Coexistence of pheochromocytoma, adrenal adenoma and hypokalemia

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A 56-year-old woman had a 22-year history of hypertension. Investigation showed hypokalemia and kaliuresis without pronounced suppression of plasma renin activity or elevation of urinary aldosterone excretion. There was biochemical evidence of catecholamine metabolite excess but the usual clinical features of pheochromocytoma were absent. Laparotomy revealed a pheochromocytoma and adrenal adenoma in the right adrenal gland. Excision of the tumours was followed by resolution of the hypertension and metabolic abnormalities.

Une femme de 56 ans a présenté une anamnèse hypertensive de 22 ans. L'examen a montré une hypokaliémie avec kaliurèse sans dépression marquée de l'activité rénine plasmatique ou élévation de l'excrétion urinaire de l'aldostérone. Il y avait bien les signes biochimiques d'un excès de métabolites des catécholamines, mais les manifestations cliniques habituelles du phéochromocytome étaient absentes. La laparotomie a révélé un phéochromocytome et un adénome de la surrénale droite. L'excision des tumeurs a été suivie de la disparition de l'hypertension et des anomalies métaboliques.

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Patients with pheochromocytoma do not demonstrate abnormalities of adrenocortical function or electrolyte disturbance. There are, however, case reports of hypokalemia associated with pheochromocytoma.[1,2] The cause of hypokalemia has not been documented but at least one case has been reported with hyperaldosteronism.[2] There are also case reports of an adrenal adenoma with Cushing's syndrome and pheochromocytoma.[3,4] In the report by Mathison and Waterhouse[3] the Cushing's syndrome resolved after removal of the adrenal adenoma, which contained cortical and medullary cells. Williams and colleagues[5] described a patient with a pheochromocytoma, an adrenal adenoma and clinical evidence of adrenocortical hyperfunction — hirsutism, acne and glucose intolerance; these abnormalities resolved after excision of the tumour. In the case reported by Cope and associates[6] there was no clinical evidence of adrenocortical hyperfunction, but hyperfunction was inferred from atrophy of the contralateral adrenal gland. None of the patients with both pheochromocytoma and adrenocortical hyperfunction had evidence of hypokalemia. The patient referred to in the following report, however, had a pheochromocytoma with hypokalemia and kaliuresis.

Case report

First admission

A 56-year-old woman was admitted to St. Paul's Hospital for investigation of hypertension, which had first been diagnosed 22 years before in the immediate postpartum period of the patient's only pregnancy. Although the hypertension persisted, therapy was not started until 9 years later.

After 5 years of antihypertensive therapy hypermetabolism was suspected and the basal metabolic rate was +57%; the protein-bound iodine value was 5.1 μg/dl. Nocturnal episodes of nausea, perspiration and tachycardia occurred 7 years later and were attributed to cardiac insufficiency; they resolved.

