Presentation of primary hyperparathyroidism to a general medical unit

P. SHERIDAN

M.B., M.R.C.P.

Department of Medicine, Leeds (St James's) University Hospital, Leeds LS9 7TF

Summary

Four patients with hyperparathyroidism who presented in atypical or uncommon ways to a general medical unit are described.

The unusual features are discussed and the value of modern procedures for localization of a parathyroid tumour is confirmed.

Introduction

Hyperparathyroidism presents most commonly in relation to renal stones and nephrocalcinosis. Manifestations of bone disease comprise the next most frequent mode of presentation. Together these two clinical pictures account for 75% of patients with primary and tertiary hyperparathyroidism. Incidental discovery, psychiatric disorders and symptoms directly due to hypercalcaemia are presentations in a further 15% of patients (Watson, 1975). Thus, other forms of presentation such as acute pancreatitis, myopathy and symptoms of osteomalacia masking primary or tertiary hyperparathyroidism are uncommon.

Four patients are described who presented in unusual ways to a general medical unit, and the value of selective venous sampling in localization of the site of the parathyroid tumour is confirmed.

Case reports

Patient 1

A 59-year-old man attended with a story of recurrent rigors and jaundice over 2 years. He was never seen in an attack and no abnormal physical signs were evident. Liver function tests were normal. Intravenous cholangiography revealed no extra-hepatic biliary disease and liver biopsy showed very mild, non-specific increase in cellularity. Plain X-ray of the abdomen showed a probable staghorn calculus on the left, and excretion urography confirmed this. The serum calcium ranged from 2.9 to 3.1 mmol/l (normal 2.25-2.60 mmol/l) and the serum phos-

phorus was 0.63-0.7 mmol/l (normal 0.8-1.3 mmol/l). Alkaline phosphatase was normal. Skeletal survey showed no radiological evidence of bone

FIG. 1. Diagram of neck veins in the four patients showing sites and value of serum immunoreactive parathormone levels (normal <1.0 ng/ml). Black dots indicate sites of parathyroid tumours.

disease and urinary hydroxyproline was normal. Urinary calcium was 14 mmol/24 hr (normal 1.25–10.0 mmol/24 hr) and urinary phosphorus 45 mmol/24 hr (normal 13–39 mmol/24 hr). Cortisone acetate, 150 mg daily for 2 weeks, failed to reduce the elevated levels of serum calcium. Selective sampling of neck veins for serum immunoreactive parathormone (PTH) gave a level of 5.7 ng/ml from the left inferior thyroid vein (Fig. 1a). Levels from other sites gave values between 0.52 and 0.91 ng/ml (normal <1.0 ng/ml). Venography showed no identifiable lesions.

At exploration, a parathyroid tumour in the left lower pole of the thyroid was found and excised. The other parathyroids appeared normal. Histology of the tumour was that of a benign chief cell adenoma. Serum calcium levels have remained normal after 2 years follow-up and the staghorn calculus has been removed. Jaundice and rigors have not recurred.

Patient 2

A 20-year-old Indian man presented to a surgical unit with acute epigastric pain and vomiting. There was epigastric tenderness, rigidity and guarding. Serum amylase was 3000 u./dl (normal 38–162 u./dl) and acute pancreatitis was diagnosed. Serum calcium at this time was 3.3 mmol/l, serum phosphorus was 0.59 mmol/l and alkaline phosphatase was 16.3

KAu. (normal 4–13 KAu.). He was treated conservatively and transferred to the medical unit. Over the next 2 weeks, the serum calcium level gradually rose to 4.8 mmol/l. Calcium excretion was 0.109 mmol/l of glomerular filtrate after an overnight fast and this was well in the hyperparathyroid range for the serum calcium level (4.6 mmol/l) the expected calcium excretion for this serum calcium level being greater than 0.40 mmol/l of glomerular filtrate (Peacock, Robertson and Nordin, 1969). Likewise, the phosphorus excretion at 0.28 mmol/l of glomerular filtrate was in the hyperparathyroid range for the serum phosphorus level (1.0 mmol/l), the expected phosphorus excretion for this level of serum phosphorus being less than 0.25 mmol/l of glomerular filtrate (Nordin and Bulusu, 1968). X-rays of hands showed changes in bone texture and sub-periosteal erosions in the phalanges compatible with hyperparathyroidism. Venography showed a blush in the region of the right lower pole of the thyroid (Fig. 2). A parathyroid subtraction scan using radioiodine and selenomethionine also indicated a tumour in the right lower pole of the thyroid. The inferior thyroid veins could not be catheterized owing to anomalous drainage. Samples from other sites in the neck were taken for PTH but no level was markedly higher than the others, although most were above normal (Fig. 1b). However, exploration of the neck revealed

