

# Phaeochromocytoma

## A report of 10 patients

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### Summary

A spectrum of presentation of phaeochromocytoma in black South Africans is described. Ten patients were reviewed over a 9-year period. Sweating, headache, and palpitations were prominent symptoms in 9 patients; postural dizziness occurred in 5; gastro-intestinal symptoms in 7; diabetes in 3; and hypertension in all. One patient developed a phaeochromocytoma crisis, characterised by hypotension and pulmonary oedema, before operation. One woman presented in pregnancy. Urinary vanillylmandelic acid was elevated in 9 out of 10 subjects tested; plasma catecholamines were elevated in 6 out of 6 tested. Computed tomography detected 7 adrenal tumours and 3 paragangliomas. All patients were stabilised pre-operatively with  $\alpha$ - and/or  $\beta$ -receptor blockers. Intra-operative pressor crises were controlled with sodium nitroprusside, phentolamine, or magnesium sulphate infusions. At operation all tumours appeared benign, each was successfully removed, and the diagnosis confirmed on histological examination. There was no operative mortality. Two patients had residual hypertension. This study highlights the various challenges presented by this catecholamine-producing tumour.

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Phaeochromocytomas are fascinating tumours, which provide an insight into the actions of the catecholamines, albeit in excess. It is a rare tumour (1 in 1 000 hypertensive subjects), which has attracted an inordinate amount of attention — probably as a result of its often dramatic presentation and the opportunity it offers for cure of hypertension. Its importance should not be underestimated, however, because it is a potentially lethal condition; rarely it may be malignant; and it may offer a clue to the presence of underlying familial diseases, such as multiple endocrine neoplasia types IIa or IIb.

Phaeochromocytomas arise from chromaffin cells, 90% of which are found in the adrenal medullae, and the remaining 10% in sympathetic ganglia. It is not surprising therefore to find that approximately 90% of tumours occur within the adrenal gland itself, and only 10% are extra-adrenal, occurring in sympathetic ganglia stretching from the carotid body in the neck to the pelvic floor.

This report describes the clinical, biochemical, and pathological features, and the therapeutic approaches used in patients with phaeochromocytoma presenting to the Baragwanath Hospital Endocrine Unit.

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### Patients and methods

The case records of patients (under the care of K.R.L.H.) with phaeochromocytoma between 1980 and 1988 were reviewed for the following information: age; sex; presenting features; family history; presence of associated disorders; diagnostic biochemistry in the form of urinary vanillylmandelic acid (VMA) levels and plasma catecholamines; localising radiological procedures including computed tomography (CT) and  $^{131}\text{I}$  metaiodobenzylguanidine (MIBG) isotopic scans; findings on histological examination; and therapeutic approaches adopted.

A colorimetric method was used to measure urinary VMA excretion (normal 10 - 90  $\mu\text{mol}/24\text{ h}$ ).

Electrochemical detection was used to measure plasma catecholamines. Blood was sampled under standardised conditions. The normal range for plasma noradrenaline is 100 - 600 pg/ml, and that for adrenaline is up to 80 pg/ml.

### Results (Table I)

There were 8 female patients (including 1 pregnant woman) and 2 male (age range 11 - 57 years). There were no familial cases, no cases of multiple endocrine neoplasia, and no associated phakomatoses.

Sweating, headache, and palpitations were prominent symptoms: 6 patients had the complete triad and in only 1 (case 1) were these symptoms absent. Postural dizziness occurred in 5 patients, 2 of whom had syncopal episodes. One or more gastro-intestinal symptoms occurred in 7 subjects, including abdominal pain, vomiting and weight loss. As expected, hypertension was found in all patients. With the exception of 2 patients (cases 5 and 6), the hypertension was severe and extremely labile.

Two subjects had grade 4 hypertensive retinopathy with papilloedema, and 3 had grade 3 changes. ECG and/or clinical evidence of left ventricular hypertrophy was evident in 7 patients. Diabetes was a feature in 3 women, 2 of whom required insulin for control. Recurrent hypertensive pulmonary oedema was the sole presenting feature in case 1.

One woman (case 5) presented primarily with an abdominal mass and weight loss. She was initially thought to have an abdominal lymphoma, following ultrasonography, and was subjected to fine-needle aspiration biopsy, fortunately without complication. This revealed histological features of phaeochromocytoma. Subsequent to this it became apparent that abdominal compression precipitated her symptoms and elevated the blood pressure. This was the only patient in whom the diagnosis had not been suspected at the time of presentation.

While awaiting surgery patient 10 suffered a florid phaeochromocytoma crisis in the ward. This was characterised by sudden onset chest pain accompanied by pallor, a cold and clammy skin, a tachycardia of 150/min, a blood pressure of 80 mmHg systolic, and bilateral chest crackles.