Hypokalemia had first been noted 3 months before admission, the following

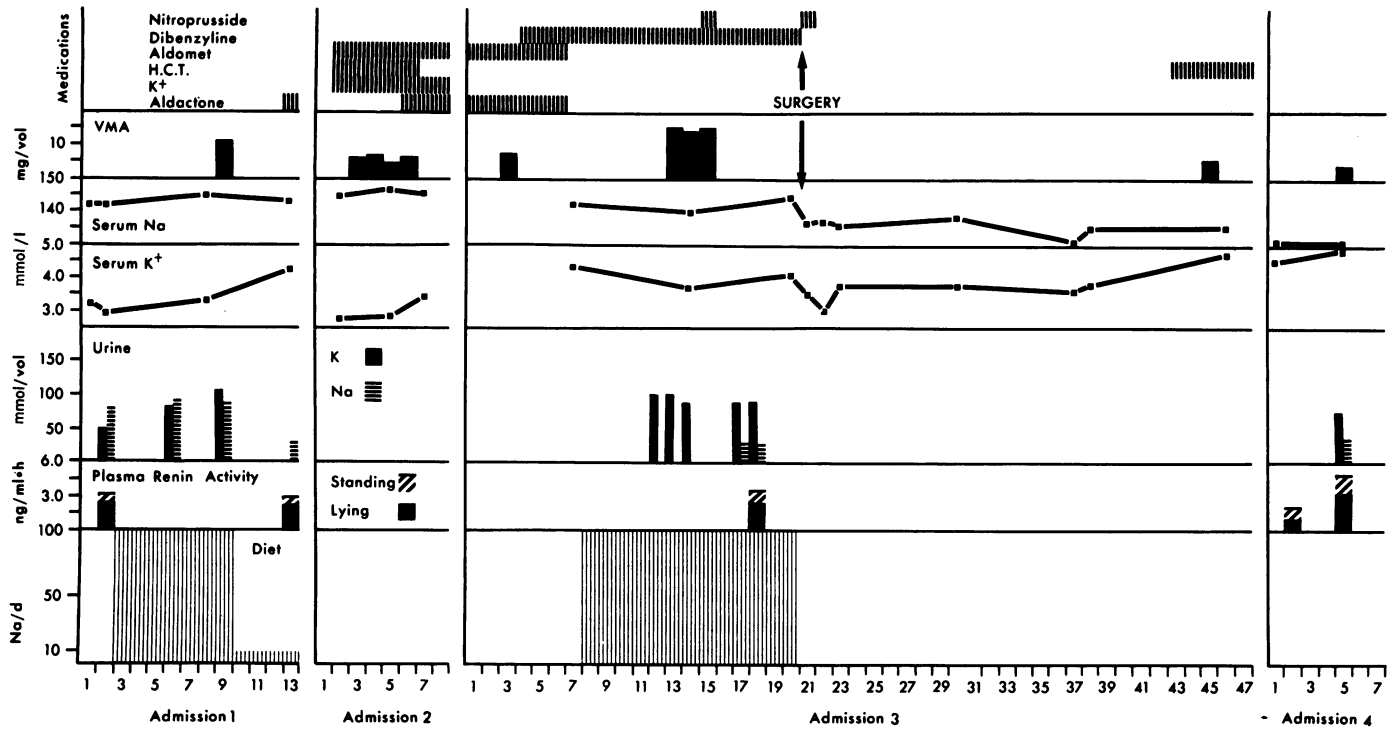

FIG. 1—Clinical data for patient with pheochromocytoma during four hospital admissions.

serum values having been recorded: sodium, 142 mmol/*l*; potassium, 2.9 mmol/*l*; and bicarbonate, 29 mmol/*l*. Hydrochlorothiazide was discontinued; 1 month later the serum sodium value was 141 mmol/*l*, the serum potassium value, 3.7 mmol/*l* and the 24-hour urine potassium value, 44 mmol/vol. At the time of admission there was no recent history of headache, pallor, perspiration or weight loss — in fact, her weight had increased by almost 7 kg in the preceding 12 months.

Hypertensive retinopathy, grade 2 (Keith–Wagener–Barker classification) was noted. There was no evidence of cardiomegaly but the electrocardiogram (ECG) showed left axis deviation and left ventricular hypertrophy. Blood pressure was 200/130 mm Hg. Diastolic pressure remained at 120 to 140 mm Hg throughout the patient's hospital stay. There were no clinical features of Cushing's syndrome.

Hemoglobin value was 16.2 g/dl. Hypokalemia (serum potassium values: 3.2, 2.9 and 3.3 mmol/*l*), persistent alkalosis (serum bicarbonate values: 34, 31 and 26 mmol/*l*) and kaliuresis were detected (Fig. 1). The sodium content of the diet was altered as indicated in Fig. 1 but the potassium content was maintained at 100 mmol/d.