FIG. 2. Neck venogram in patient 2 showing a tumour blush indicated by the arrow in the region of the right lower lobe of the thyroid.

parathyroid tumour in the region of the right lower pole of the thyroid as suggested by venography and scanning. The tumour was excised and histology showed a benign chief cell adenoma. Six months later, he is well with normal serum calcium levels.

Patient 3

A 34-year-old Indian woman presented with acute upper left chest pain. Associated features were back-ache, weakness, anorexia and weight loss for six weeks. Chest X-ray showed pathological fractures of the right and left upper ribs. Lateral skull X-ray showed a 'peppered' appearance and X-rays of ribs, spine and pelvis showed altered trabecular pattern with open reticulation and unsharp margins. X-rays of hands showed loss of differentiation of cortex and medulla of metacarpals and phalanges with loss of bone density, open trabecular pattern and subperiosteal erosions. All these changes are consistent with hyperparathyroidism.

Serum calcium was normal on several occasions and serum phosphorus was 0.51–0.99 mmol/l. Alkaline phosphatase was 60–110 KAu. Bone biopsy showed changes of both osteomalacia and hyperparathyroidism. Serum B_{12} , serum iron and serum and red cell folate levels were below normal. Small bowel studies including radiology, biopsy and faecal fat revealed nothing to suggest a malabsorption syndrome and renal function was normal.

It was concluded that this patient was most likely suffering from osteomalacia of the type seen in Asian immigrants, with secondary hyperparathyroidism. In view of the possibility of concomitant primary hyperparathyroidism (Dent, Jones and Mullan, 1975), treatment with ergocalciferol was given in doses that were not excessive (80 000 u. intramuscularly daily for ten days and 1000 u. weekly thereafter). She became hypercalcaemic (2.71 mmol/l) 5 months later. At this time a PTH level from a peripheral vein was elevated at 2.3 ng/ml and X-ray of the pelvis showed the appearance of a brown cyst. It was then considered that the patient had masked primary or tertiary hyperparathyroidism and neck vein sampling was carried out. Levels of PTH exceeding 10 ng/ml were obtained from the left superior and left middle thyroid veins and a level of 10 ng/ml from a common inferior thyroid vein. PTH levels from elsewhere in the neck did not differ from that in the inferior vena cava (Fig. 1c). Venography showed no lesion. At surgery, a parathyroid tumour was found in the left upper pole of the thyroid. The other parathyroids were not identified. Histology of the tumour showed a benign adenoma.

Patient 4

A 51-year-old woman presented to a general surgical unit with acute cholecystitis. Radiology

showed gall stones and cholecystectomy was carried out. At this time the serum calcium was 2.8 mmol/l, serum phosphorus 0.99 mmol/l and alkaline phosphatase 18 KAu. She was transferred to the medical unit and hypercalcaemia was confirmed. Urinary calcium was elevated at 12.1 mmol/24 hr. Skeletal survey showed no changes of hyperparathyroidism. Excretion urography showed a poorly functioning, hydronephrotic right kidney because of a stone at the pelvic-ureteric junction. Serum PTH from a peripheral vein was 2.15 ng/ml. Selective neck vein sampling revealed a PTH level of 10.0 ng/ml from the right inferior thyroid vein, levels elsewhere not exceeding 3.0 ng/ml (Fig. 1d). Venography revealed no lesion.

At exploration, a parathyroid tumour was removed from the region of the right lower pole of the thyroid. The other parathyroids appeared normal. Histology showed a benign tumour consisting predominantly of water clear (wasserhelle) cells. The right hydronephrosis was treated by nephrectomy. At follow-up 6 months later the serum calcium levels had remained normal.

