Primary hyperparathyroidism associated with primary hyperaldosteronism

J. B. Ferriss1, J. J. Brown, A. M. M. Cumming, R. Fraser, A. F. Lever, M. Peacock2 and J. I. S. Robertson

Abstract. Two patients with both primary hyperparathyroidism and primary hyperaldosteronism are described. Each presented with high blood pressure and a history of renal calculi. Mild hypercalcaemia was associated with raised plasma parathyroid hormone concentrations and a parathyroid adenoma was excised from each. Both patients also had hypokalaemia, hyperaldosteronism and low plasma renin concentrations. Quadric analysis, adrenal vein plasma aldosterone concentrations, adrenal venography and CT scanning all suggested an adrenal adenoma in each patient. This suspicion was confirmed at operation in one patient; the other patient was unfit for adrenal surgery but her blood pressure and plasma potassium concentration have remained within the normal range during prolonged treatment with either spironolactone or amiloride. Because of this unusual association a search was made for parathyroid hormone excess in patients with primary hyperaldosteronism and for aldosterone excess in primary hyperparathyroidism. None was found.

Several endocrine abnormalities occasionally occur together in the same patient. In the Multiple Endocrine Neoplasia Syndrome Type 1, primary hyperparathyroidism is associated with pituitary and pancreatic adenomas (Wermer 1963; Johnson et al. 1967; Steiner et al. 1968) and occasionally with adenomas or hyperplasia of the adrenal cortex (Wermer 1963; Ballard et al. 1964; Boey et al. 1975). Hyperparathyroidism can be associated with medullary carcinoma of the thyroid, phaeochromocytoma and Cushing’s syndrome – Multiple Endocrine Neoplasia Syndrome Type 2 (Steiner et al. 1968; Melvin et al. 1972). Finally, primary hyperaldosteronism and acromegaly can be associated in some patients (Dluhy & Williams 1969; Strauch et al. 1972). In this report we describe in 2 patients, another association – primary hyperaldosteronism with primary hyperparathyroidism. This unusual combination prompted us to look retrospectively at plasma calcium and inorganic phosphate values in 25 previously studied patients with primary hyperaldosteronism and to search prospectively for evidence of aldosterone excess in newly presenting patients (8) with primary hyperparathyroidism. These findings are summarized.

Methods

Plasma for biochemical measurements was drawn between 09.00 and 10.00 h, from fasting patients who had remained supine overnight. Forearm exercise was not allowed during venepuncture, as this may falsely raise plasma potassium (Brown et al. 1970) but use of a tourniquet was not systematically avoided, except in patients in whom hyperparathyroidism was suspected or known.

Enzyme-kinetic techniques were used for measurement of plasma total renin (Brown et al. 1964) and active renin (Millar et al. 1980) concentrations. Plasma angiotensin II (Düsterdieck & McElwee 1971), aldosterone (Fraser et al. 1973) and parathyroid hormone (Peacock 1976) were measured by radioimmunoassay. Plasma calcium, inor-
### Table 1

Plasma variables while untreated and after parathyroidectomy in 2 patients with primary hyperparathyroidism and primary hyperaldosteronism. Measurements of renin, angiotensin II and aldosterone were made while patients received fixed normal intake of sodium (137–150 mmol/day) and potassium (52–68 mmol/day).

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<th>Phosphate N 0.8–1.5 mmol/l</th>
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<th>Sodium N 135–145 mmol/l</th>
<th>Potassium N 3.5–5.2 mmol/l</th>
<th>Urea N 2.5–7.5 mmol/l</th>
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N = normal range. * International standard renin.
ganic phosphate, total proteins, albumin, sodium, potassium, urea and creatinine were measured by multichannel auto-analyser. The statistical technique of quadric analysis has been described elsewhere (Ferriss et al. 1970, 1978a; other statistical assessments were made using group and paired t-tests and by Pearson correlation analysis.