The portable chest radiograph showed extensive pulmonary oedema (Fig. 1). Arterial blood gas analysis (on 40% oxygen) revealed pH 7.0; oxygen pressure 37 mmHg; carbon dioxide pressure 38 mmHg; base excess -19 mmol/l. The mean pulmonary capillary wedge pressure was 10 mmHg. The patient

**TABLE I. SUMMARY OF CLINICAL, BIOCHEMICAL AND RADIOLOGICAL FEATURES OF PATIENTS WITH PHAEOCHROMOCYTOMA**

Case	Age (yrs)	Sex	Presenting features	24-h urinary VMA ( $\mu$ mol)	Plasma catecholamines (pg/ml)		CT	MIBG scan
					Nor-adrenaline	Adrenaline		
1	20	M	Recurrent pulmonary oedema, hypertension	113	—	—	Right paraganglioma	—
2	57	F	Sweating, headache, palpitations, dizziness, syncope, backache, weight loss, hypertension, diabetes	157	—	—	Left adrenal	—
3	38	F	Sweating, headache, palpitations, syncope, weight loss, hypertension, retinopathy	140	—	—	Left adrenal	—
4	11	F	Sweating, headache, palpitations, abdominal pain, constipation, dizziness, hypertension, retinopathy	286	3000	3040	Right adrenal	+
5	43	F	Headache, palpitations, chest and abdominal pain, vomiting, weakness, weight loss, hypertension, abdominal mass	53	—	—	Left paraganglioma	+
6	51	F	Sweating, palpitations, recurrent diabetic keto-acidosis, hypertension	162	9993	233	Left adrenal	—
7	26	F	Sweating, headache, palpitations, dizziness, backache, hypertension, pregnant	123	1164	0,2	Right adrenal	+
8	23	F	Sweating, headache, palpitations, abdominal pain, vomiting, weakness, dizziness, hypertension, retinopathy	300	2215	55	Right adrenal	+
9	49	F	Sweating, headache, palpitations, weakness, vomiting, hypertension, retinopathy	329	2035	66	Right adrenal	+
10	15	M	Sweating, palpitations, abdominal pain, vomiting, hypertension, retinopathy, crisis in ward	253	9432	169	Right paraganglioma	—

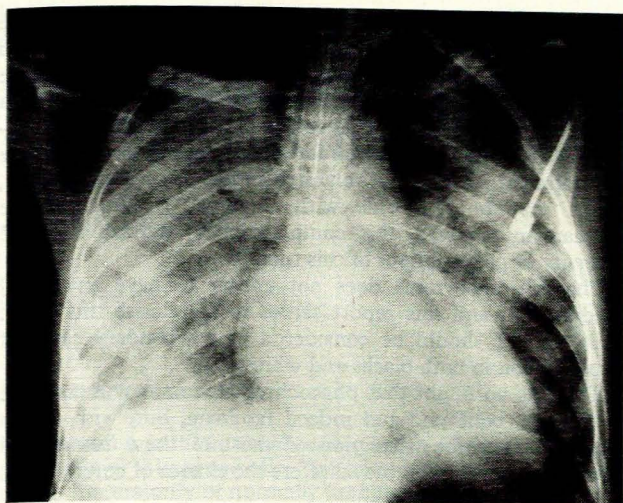


Fig. 1. Chest radiograph showing features of pulmonary oedema.

was mechanically ventilated and given nitroprusside, dopamine and furosemide. Despite the development of acute tubular necrosis, he made a full recovery and underwent successful tumour removal.

### Investigations

Biochemical confirmation of the diagnosis was established in all cases following measurement of catecholamine metabolites in the urine: 9 patients had elevated VMA levels; the exception (case 5) had an elevated metanephrine level. Six out of 6 patients tested had elevated plasma noradrenaline levels, 3 of whom also had elevated plasma adrenaline levels.

CT proved reliable as a tumour localising procedure (Fig. 2): all tumours were intra-abdominal, ranging in diameter from 3 cm to 14 cm. Seven arose from the adrenal gland and 3 were paragangliomas. In the 5 patients undergoing an MIBG scan, positive uptake was seen in the area of the tumour identified by CT. No evidence of multiple or extra-abdominal tumours was seen.

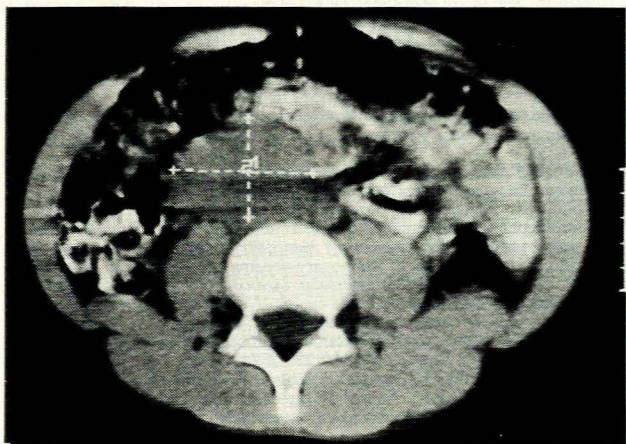


Fig. 2. CT of abdomen showing right paraganglioma (outlined by markers).