Discussion

These four patients were consecutively encountered cases of hyperparathyroidism during a 2-year period on this medical unit and in this sense were unselected. The cause of the recurrent jaundice and rigors in the first patient was never determined. Certainly, there was no evidence of primary disorder of the hepato-biliary system. It is possible that recurrent urinary infections associated with the renal calculus were responsible. Extrahepatic infections may cause jaundice (Eley, Hargreaves and Lambert, 1965; Neale *et al.*, 1966) and, especially in childhood, urinary tract infection may do so (Gorter and Lignac, 1928; Arthur and Wilson, 1967). However, this patient was never seen in an attack and urine cultures were negative when he was under investigation.

The second patient presented with acute pancreatitis, an uncommon though well recognized manner in which primary hyperparathyroidism may present (Cope *et al.*, 1957). It has recently been suggested that the incidence of pancreatitis related to primary hyperparathyroidism might be underestimated in the United Kingdom (Rosin, 1976). In this respect it is worth re-emphasizing that an elevated serum calcium may be reduced to normal values during acute pancreatitis and only when the pancreatitis has settled down does the elevated calcium level become apparent. Thus, in this second patient, although the serum calcium level was elevated during the acute illness, it rose further when the pancreatitis had improved.

The third patient presented with bone disease but

had normal serum calcium levels. She was nutritionally deficient but there was no evidence of intestinal or renal disease. She was therefore thought to be suffering from osteomalacia of the type which is becoming increasingly recognized in Asian immigrants (Dunnigan *et al.*, 1962; Swan and Cooke, 1971) and which is due to vitamin D deficiency the reasons for which are not fully understood (Preece *et al.*, 1973). Although secondary hyperparathyroidism was suspected, it soon became apparent that her parathyroid function was autonomous. The question arises as to whether she was suffering from masked tertiary hyperparathyroidism (Dent *et al.*, 1975) or masked primary hyperparathyroidism (Keynes and Hockaday, 1975). The finding of a parathyroid adenoma, the other parathyroids being unidentifiable, suggests masked primary hyperparathyroidism since in tertiary disease the other glands usually show hyperplasia (Roth, 1968).

The fourth patient was admitted with gall bladder disease and it has been suggested that cholelithiasis is a common complication of primary hyperparathyroidism (Cope, 1960; Selle *et al.*, 1972). However, a recent study from Sweden has not supported this view (Christensson and Einarsson, 1977). Although the hypercalcaemia was an incidental finding, it became obvious that an unsuspected, severe renal complication was present.

Selective venous sampling from neck veins has been well authenticated as a useful procedure in diagnosis and localization of parathyroid tumours (Potts *et al.*, 1971; O'Riordan, Kendall and Woodhead, 1971) and the present authors found it to be so. In patients one, three and four, the site of the tumour was clearly indicated. For the second patient, the procedure was less useful because of anomalous drainage of the inferior thyroid veins although the samples obtained suggested that the tumour was neither on the left nor in the right upper pole (Fig. 2b). However, localization is achieved on the basis of relative difference rather than absolute values of PTH (Shimkin *et al.*, 1972b). Fortunately, a 'tumour blush' was demonstrated on venography and parathyroid scan showed increased take-up at a site which proved to be that of the tumour. Venography in the other three patients failed to reveal radiological evidence of a tumour. Only rarely does forceful retrograde venous injection outline a parathyroid adenoma (Shimkin *et al.*, 1972a) and it was fortunate that the technique proved useful in the one patient in whom venous sampling did not indicate the site of the tumour.

None of these patients presented in any of the common ways that this condition can present. Although two had renal stone disease and one had major bone disease, these manifestations were not suggested by the presenting features.

Acknowledgments

I am grateful to Professor M. S. Losowsky for permission to describe these patients and for constructive criticism. I acknowledge the radiological expertise of Professor M. S. F. McLachlan, Dr P. Robinson and Dr H. Herlinger and the surgical skill of Professor G. Giles in the management of them. Dr R. B. Payne was a constant source of biochemical wisdom. The PTH estimations were carried out by the supra-regional assay service.

I am also grateful to Dr S. I. Jacobs, Dr J. A. Dosset and Dr E. B. Allibone for the histological assessments of the excised parathyroid glands. Finally, I am grateful to the Department of Medical Illustration, St James's Hospital, Leeds, for help with the figures.