Plasma renin activity (PRA) was measured by the method of Haber and colleagues[7] three times prior to operation. From the first assay, performed at an independent laboratory, the value in blood collected with the patient upright was 2.10 ng/ml•h with a urine sodium excretion of 131 mmol/vol (normal, 1.9 to 3.6 mmol/vol). The two values obtained in our laboratory were 2.5 ng/ml•h with the patient lying and 2.9 ng/ml•h with the patient standing for 2 hours with a urine sodium excretion of 85 mmol/vol, and 2.1 ng/ml•h lying and 2.8 ng/ml•h standing with a urine sodium excretion of 31 mmol/vol. The former value was normal and the latter was low. PRA did not increase with sodium restriction. (In 10 patients with primary aldosteronism that we have studied, the PRA has been less than 0.40 ng/ml•h with the patient upright after salt restriction.)

The 24-hour urinary aldosterone excretion was 16 μg/vol (normal, 2 to 26 μg/vol according to Bio-Science Laboratories, Van Nuys, California). The 24-hour sodium excretion at that time was 94 mmol/vol. Creatinine clearance was 116 ml/min. Plasma cortisol values were 22 μg/dl at 8 am and 10 μg/dl at 8 pm.

The patient was discharged from hospital taking spironolactone, 400 mg daily, while results of investigations were awaited. Twelve days after spironolactone therapy was started her blood pressure had not improved and she was having nausea. Propranolol therapy was started at 20 mg *tid* orally, and later that day the patient was admitted to her local hospital with tachycardia, perspiration and chest pain. ECG showed subendocardial ischemia but no evidence of infarction. Spironolactone and propranolol were discontinued and the patient was discharged taking methyldopa and hydrochlorothiazide. The possibility of pheochromocytoma was raised by the referring physician. One of the 24-hour urine samples from the previous admission showed a vanillylmandelic acid (VMA) value of 11.8 mg/vol (normal, 2 to 7 mg/vol) and a value for catecholamines of 408 μg/vol (normal, up to 100 μg/vol).

Second admission

The patient was readmitted to St. Paul's Hospital 2 months after the first admission for investigation of possible pheochromocytoma. Medication was methyldopa, 250 mg *tid*, and hydrochlorothiazide, 50 mg *od*. Electrolyte studies showed persistent hypokalemia (Fig. 1). Intravenous pyelography with nephrotomography yielded abnormal results, a faint triangular blush being noted above the right kidney. VMA values in 24-hour urine samples were 4.8, 5.9, 6.7 and 6.1 mg/vol. Catecholamine studies were not done because the patient was receiving methyldopa. Blood pressure was 140 to 180/90 to 120 mm Hg when the urine samples were collected.

After 1 week she was discharged taking methyldopa, 250 mg *tid*, and spironolactone, 25 mg *tid*.

Third admission

The patient was readmitted 1 month later for abdominal angiography. Blood pressure was 200/120 mm Hg but this decreased with bed rest. On the 2nd day abdominal angiography was performed by the retrograde femoral route, blood pressure being monitored by a transducer on the catheter. With injection of the dye the blood pressure increased from 160/100 to 280/140 mm Hg. Phentolamine, 5 mg, was given intravenously and the blood pressure decreased promptly to 200/100 mm Hg but a gallop rhythm developed. A total of 15 mg of phentolamine was required over 15 minutes to control the blood pressure. The procedure was terminated without selective adrenal arteriography and the aortic flush was interpreted as normal.

Oral therapy with phenoxybenzamine hydrochloride was started and angiography repeated with a nitroprusside infusion. A large right adrenal mass was visualized. The daily dose of phenoxybenzamine was increased to 120 mg. Blood pressure remained elevated at 150 to 170/90 to 110 mm Hg. VMA values in 24-hour urine samples on the 9th, 10th and 11th days after phenoxybenzamine therapy was instituted were 16.9, 14.9 and 15.8 mg/vol. Twenty-four-hour urinary potassium excretion remained elevated at 90 to 100 mmol/vol but serum potassium values began to increase. PRA was in the same range as during the first admission.

Phenoxybenzamine therapy was continued until the 21st hospital day, when laparotomy was performed. Sodium nitroprusside was administered to control blood pressure during the operation. A large right-sided adrenal gland was removed (Fig. 2); it contained a pheochromocytoma, an adrenal adenoma (Fig. 3) and associated focal hyperplasia of the zona glomerulosa. The left adrenal gland was grossly normal.

