Hypo-hyperparathyroidism

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In 1963 Costello and Dent described a patient with a low serum calcium and a high serum inorganic phosphorus but who had radiological evidence of hyperparathyroidism. They attributed this paradox to the simultaneous development of hypo- and hyperparathyroidism. This paper reports the findings in a similar patient, and the aetiology is discussed.

Case History

J.D., born in 1953, was the first child of a mother who had had a normal pregnancy. Both parents were well, there was no consanguinity, and their serum calcium, phosphorus, and alkaline phosphatase were normal. Two brothers died from congenital heart disease. One sister is alive and well. J.D.'s birthweight was 3.8 kg. He was breast-fed for 4 months and given supplementary vitamins. His early development was normal and he walked at 17 months. At the age of 6 his mother noticed that he was walking badly; at 9 his gait became worse, he tired easily, and noticed occasional pains in the arms and legs. There was no history suggestive of tetany and no evidence that growth had slowed up recently. At the age of 10 he was admitted to the Royal National Orthopaedic Hospital for investigation.

On examination he was a tall healthy-looking boy with a waddling gait, height 146 cm., within the 90th centile (Fig. 1). The upper segment measured 75 cm., the lower segment 71 cm., and the span 146 cm. He weighed 37 kg. There was slight swelling of the costochondral junctions but no detectable swelling of the metaphyses of the long bones. There was no corneal calcification. The sternum was slightly depressed and there was a short systolic murmur. The blood pressure was 120/70 mm. Hg. Chvostek's and Trousseau's signs were negative.

Serum calcium, 8.4 mg./100 ml. (normal 9.5-10.5); phosphorus, 6.5 mg./100 ml. (normal 4-5); alkaline phosphatase, 22.4 King-Armstrong units; sodium 134 mEq/l.; chloride, 97 mEq/l.; potassium, 4.0 mEq/l.; urea, 29 mg./100 ml. Plasma CO₂-combining power, 24.9 mEq/l. Serum protein, 6.4% (albumin 4.3, globulin 2.1); electrophoresis, normal. Urine, no protein or cells, sterile. Urinary chromatogram,

normal. Creatinine clearance, 134.5 ml./min. Urinary 17-ketosteroids, 2.0 mg./24 hr.; 17-hydroxycorticosteroids, 8.2 mg./24 hr. Faecal fat, 4.1 g./24 hr. FIGLU excretion, 5.6 mg. in 8 hours (15 g. histidine load). ECG, EMG, chest x-ray, normal. Intensity duration curves and nerve conduction, normal. In summary, the outstanding findings were a low serum calcium and a high phosphorus.

X-rays (Fig. 2-5) showed that the metaphyses were unusually dense and irregular, and that some of the epiphyseal plates were widened. These changes were more marked at the shoulder and hip than at the wrist and knee.

FIG. 1.—Growth curve. Growth is steady corresponding approximately to the 90th centile.

Received October 27, 1967.

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FIG. 2.—(a) Before April 1963 and (b) after August 1966 treatment. Before treatment the epiphysial plate of the humerus is widened though it shows some calcification centrally. The metaphysis is dense and irregular. The metaphysial area of the acromium is frayed. After treatment the humerus has returned to normal, apart from a slight residual density of the metaphysis: the acromium is still irregular.

Cortical erosions were present in several phalanges (Fig. 6) and in the lateral aspect of the lower end of the left radius (Fig. 4). Cysts (localized areas of increased radiolucency) were present in the upper end of the tibia (Fig. 5), third metacarpal of the right hand, and the proximal phalanx of the fifth finger of the left hand (Fig. 6). The costochondral junctions were widened. The dorsal and lumbar vertebrae showed alternating bands of increased and decreased density, and the distal ends of the clavicles were irregular. There was no bowing of the long bones. The skull was normal. Thus the radiological changes of hyperparathyroidism were present, and some of the metaphyses were abnormal.

Calcium, phosphorus, and nitrogen balance studies were carried out according to the method of Reifenstein, Albright, and Wells (1945); a detailed description of the method is given by Walker and Collins (1963). Results are shown in Fig. 7. The patient was not easy to balance and the results were irregular, but 5 control periods each of 6 days showed a positive calcium balance of 50–500 mg./24 hr., with a low urinary calcium of approximately 40 mg./day. Phosphorus and nitrogen balances were also positive. After treatment with vitamin D as dihydrotachysterol (DHT) 0.5 mg. daily, there was a consistently positive calcium balance of approximately 500 mg./24 hours. DHT was increased to 1.0 mg. and subsequently to 1.5 mg. per day. Urinary calcium rose to 90 mg./24 hr. and the dose of DHT was reduced to 0.5 mg./day.