References

- ARTHUR, A.B. & WILSON, B.D.R. (1967) Urinary infection presenting with jaundice. *British Medical Journal*, **1**, 539.
- CHRISTENSSON, T. & EINARSSON, K. (1977) Cholelithiasis in subjects with hypercalcaemia and primary hyperparathyroidism detected in a health screening. *Gut*, **18**, 543.
- COPE, O., CULLVER, P.J., MIXTER, C.G. & NARDI, C.A. (1957) Pancreatitis. A diagnostic clue to hyperparathyroidism. *Annals of Surgery*, **145**, 857.
- COPE, O. (1960) Hyperparathyroidism: diagnosis and management. *American Journal of Surgery*, **99**, 394.
- DENT, C.E., JONES, P.E. & MULLAN, D.P. (1975) Masked primary (or tertiary) hyperparathyroidism. *Lancet*, **i**, 1161.
- DUNNIGAN, M.G., PATON, J.P.J., HAASE, S., MCNICOL, G.W., GARDNER, M.D. & SMITH, D.M. (1962) Late rickets and osteomalacia in the Pakistani community in Glasgow. *Scottish Medical Journal*, **7**, 159.
- ELEY, A., HARGREAVES, T. & LAMBERT, H.P. (1965) Jaundice in severe infections. *British Medical Journal*, **2**, 75.
- GORTER, E. & LIGNAC, G.O.E. (1928) On pyelitis complicated by jaundice. *Archives of Disease in Childhood*, **3**, 232.
- KEYNES, W.M. & HOCKADAY, T.D.R. (1975) Masked primary (or tertiary) hyperparathyroidism. *Lancet*, **ii**, 503.
- NEALE, G., CAUGHEY, D.E., MOLLIN, D.L. & BOOTH, C.C. (1966) Effects of intrahepatic and extrahepatic infection on liver function. *British Medical Journal*, **1**, 382.
- NORDIN, B.E.C. & BULUSU, L. (1968) A modified index of phosphate excretion. *Postgraduate Medical Journal*, **44**, 93.
- O'RIORDAN, J.L.H., KENDALL, B.E. & WOODHEAD, J.S. (1971) Pre-operative localisation of parathyroid tumours. *Lancet*, **ii**, 1172.
- PEACOCK, M., ROBERTSON, W.G. & NORDIN, B.E.C. (1969) Relation between serum and urinary calcium with particular reference to parathyroid activity. *Lancet*, **i**, 384.
- POTTS, J.T., MURRAY, T.M., PEACOCK, M., NIALI, H.D., TREGGAR, G.W., KEUTMANN, H.T., POWELL, D. & DEFTOS, L.J. (1971) Parathyroid hormone: sequence, synthesis, immunoassay studies. *American Journal of Medicine*, **50**, 639.
- PREECE, M.A., FORD, J.A., MCINTOSH, W.B., DUNNIGAN, M.G., TOMLINSON, S. & O'RIORDAN, J.L.H. (1973) Vitamin-D deficiency among Asian immigrants to Britain. *Lancet*, **i**, 907.
- ROSIN, R.D. (1976) Pancreatitis and hyperparathyroidism. *Postgraduate Medical Journal*, **52**, 95.
- ROTH, S.I. (1968) quoted by Keynes, W.M. and Hockaday, T.D.R. (1975).
- SELLE, J.G., ALTEMEIER, W.A., FULLEN, W.D. & GOLD-SMITH, R.E. (1972) Cholelithiasis in hyperparathyroidism. A neglected manifestation. *Archives of Surgery*, **105**, 369.

- SHIMKIN, P.M., DOPPMAN, J.L., POWELL, D., MARX, S.J. & KETCHAM, A.S. (1972a) Demonstration of parathyroid adenomas by retrograde thyroid venography. *Radiology*, **103**, 63.
- SHIMKIN, P.M., POWELL, D., DOPPMAN, J.L., MARX, S.J., PEARSON, K.D., WELLS, S. & KETCHAM, A.S. (1972b) Parathyroid venous sampling. *Radiology*, **104**, 571.
- SWAN, C.H.J. & COOKE, W.T. (1971) Nutritional osteomalacia in immigrants in an urban community. *Lancet*, **ii**, 456.
- WATSON, L. (1975) Disorders of the parathyroid glands. *Medicine* (2nd series), **8**, 341.