Postoperatively pneumonia and pul-

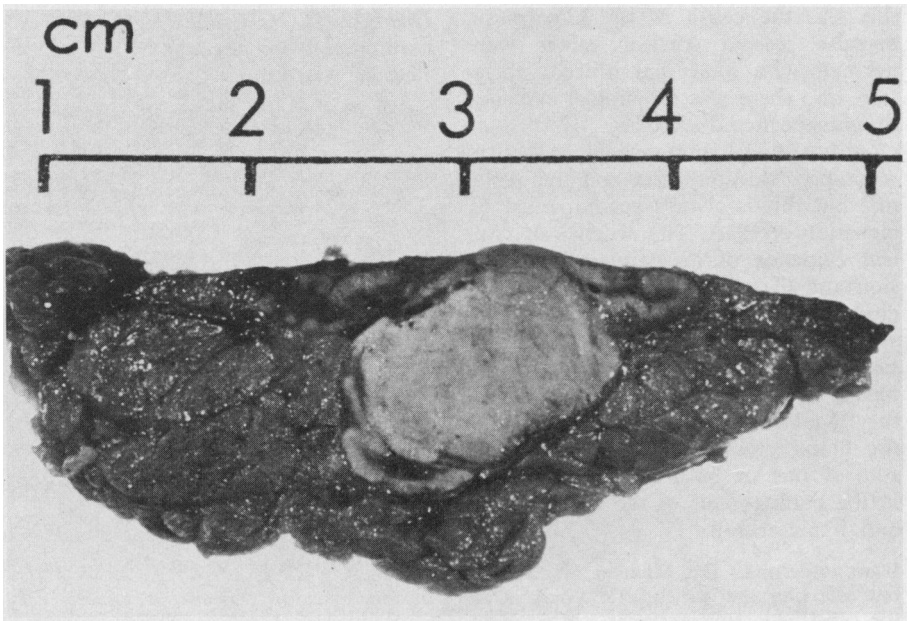

FIG. 2—Right adrenal gland: pheochromocytoma on left; adrenal adenoma in centre.

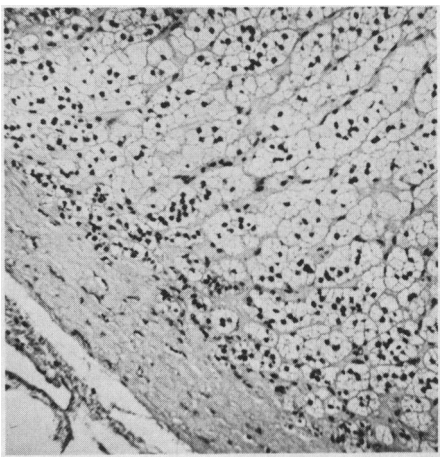

FIG. 3—Adrenal adenoma (hematoxylin–eosin; x100, reduced 50%).

monary embolism occurred. The patient was discharged almost 4 weeks after operation; her blood pressure was 140/100 mm Hg and she was taking digoxin and hydrochlorothiazide.

Fourth admission

Four months after the previous discharge the patient was readmitted for investigation of her endocrine status. She felt well and was not taking any medication. Blood pressure was 140/100 mm Hg; throughout her hospital stay it was 120 to 150/90 to 105 mm Hg. The 24-hour urine aldosterone excretion was 8.7 μg/vol (normal, 2 to 17 μg/vol). Serum potassium values were 4.5 and 4.9 mmol/*l*. Serum sodium values had decreased to 131 and 130 mmol/*l*. PRA was normal and there was an excellent response to salt restriction (Fig. 1).

