Normocalcaemic primary hyperparathyroidism with osteitis fibrosa

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THE diagnosis of primary hyperparathyroidism has been classically based upon the demonstration of high plasma calcium and low plasma phosphorus concentrations and an excessive urinary excretion of calcium. In recent years, however, it has become recognized that patients with primary hyperparathyroidism may present with plasma calcium concentrations that are within the normal range (George *et al.*, 1965; Nichols & Flanagan, 1967; Wills *et al.*, 1969). In these reports the patients had all presented with a long history of recurrent renal calculi and excessive urinary excretion of calcium. The only previously reported cases of normocalcaemic primary hyperparathyroidism with osteitis fibrosa, of which we are aware, were recorded by Mather (1953) and Eisenberg & Gotch (1968). We report here a third case of normocalcaemic primary hyperparathyroidism with overt osteitis fibrosa.

Case history

M.W.H. This 40-year-old woman was first seen as an out-patient in August 1961. She was complaining at that time of low back pain of 6 months' duration, associated with aching pains in the shoulders, knees and thighs. X-ray examination of her sacro-iliac joints at that time showed no abnormality. She was seen again 1 month later, in the out-patient department, and in view of mild chest pains a chest X-ray was taken. This revealed possible fractures of the left sixth and seventh ribs posteriorly, and the left fourth and eighth ribs anteriorly. It was also noted that the anterior end of the ninth rib had disappeared, and the findings were considered to be consistent with either multiple myelomatosis or carcinomatosis. In view of these radiological findings she was admitted to hospital. The only other possible significant points in her history were mild constipation, thirst and polyuria.

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On admission her plasma calcium concentration was 9.9 mg/100 ml with a phosphorus concentration of 2.5 mg/100 ml, total protein 7.2 g/100 ml, plasma magnesium 3.2 mg/100 ml, blood urea 46 mg/100 ml and an alkaline phosphatase of 80 KA units/100 ml. Protein electrophoresis showed a normal pattern with no evidence of an abnormal band in the globulin fraction, nor was any protein detected in her urine. Six days after admission her plasma calcium concentration was 10.0 mg/100 ml with a phosphorus concentration of 2.6 mg/100 ml. The blood urea was 46 mg/100 ml, plasma sodium 138, potassium 4.0, chloride 109, bicarbonate 20 mEq/l, total serum proteins 7.0 g/100 ml, alkaline phosphatase 82 KA units/100 ml. She was shown at this time to have hypercalciuria with a urinary calcium/creatinine ratio of 0.64 at a urinary creatinine concentration of 26 mg/100 ml (Wills, 1969). Urea clearance was 58% normal. There was a diminution in the ability of the kidneys to concentrate urine, the maximum specific gravity reached was 1007, in four separate urine specimens collected at 1-hourly intervals after overnight fasting and fluid restriction. Further X-ray examination at this time revealed an abnormal bony texture of the skull, changes in both the mandible and hands, which were reported as being characteristic of hyperparathyroidism, and there was well marked nephrocalcinosis in both kidneys.

Operation. In view of the radiological findings she was submitted to neck exploration (October 1961). At operation (Mr R. V. Cooke) a parathyroid chief cell adenoma measuring 3.5 × 2.5 × 2 cm and weighing 5 g was removed. After operation both her plasma calcium and magnesium concentrations fell and by the fifth postoperative day she was both hypocalcaemic and hypomagnesaemic. At this time her Chovstek sign was strongly positive and she was started on calciferol 50,000 units/day with calcium gluconate 10 g/day. These were continued for 6 weeks, by which time both her plasma calcium and magnesium concentrations had returned to the normal range. The full details of her pre- and post-operative plasma biochemical findings are shown in

FIG. 1. M.W.H. ♀, 40 years. Plasma values before and following parathyroidectomy.