Results

Two patients with primary hyperparathyroidism and primary hyperaldosteronism

Patient 1. This 34-year-old female presented with headaches and nocturia. Hypertension had been diagnosed 3 years before and she also gave a history of renal calculi 8 and 6 years previously. There was no family history of hypertension or of endocrine disease. Untreated blood pressure ranged from 180/120 to 194/132 mmHg. She was obese and there was slight diffuse enlargement of the thyroid gland, but clinical examination was otherwise normal; in particular the optic fundi appeared normal.

Investigations indicated primary hyperparathyroidism (Table 1). Intermittent hypercalcaemia was associated with raised plasma parathyroid hormone concentrations (2.6 and 3.1 ng/ml; normal 0.5–1.5 ng/ml), while plasma proteins and urea were normal. There was also evidence of primary hyperaldosteronism, hypokalaemia being associated with intermittently raised plasma aldosterone values and subnormal plasma renin concentration. Urinary normetadrenaline, fasting blood glucose and skull X-ray were normal.

At neck exploration (Mr. Douglas Clark) a single 8 mm diameter parathyroid adenoma was removed. Histologically this consisted predominantly of chief cells surrounded by a rim of normal tissue. Following operation plasma calcium returned to normal, but blood pressure remained high (180/116–190/120 mmHg while untreated) and the biochemical stigmata of primary hyperaldosteronism persisted (Table 1).

During treatment with spironolactone (400 mg daily) blood pressure fell to a mean of 151/101 mmHg. When changed to amiloride (40 mg daily) because of spironolactone-induced amenorrhoea, mean blood pressure was 155/111 mmHg. Hypokalaemia was corrected during each treatment. However, hypertension and hypokalaemia were not reversed by dexamethasone 2 mg daily for 14 days.

Adrenal vein plasma aldosterone concentrations suggested a right-sided adenoma (right side 218 and 329 ng/100 ml; left side 94 and 125 ng/100 ml; inferior vena cava 19 ng/100 ml). Appearances on adrenal venography (Dr. J. K. Davidson) also favoured a right-sided adrenal adenoma and on adrenal CT scanning a 12 mm lesion was seen in the right gland. Quadric analysis of the data before parathyroidectomy also suggested the presence of an adrenocortical adenoma (likelihood ratio 2:1). At laparotomy (Sir Andrew Watt Kay and Mr. S. G. MacPherson) a 12 mm diameter golden yellow tumour was found in the right adrenal gland which also contained a number of smaller nodules. There was no palpable abnormality in the left gland. On histological examination the tumour consisted of large clear lipid-laden cells of zona fasciculata type, with considerable cellular pleomorphism and occasional nuclear inclusions. Aldosterone was extracted from the lesion which also produced aldosterone on tissue culture, confirming a diagnosis of adenoma (Prof. A. M. Neville). After operation the blood pressure remained high, measurements in the outpatient department over the next 3 months ranging from 162/104 to 182/128 mmHg. Biochemical review then revealed a consistently normal plasma potassium (range 3.8–4.3 mmol/l) and normal plasma aldosterone concentration (8 ng/100 ml), although the plasma concentrations of both active renin (7–10 µU/ml) and angiotensin II (5–11 pg/ml) remained at the lowermost ends of the respective normal ranges. Hypotensive treatment with atenolol 100 mg daily was then started and recently the patient has remained well, but with a slightly high blood pressure (166/106 mmHg).

Patient 2. When first seen by us this 42-year-old female gave an 8 year history of high blood pressure and had passed a renal calculus 7 years previously. Her mother also had high blood pressure but there was no family history of endocrine disease. Her blood pressure ranged between 160/100 and 200/140 mmHg while untreated but examination, including inspection of the optic fundi, was otherwise normal.