Discussion

The pheochromocytoma in our patient was not typical, in that the usual associated features — attacks of perspiration, palpitations, headaches and pallor — were absent; at the time of her first admission to our hospital she had forgotten the episodes of a year earlier that were suggestive of a pheochromocytoma. Most patients with a pheochromocytoma lose weight because of hypermetabolism but this patient had gained weight. Yet there is no doubt that the pheochromocytoma was active: the great increase in blood pressure at abdominal angiography and the prompt decrease with phentolamine administration confirm its metabolic activity. Another historical feature supporting the activity of the pheochromocytoma is the exacerbation of symptoms shortly after propranolol therapy was begun. Beta-adrenergic blockade will decrease vasodilatation with resultant exacerbation of hypertension. The normal urinary VMA values are difficult to explain. Episodic secretion of catecholamines does occur and a small proportion of patients with pheochromocytoma have normal VMA excretion even when hypertensive.[8]

Hypokalemia, alkalosis and kaliuresis support a diagnosis of mineralocorticoid excess. A diagnosis of primary aldosteronism is not excluded by the normal urinary aldosterone excretion because the value may be normal, especially in patients with hypokalemia.[9] It would have been worth while to study plasma aldosterone concentration in this patient during both postural changes and sodium loading; elevated values unaffected by postural change or sodium loading would have indicated that the adrenal tumour was producing excessive amounts of aldosterone.[9] The main factor against the diagnosis of primary aldosteronism is the lack of suppression of PRA.

It is possible that the adrenal adenoma was a coincidental finding and unrelated to the hypertension and hypokalemia. The incidence of adrenal hyperplasia and adenomas is increased in hypertensive patients.[10] In one report of 2425 consecutive autopsies 4.2% of the hypertensive patients had an adrenal adenoma.[11]

If the adrenal adenoma was not the cause of the hypokalemia, then other explanations must be considered. Infusion of catecholamines does produce hypokalemia, which can be blocked with propranolol.[12] The catecholamines, however, lead to a decrease in urinary potassium[13] excretion and the acute hypokalemia is thought to be secondary to an intracellular shift of potassium. Our patient had excessive urinary excretion of potassium. This plus the absence of hypokalemia in most patients with pheochromocytoma indicate that the hypokalemia was almost certainly not secondary to the direct effects of catecholamine excess.

Catecholamines lead to release of renin.[14] It is possible that the catecholamine excess could lead to secondary aldosteronism with hypokalemia. The points against this hypothesis are that the PRA was not elevated and aldosterone excess was not documented.

Administration of the alpha-adrenergic blocker phenoxybenzamine hydrochloride was followed by an increase in plasma potassium concentration but renal loss of potassium continued. It is difficult to interpret that because spironolactone was given at the same time.

Some pheochromocytomas have been reported to produce adrenocorticotropic hormone.[15] This could lead to adrenocortical hyperplasia and adenoma formation. It is most unlikely that this was the cause of the hyperplasia because plasma cortisol values were normal, with a normal diurnal variation, and there was no clinical evidence of glucocorticoid excess.

Accelerated hypertension can lead to secondary aldosteronism and hypokalemia but this is always accompanied by elevation of PRA. The absence of clinical evidence of accelerated hypertension and the normal PRA virtually exclude that possibility.

The cause of hypokalemia in this patient remains unresolved but the removal of the right adrenal gland cured the hypokalemia and greatly decreased the blood pressure. This confirms the role of one or both of the neoplasms in the pathogenesis of the hypokalemia and hypertension.