Bone biopsy from the iliac crest before treatment showed excess osteoid. Using the method of measure-

ment described by Sissons, Holley, and Heighway (1967), 45% of the bone surface was covered with osteoid (normal 8–15%) and bone reabsorption was at the upper limit of normal. There was no marrow fibrosis. The biopsy included part of the growth cartilage of the iliac crest. The area of bone formation was well ordered, but the growth cartilage was thin, compared with normal controls of the same age, suggesting that growth was less active than normal. A subsequent biopsy from the proximal tibial metaphysis after treatment of 6 weeks showed that only 20% of the bone surface was covered with osteoid and that reabsorption was also reduced. The growth cartilage was not included in the second biopsy. Comparison of figures for surface activity are complicated by the different sites of the two biopsies, but the marked difference in bone reabsorption and formation is probably the result of treatment.

The patient's symptoms rapidly improved after treatment with DHT. He has been followed up for 3½ years and has been entirely free of symptoms. His growth has been normal and has remained within the 90th centile (Fig. 1). There was no growth spurt following the beginning of treatment. X-rays showed disappearance of the erosions and cysts, and the affected metaphyses have become less abnormal (Fig. 2–3). Slight swelling of the costochondral junctions has persisted. The serum calcium rose to normal and has remained within normal limits (Fig. 8). The phosphorus fell and though occasional high levels of up to 5.9 mg./100 ml. have been recorded, the majority of readings have been within normal limits. The alkaline phosphatase

FIG. 3.—Pelvis (a) before June 1963 and (b) after August 1966 treatment. Before treatment the depth of the epiphyseal plates at the upper ends of the femora are increased, and the metaphyses are widened and irregular. After treatment the femora are normal.

tase rose to 30 King-Armstrong units before treatment and then fell; subsequently it has varied between 15 and 28 units. DHT was increased from 0.5 mg. daily to 0.75 mg. daily in October 1966, but the alkaline phosphatase has remained within the same range, and is probably normal for a boy of this age (Clark and Beck, 1950).

Discussion

Clinically and radiologically our patient is strikingly similar to the girl described by Costello and Dent. Both had the following features in common: (i) a healthy infancy and the development of an abnormal gait at the age of 6; (ii) satisfactory growth within the 90th centile; (iii) a low serum

calcium and a high phosphorus; (iv) x-rays showing cortical erosions, bone cysts, and similar metaphyseal changes; (v) a positive calcium balance immediately before treatment and a good response to treatment with a form of vitamin D.

A similar case has been described by Fanconi, Heinrick, and Prader (1964), and the case of Nordio, Bertolotti, and Gatti (1965) may possibly have suffered from the same condition. The two cases described by Kolb and Steinbach (1962) had similar radiological and biochemical findings, but also had changes suggesting pseudo-hypoparathyroidism.

Costello and Dent considered that a low serum

FIG. 4.—Left wrist before treatment May 1963. There is cortical erosion of the lateral side of the distal end of the radius. Note that the unevenness of the outline of the metaphysis is slight compared with the changes at the shoulder.

FIG. 5.—Right knee before treatment (June 1963). There is slight irregularity and increased density of the metaphyses of the lower femur and upper tibia. Areas of increased radiolucency are present in the cortex of the tibial shaft. The epiphysal plates are not widened.

FIG. 6.—Fifth finger of left hand (a) before (May 1963) and (b) after (May 1964) treatment. Before treatment there are cortical erosions in the phalanges and areas of increased radiolucency in the proximal and distal phalanges. The metaphyses are normal, and the epiphysal plates are not widened.

calcium and a raised phosphorus, together with radiological evidence of hyperparathyroidism, were due to the simultaneous development of hypo- and hyperparathyroidism. They postulated that the parathyroid secretes two hormones, one that raises the serum calcium and lowers the phosphorus, and another that causes osteitis fibrosa and raises the alkaline phosphatase. They suggested that in their patient the first hormone was deficient and the second produced in excess. Alternatively, there was a single hormone acting on the calcium and phosphorus and on the bones, with a circulating substance antagonizing its action on the calcium and phosphorus. However, the simultaneous development of hypo- and hyperparathyroidism as an explanation of the findings in these patients presents several difficulties. First, the diagnosis of hyperparathyroidism rests on the radiological findings only. Cortical erosions and bone cysts are characteristic of hyperparathyroidism but are not an absolute proof of its existence. Secondly, assuming that hyperparathyroidism is present, Costello and Dent's theory does not explain its cause. Hyperparathyroidism may be primary or may be secondary to a condition that tends to lower the serum calcium. The response to a moderate dose of vitamin D and the subsequent course of the disease make primary hyperparathyroidism unlikely. No condition likely to cause secondary hyperparathyroidism was detected in either patient, but there may have been some unknown condition causing a low serum calcium, to which the parathyroids responded. Finally, the bone biopsy showed an excess of osteoid which is unusual in either hypo- or hyperparathyroidism, unless of course the hyperparathyroidism is secondary to rickets.