There was biochemical evidence of both primary hyperparathyroidism and primary hyperaldosteronism (Table 1). Hypercalcaemia, although intermittent, was associated with unequivocally raised parathyroid hormone concentrations (4.1 and 5.0 ng/ml: normal 0.5–1.5 ng/ml), while plasma pro-
teins and urea were normal. Hypokalaemia (2.8–3.3 mmol/l) was associated with consistently raised plasma aldosterone values and low total plasma renin concentrations. Urinary normetadrenaline and fasting blood glucose were normal. The high blood pressure and hypokalaemia were not corrected by dexamethasone (2 mg daily for 14 days) but during treatment with spironolactone (150 mg daily) blood pressure ranged from 110/70 to 120/72 mmHg. When subsequently changed to amiloride 40 mg daily blood pressure varied between 120/80 and 130/82 mmHg. Serum potassium concentration increased into the normal range during treatment with each drug. At neck exploration (Mr. Douglas Clark) a single 6 mm diameter parathyroid adenoma was removed. Histologically this consisted predominantly of chief cells surrounded by a thin rim of compressed normal cells. Plasma concentrations of calcium and parathyroid hormone returned to normal thereafter (Table 1). However, high blood pressure (160/110–171/112 mmHg) and the biochemical features of primary hyperaldosteronism persisted (Table 1).

Quadric analysis strongly predicted the presence of an adenoma (likelihood ratio 35:1) which was located in the left adrenal by adrenal venography, adrenal CT scans and adrenal vein plasma aldosterone concentrations (left side 60 and 55 ng/100 ml; right side 30 and 20 ng/100 ml; inferior vena cava 19 ng/100 ml).

Because the patient subsequently developed subternal pain related to exercise and since the high blood pressure and hypokalaemia are well controlled by amiloride, surgical exploration of her adrenal glands has not been undertaken.

Search for primary hyperparathyroidism in patients with primary aldosterone excess

Evidence of primary hyperparathyroidism was sought retrospectively in 25 previous patients with primary hyperaldosteronism (each with high BP, raised plasma aldosterone and low plasma renin concentrations). Fourteen of the 15 patients in this series treated surgically had an adrenocortical adenoma (ages 33–60 years; 13 females); 7 of the remaining 10 patients were predicted to have an adrenocortical adenoma by quadric analysis (Ferriss et al. 1970), while the remaining 3 were predicted to belong to the non-adenoma group. For the purposes of this analysis, patients with proved and predicted adenoma have been grouped together (n = 21), while proved and predicted non-adenoma patients have also been grouped (n = 4).

No evidence in favour of hyperparathyroidism was revealed in either group, plasma calcium was slightly low, 2.0–2.2 mmol/l, in 8 adenoma and in 2 non-adenoma cases and was within the normal range of 2.2–2.6 mmol/l in each of the remaining patients; plasma phosphate was slightly subnormal in 4 patients (3 adenoma) and normal (0.8–1.5 mmol/l) in the remainder.

Search for primary aldosterone excess in patients with primary hyperparathyroidism

In a further 8 newly presenting patients with primary hyperparathyroidism (age 23–68 years, 6 females), concurrent plasma measurements of total renin concentration, angiotensin II, aldosterone, calcium and phosphate were made. All had hypercalcaemia with a concurrently raised plasma parathyroid hormone concentration and a parathyroid adenoma was subsequently excised in each of the 4 patients subjected to operation. Mean outpatient diastolic blood pressure was greater than 100 mmHg in 5 cases. In 2 of these 8 patients, total plasma renin concentration was slightly below normal (35 and 39 μU/ml, respectively; normal 44–182 μU/ml); all other renin values and all angiotensin II and aldosterone concentrations were within their normal ranges. Plasma calcium and phosphate each failed to correlate with either renin, angiotensin II or aldosterone values. Plasma concentrations of renin, angiotensin II and aldosterone did not correlate with either systolic or diastolic blood pressure but there was a significant relationship between plasma calcium and the outpatient diastolic blood pressure (r = 0.71, P < 0.03).