Fig. 1. This patient has now been followed for a total of 9 years since the parathyroidectomy and has remained well without any symptoms. Two years after operation radiological bone survey showed that her bone density had returned to normal. The areas of subcortical resorption in her phalanges had been refilled, a cystic lesion which had been previously demonstrated in the lower left radius had been replaced by sclerotic bone, and the lamina dura had reappeared in her mandible. Her blood urea concentration has remained in the range of 40–45 mg/100 ml. and there has been no further evidence of any deterioration in her renal function as assessed by urea clearance. Routine follow-up investigations in August 1970 revealed the presence of an iron deficiency anaemia with a haemoglobin of 8.7 g/100 ml. At the same time the serum folate was found to be reduced at 2.5 µg/ml (normal 4–12) and this raised the possibility of an underlying malabsorptive state. However, a 5-day faecal fat collection was normal (3.1 g of fat being excreted/day) and 25.2% of a 5 g oral dose of xylose was excreted within 5 hr (normal greater than 23%).

Discussion

We consider that the findings in this patient of

marked radiological bone disease which disappeared after parathyroidectomy are consistent with a diagnosis of normocalcaemic primary hyperparathyroidism with osteitis fibrosa. In 1968 Davies, Dent & Watson described the condition of tertiary hyperparathyroidism which they considered to be the end phase of secondary hyperparathyroidism during which one or more of the glands developed into an autonomous adenoma. In the twelve cases that they reported there was a long history either of a malabsorption syndrome or of chronic renal glomerular failure. In the case reported here there was evidence of mild renal disease with a slightly elevated blood urea and a reduced urea clearance. There has been, however, no deterioration in these indices during the 9 years of follow-up and it seems unlikely that this degree of renal involvement could have led to the parathyroid disorder. The recent findings of normal fat excretion and a normal xylose tolerance test suggest that any significant degree of malabsorption was unlikely. The known causes of tertiary hyperparathyroidism have therefore been excluded in this case, thus justifying the use of the term primary hyperparathyroidism. If the primary disorder in this case was the over-production of parathyroid hormone then the finding of a normal

total calcium with overt bone disease is hard to explain. The history of constipation, nocturia and polyuria, albeit mild, do suggest hypercalcaemia and it may be that the ionized calcium was elevated without the total calcium being raised.

There are many points of similarity in the patient reported here with the case reported by Mather in 1953. His patient was a 39-year-old woman who had developed diffuse aching pains in the lower limbs and back 6 months before admission to hospital. His patient was shown to have evidence of osteitis fibrosa both by skeletal X-ray survey and sternal bone biopsy. Four values for the serum calcium concentration during the 3 months prior to the removal of a Wasserhelle cell parathyroid adenoma were all within the normal range. Studies of intestinal function were not, however, reported. Mather's patient is of considerable interest, not only because of the short duration of symptoms but also because, as far as we are aware, it is the only other reported case that was persistently normocalcaemic until the time of operation.

The importance of the detection of cases of normocalcaemic primary hyperparathyroidism is stressed by the report of Nichols & Flanagan (1967). They reported six patients, with this syndrome, which represented 37% of all the patients in whom they had made a diagnosis of parathyroid hyperfunction in a 3-year period. Similarly the occurrence of eleven

cases with this syndrome seen in one centre (George *et al.*, 1965; Wills *et al.*, 1969) over a 9-year period suggests a high incidence among patients with recurrent renal calculi. The patient reported here, together with that of Mather (1953), suggest that normocalcaemia in primary hyperparathyroidism may also be present in some patients with osteitis fibrosa.

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Axial osteomalacia

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In 1961 Frame and his co-workers reported three patients who presented with mild back discomfort and in whom radiological studies showed a coarsening and distortion of the trabecular pattern of the cervical vertebrae, lumbar vertebrae, ribs and pelvis. Iliac crest biopsy in each of these patients showed widening of the osteoid seams and because all the known causes of osteomalacia were excluded, the disorder was called 'atypical osteomalacia involving the axial skeleton'. With the exception of a slightly raised plasma alkaline phosphatase in one subject, plasma calcium, phosphate and alkaline phosphatase values were normal in all patients; 24-hr urinary calcium

estimations were also normal. Only two other examples of this syndrome have been reported (Arnstein, Frame & Frost, 1967).

We are reporting a sixth patient who has had this disorder for 18 years and, therefore, gives some indication of the natural history of the disease. The results of calcium, phosphorus and nitrogen balance studies are documented; the effect of prolonged therapy with vitamin D on the symptoms, radiological picture and bone biopsy histology are reported. The possibility that the disorder is not due to any abnormal metabolism of calcium, phosphorus, alkaline phosphatase and vitamin D is discussed.