It is possible that these patients did suffer from an unusual form of rickets with secondary hyperparathyroidism. This would explain the marked increase of osteoid found in the bone biopsy. However, the appearance of the biopsy was not conclusive; there was no disturbance of the growth cartilage, as might be expected in rickets and there was no clinical evidence to support this diagnosis. The radiological appearance of the metaphyses superficially resembles rickets, but differs in several ways. The increased density is not seen in untreated rickets. The widening of the metaphyses is less than it is in rickets and the area of increased radiolucency in the region of the epiphyseal plate is less marked. The widening of the costochondral junctions is suggestive of rickets, but this did not completely disappear after treatment with vitamin D. Finally, the changes were more marked proximally around the shoulder and hip joints than

FIG. 7.—Balance data. Intake is recorded downwards from the zero line and output upwards from this. Each block is divided into faecal output below, and urinary output above. The blocks represent 6 days' intake and output. The space between the zero line and the top of the blocks represents the positive balance. Before treatment the patient was in positive calcium, phosphorus, and nitrogen balance. He was given vitamin D and the dietary intake was reduced. After treatment with vitamin D there is an increase in the amount of calcium retained.

distally, whereas in rickets the distal epiphyses are more severely affected.

If rickets were the underlying cause it is difficult to explain how this could have developed. Both our patient and the patient described by Costello and Dent had an adequate diet, and neither had evidence of malabsorption or renal failure. Further-

FIG. 8.—Serum calcium, phosphorus, and alkaline phosphatase. Before treatment the calcium is low and the phosphorus and alkaline phosphatase are raised. The calcium and subsequently the phosphorus return to normal after treatment with vitamin D. The alkaline phosphatase falls.

more, patients with rickets are usually stunted, and both these patients were well developed and above average height. A possible explanation is that the patients suffered from a relative deficiency of vitamin D. This could have been due to a high demand during a rapid period of growth, combined with a defect of vitamin D absorption or resistance to vitamin D. Increased demand alone would not be sufficient cause. Although both children were tall and were growing fast, their growth rate was not abnormal, and rickets is not a feature of rapidly growing children on an English diet. Malabsorption, if present, must have been slight or specific for vitamin D, since routine tests of gastro-intestinal function were normal. An increased level of growth hormone during a period of rapid growth could raise the serum phosphorus, but is unlikely to cause such high levels as were found in these patients.

The x-rays in our patient showed increased density of the metaphyses. Doyle (1966) has

suggested that the increased bone density seen in some patients with hyperparathyroidism is due to excess calcitonin. This could account for the low serum calcium, but would also cause a low phosphorus which was not found in our patient.

The interpretation of the metaphysal changes in our patient is difficult. Costello and Dent considered that the very similar metaphysal changes in their patient were probably due to cortical erosions; these have been observed in the region of the metaphyses in a case of primary hyperparathyroidism (Dent and Hodson, 1954). In our opinion the metaphysal changes in our patient are not the same as in the patient of Dent and Hodson, and are probably not due to cortical erosions. However, changes similar to those seen in our patient have been described in children between the ages of 11 and 17 years with primary hyperparathyroidism (Mimpriss and Butler, 1933-34; Anspach and Clifton, 1939; Shallow and Fry, 1948; Wood, George, and Robinson, 1958; Lloyd, Aitkin, and Ferrier,

1965). Therefore, both cortical erosions and metaphysial changes, superficially resembling rickets, may be manifestations of hyperparathyroidism in childhood.

The simultaneous development of hypo- and hyperparathyroidism is an attractive theory and we can offer no satisfactory alternative. However, we feel that the matter needs further investigation and that at present 'hypo-hyperparathyroidism' should be used as a descriptive term for patients with the biochemical changes of hypoparathyroidism together with the radiological changes of hyperparathyroidism.

Summary

The findings in a child of 10 who presented with an abnormal gait are described. X-rays showed abnormal metaphyses, multiple cysts, and cortical erosions. The serum calcium was low and the phosphorus raised. Administration of dihydroxycholesterol led to recovery.

We are grateful to Miss A. Hilb and to the Sister and staff of the Metabolic Ward for the balance studies, to Dr. P. Byers for the report on the bone biopsy, and to Professor C. E. Dent, Dr. F. H. Doyle, and Dr. J. A. Jenkins for advice.

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