Discussion

We have found references to 5 other patients in whom the syndromes of primary aldosteronism and primary hyperparathyroidism occurred together. Madhavan et al. (1970) referred to a patient who was found to harbour an aldosterone-secreting adenoma several years after surgical correction of primary hyperparathyroidism. One of the patients with aldosterone-producing adenomas described by Novak et al. (1972) subsequently had a parathyroid adenoma removed. The acromegalic pa-
tients reported by Strauch et al. (1979) included one with both an aldosterone-producing adenoma and hyperparathyroidism. Fertig et al. (1980) studied a patient with primary hyperparathyroidism who had an adrenocortical adenoma removed 10 years previously when she presented with high blood pressure and hypokalaemia. Measurements of the renin-angiotensin-aldosterone system in this patient were not recorded. Recently Hellman et al. (1980) described a patient presenting with both primary hyperparathyroidism and an aldosterone-secreting adenoma, each biochemically and pathologically confirmed.

The multiple endocrine neoplasia syndrome (type 1) is sometimes associated with adrenocortical adenomas or hyperplasia (Wermer 1963; Ballard et al. 1964; Boey et al. 1975). Such adenomas are usually non-functioning, but Cushing's syndrome has occasionally been associated with adrenocortical hyperplasia. Our findings suggest that primary hyperaldosteronism may be another variant of the syndrome. If so, the scarcity of references to this association suggests that it is uncommon; in support of this view we failed to reveal any evidence in favour of primary hyperparathyroidism in a retrospective review of 25 patients with primary hyperaldosteronism (14 with adenoma excised, a further 7 with adenoma predicted) or of primary hyperaldosteronism in 8 patients with primary hyperparathyroidism (adenoma excised in each of the 4 cases operated upon).

Alternative explanations for the association of these two uncommon disorders include the possibility that the combination is a chance finding, that primary hyperparathyroidism induces primary hyperaldosteronism or vice versa. While we are not aware of any obvious functional interrelationships, high blood pressure has been reported in 20–50% of patients with primary hyperparathyroidism (Hellstrom et al. 1958; Madhavan et al. 1970; Rosenthal & Roy 1972; Malette et al. 1974) and it has been suggested elsewhere that idiopathic hyperaldosteronism might result from prolonged hypertension of another cause (Davies et al. 1979; Padfield et al. 1981). However, the adrenal glands of patients with idiopathic hyperaldosteronism have either diffuse zona glomerulosa hyperplasia or normal appearances (Ferriss et al. 1970) while one of the cases reported here had an adrenocortical adenoma excised and in the other, the evidence strongly favours the presence of an adenoma.

Barkan et al. (1980) described a patient with primary hyperparathyroidism in whom the biochemical evidence of primary hyperaldosteronism disappeared after removal of a parathyroid adenoma. They postulated that prolonged hypercalcaemia produced changes in the renin-angiotensin-aldosterone system which mimicked primary hyperaldosteronism. However, in both of the cases presented here, the biochemical indications of primary hyperaldosteronism remained after the parathyroid operations. Moreover, in our group of 8 further patients with primary hyperparathyroidism we did not find evidence of primary hyperaldosteronism. Brinton et al. (1975) reported elevated plasma renin activity in 4 of 7 hypertensive patients with primary hyperparathyroidism.

The failure of blood pressure to return to normal after adrenal surgery in patient 1 is not unexpected since a similar sequence has been reported in almost 50% of patients after removal of an aldosterone secreting adenoma (Ferriss et al. 1975, 1978b).

While renal potassium wasting, leading to hypokalaemia, can occur with hypercalcaemia of various causes (Howard et al. 1959; Ferris et al. 1962; Sanderson 1967; Aldinger & Samaan 1977), hypokalaemia in a patient with primary hyperparathyroidism, particularly if associated with hypertension, should alert the clinician to the possibility of associated primary aldosterone excess. Similarly, patients with primary hyperaldosteronism should be screened for evidence of primary hyperparathyroidism.

Acknowledgments

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References


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