies not hitherto associated with resistance to PTH. Secondly, the finding of radiological osteosclerosis distinguishes him from other children with resistance to PTH, although hyperparathyroidism with a high plasma phosphate is

often stated to be the cause of osteosclerosis in uraemia. Thirdly, his ability to maintain a normal plasma calcium until parathyroidectomy, and the development of hypocalcaemia 6 days after operation show that resistance to PTH, at least at the skeletal level, was far from complete. On the other hand the normocalcaemia in the face of very high levels of serum immunoreactive PTH and in the presence of hyperparathyroid skeletal changes indicates some degree of resistance to the calcium-raising action of the hormone.

Lastly, the responses to vitamin D and later to parathyroidectomy require explanation. Treatment with nontoxic quantities of vitamin D produced hypercalcaemia. Plasma calcium remained high for 4 months until parathyroidectomy, despite the fact that his 25-OHD levels had returned to normal within one month of a 10-day course of vitamin D. At the same time vitamin D treatment led to a sustained fall in plasma phosphate presumably by restoring some degree of renal tubular sensitivity to endogenous PTH.

Fig. 4 Plasma cyclic AMP response to two intravenous bovine PTH injections.

Restoration of the calcium-raising and phosphaturic capabilities of PTH by vitamin D treatment in pseudohypoparathyroidism has been described (Stogmann and Fischer, 1975). This was regarded as evidence that the disease was due to occupation of receptor sites by an abnormal form of PTH. In our case the abnormal cAMP response to injected PTH persisted even after total parathyroidectomy. We suggest that this observation shows that the primary cause of PTH resistance lies at a renal tubular level rather than in an abnormality of PTH.

The patient's tubular unresponsiveness to PTH may have been exacerbated by a deficiency of 1:25 dihydroxyvitamin D (1:25 diOHD), shown in pseudohypoparathyroidism by Drezner *et al.* (1976). The administration of vitamin D and the consequent fall in plasma phosphorus could have led to a new equilibrium with higher levels of 1:25 diOHD and less resistance to PTH (Fig. 5).

Although our patient resembles patients classified by Nusynowitz *et al.* (1976) as 'hypohyperparathyroidism, renal resistance, and skeletal responsiveness to PTH with normal somatic features', he differs in some important respects. His case supports the view that there are many separate disease states which share a degree of resistance to PTH.

Fig. 5 Suggested inter-relationship of plasma and urinary phosphorus, sensitivity to PTH, and activation of vitamin D in patient. 1:25 diOHD=1:25 dihydroxy-vitamin D.

We are grateful to Dr Jean Clark of Birmingham Children's Hospital for referring the patient and granting permission to publish his case; to the late Professor C. E. Dent, Dr J. L. H. O'Riordan, and Dr D. B. Brenton for encouragement and advice; and to the nursing and biochemical staff of Ward 1/1 at UCH. S.T. was in receipt of an MRC Clinical Research Fellowship.

References

- Albright, F., Burnett, C. H., Smith, P. H., and Parson, W. (1942). Pseudo-hypoparathyroidism: an example of 'Seabright-Bantam syndrome'. *Endocrinology*, **30**, 922-932.
- Cohen, R. D., and Vince, F. P. (1969). Pseudohypoparathyroidism with raised alkaline phosphatase. *Archives of Disease in Childhood*, **44**, 96-101.
- Costello, J. M., and Dent, C. E. (1963). Hypo-hyperparathyroidism. *Archives of Disease in Childhood*, **38**, 397-407.
- Drezner, M. K., Neelon, F. A., Haussler, M., McPherson, H. T., and Lebowitz, H. E. (1976). 1:25 dihydroxy-cholecalciferol deficiency: the probable cause of hypocalcemia and metabolic bone disease in pseudohypoparathyroidism. *Clinical Endocrinology and Metabolism*, **42**, 621-628.
- Frame, B., and Parfitt, A. M. (1973). The syndromes of parathyroid hormone resistance. *Clinical Aspects of Metabolic Bone Disease*, pp. 454-464. Ed. by B. Frame, A. M. Parfitt, and H. Duncan. Excerpta Medica, Amsterdam.
- Nusynowitz, M. L., Frame, B., and Kolb, F. O. (1976). The spectrum of the hypoparathyroid states: a classification based on physiologic principles. *Medicine*, **55**, 105-119.
- Stogmann, W., and Fischer, J. A. (1975). Pseudohypoparathyroidism. Disappearance of the resistance to parathyroid extract during treatment with vitamin D. *American Journal of Medicine*, **59**, 141-144.
- Tomlinson, S., Barling, P. M., Albano, J. D. M., Brown, B. L., and O'Riordan, J. L. H. (1974). The effects of exogenous parathyroid hormone on plasma and urinary adenosine 3'5' cyclic monophosphate in man. *Clinical Science and Molecular Medicine*, **47**, 481-492.

Correspondence to Dr J. M. Gertner, Section of Pediatric Endocrinology, Department of Pediatrics, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510, USA.