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References

1. MELMON KL, GOLDFIEN A: The adrenals, in *Textbook of Endocrinology*, 5th ed, WILLIAMS RH (ed), Philadelphia, Saunders, 1974, p 308
2. WILSON RJ, CRAIG GM, MILLS IH: Metabolic studies in a patient with a pheochromocytoma associated with hypokalemia and hyperaldosteronism. *J Endocrinol* 56: 69, 1973
3. MATHISON DA, WATERHOUSE CA: Cushing's syndrome with hypertensive crisis and mixed adrenocortical adenoma-pheochromocytoma (corticomedullary adenoma). *Am J Med* 47: 635, 1969
4. MELONI CR, TUCCI J, CANARY JJ, et al: Cushing's syndrome due to bilateral adrenocortical hyperplasia caused by a benign adrenal medullary tumor. *J Clin Endocrinol Metab* 26: 1192, 1966
5. WILLIAMS GA, CROCKETT CL, BUTLER WWS, et al: The coexistence of pheochromocytoma and adrenocortical hyperplasia. *J Clin Endocrinol Metab* 20: 622, 1960
6. COPE O, LABBE JP, RAKER JW, et al: Pheochromocytoma and adrenocortical adenoma. Report of a case with both tumors and discussion of their relation. *J Clin Endocrinol Metab* 12: 875, 1952
7. HABER E, KOENER T, PAGE LB, et al: Application of a radioimmunoassay for angiotensin I to the physiologic measurement of plasma renin activity in normal subjects. *J Clin Endocrinol Metab* 29: 1349, 1969
8. SJOERDSMA A, ENGELMAN K, WALDMAN TA, et al: Pheochromocytoma: current concepts of diagnosis and treatment. *Ann Intern Med* 65: 1302, 1966
9. CAIN JP, TUCK ML, WILLIAMS GH, et al: The regulation of aldosterone secretion in primary aldosteronism. *Am J Med* 53: 627, 1972
10. RUSSELL RP, MASI AT: Significant associations of adrenocortical abnormalities with "essential" hypertension. *Am J Med* 54: 44, 1973
11. GRANGER P, GENEST J: Autopsy study of adrenals in unselected normotensive and hypertensive patients. *Can Med Assoc J* 103: 34, 1970
12. MASSARA F, TRIPODINA A, ROTUNNO M: Propranolol block of epinephrine-induced hypokalemia in man. *Eur J Pharmacol* 10: 404, 1970
13. NICKEL JF, SMYTHE CM, PAPPER EM, et al: A study of the mode of action of the adrenal medullary hormones on sodium, potassium and water excretion in man. *J Clin Invest* 33: 1687, 1954
14. REID, I, SCHRIER RW, EARLEY LE: An effect of extrarenal beta adrenergic stimulation on the release of renin. *J Clin Invest* 51: 1861, 1972
15. ODELL WD: Humoral manifestations of nonendocrine neoplasms, in *Textbook of Endocrinology*, op cit, p 1107

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15. GOLD WM, KESSLER GF, YU DYC: Role of vagus nerves in experimental asthma in allergic dogs. *J Appl Physiol* 33: 719, 1972
16. SEAL RM, HAPKE EJ, THOMAS GO, et al: The pathology of the acute and chronic stages of farmer's lung. *Thorax* 23: 469, 1968
17. HANSEN PJ, PENNY R: Pigeon-breeder's disease: study of the cell-mediated immune response to pigeon antigens by the lymphocyte culture technique. *Int Arch Allergy Appl Immunol* 47: 498, 1974
18. BICE DE, SALVAGGIO J, HOFFMAN E: Passive transfer of experimental hypersensitivity pneumonitis with lymphoid cells in the rabbit. *J Allergy Clin Immunol* 58: 250, 1976
19. JOUBERT JR, ASCAH K, MOROZ LA, et al: Acute hypersensitivity pneumonitis in the rabbit. I. An animal model with horseradish peroxidase as antigen. *Am Rev Respir Dis* 113: 503, 1976
20. HENSLEY GT, FINK JN, BARBORIAK JJ: Hypersensitivity pneumonitis in the monkey. *Arch Pathol* 97: 33, 1974
21. WARREN CP, TSE KS: Extrinsic allergic alveolitis owing to hypersensitivity to chickens — significance of sputum precipitins. *Am Rev Respir Dis* 109: 672, 1974
22. WARREN P, CHERNIACK RM, TSE KS: Hypersensitivity reactions to grain dust. *J Allergy Clin Immunol* 53: 139, 1974
23. SINHA M, MUIR WE: *Grain Storage: Part of a System*, Westport, CT, Avi, 1973, p 71
24. ROBERTSON DG, KERIGAN AT, HARGREAVE FE, et al: Late asthmatic responses induced by ragweed pollen allergen. *J Allergy Clin Immunol* 54: 244, 1974