### Management

Pre-operative stabilisation was carried out in all patients for several weeks before surgery. Three patients were controlled on phenoxybenzamine plus  $\beta$ -blocker; 3 on prazosin plus  $\beta$ -

blocker; 3 on prazosin alone; and 1 on labetalol. Volume expansion with blood or saline was undertaken in all cases 24 hours before surgery. Intra-operative pressor crises were effectively controlled using sodium nitroprusside and phentolamine in 5 cases.

More recently, an intravenous infusion of magnesium sulphate was the sole agent used in the last 5 patients. No arrhythmias occurred. Vigorous fluid replacement, given both during and after operation, prevented any significant hypotensive episodes. Once fetal maturity was confirmed in the pregnant woman (case 7) she underwent caesarean section and was delivered of a healthy baby. Tumour localisation and removal were successfully carried out several weeks later.

At operation the 10 tumours were confirmed and removed. Histological examination showed them to be typical of pheochromocytoma in all, and there were no obvious signs of malignant disease. There was no operative mortality and no significant morbidity. VMA measurements performed at least 1 week after surgery were normal in all 9 patients tested. The remaining patient had normal plasma catecholamine levels. Hypertension persisted in 2 patients for several months after surgery, and 1 of these patients had persistent diabetes. Repeated biochemical and radiological investigations for pheochromocytoma in these 2 patients have proved negative.

### Discussion

The clinical diagnosis of pheochromocytoma requires a high index of suspicion in the attending physician. Most patients are symptomatic, with the triad of headache, sweating and palpitations being reliable indicators of the presence of this tumour.<sup>1,2</sup> This was borne out in this small series. However, clinically unsuspected pheochromocytomas do occur.<sup>3</sup> Hypertension is the most consistent feature of this tumour<sup>1,4</sup> and was found in all patients in this study; it was the sole presenting feature in case 1 (previously described<sup>5</sup>). It should be remembered, however, that orthostatic hypotension occurs in approximately two-thirds of untreated patients with pheochromocytoma and is probably related to a type of autonomic dysfunction that simulates ganglionic blockade.<sup>4</sup> Half the patients in the present study had postural hypotension, severe enough in 2 to produce syncope.

Biochemical confirmation of the diagnosis of pheochromocytoma is readily available: urinary catecholamines, their metabolites (VMA and metanephrine) and/or plasma catecholamines can be measured in most laboratories.<sup>1,6</sup> Plasma catecholamine measurement appears to be the most sensitive test, urinary VMA level the least. When elevated, plasma catecholamines, urinary VMA and metanephrine have excellent specificity.<sup>1</sup> These three measurements proved useful in the present series. Tumour localisation can be accurately determined by CT with a precision of about 96%,<sup>1</sup> thus obviating the need for more invasive tests.

All 10 tumours in this study were detected by CT. A newer development has been the discovery of a radioactive compound which is selectively taken up by adrenergic cells — <sup>131</sup>I meta-iodobenzylguanidine (MIBG). This should prove helpful in the detection of extra-adrenal tumours or metastatic deposits.<sup>6</sup> The MIBG scan was positive in all 5 patients tested; there was no evidence of multiple tumours or metastatic deposits.

Preoperative  $\alpha$ -adrenergic blockade is thought by many to reduce morbidity and mortality associated with intra-operative cardiovascular complications.<sup>1,4</sup> It does allow re-expansion of the intravascular volume, prevents symptomatic paroxysms and controls the blood pressure. However, it must be remembered that this pre-operative preparation is insufficient to prevent intra-operative pressor crises. Irrespective of the  $\alpha$ -adrenergic blocker used before surgery in this study, all patients

required antihypertensive therapy during the induction of anaesthesia and/or the operation.

It is clear that the overall outcome is dependent on adequate pre-operative stabilisation, appropriate anaesthetic management and postoperative care, and good surgical technique, all of which requires teamwork. Prazosin, a specific  $\alpha_1$ -postsynaptic antagonist, was used before surgery in 6 patients in this study. It was found to be effective in controlling the hypertension in divided doses ranging from 2 mg to 16 mg/d. It has a theoretical, if not practical, advantage over phentolamine and phenoxybenzamine; these two  $\alpha$ -adrenergic blockers act non-selectively as  $\alpha_1$ - and  $\alpha_2$ -receptor blockers. This results in increased circulating levels of nor-adrenaline, which in turn causes tachycardia, increased renin release, and attenuation of the desired postsynaptic blockade.<sup>7</sup> On the other hand, phenoxybenzamine, being a non-competitive antagonist, is preferred by some authors on the grounds that a sudden increase in circulating catecholamine levels would be less likely to produce a severe hypertensive response in the presence of a non-competitive blockade than in the presence of a competitive blockade. Which of the two drugs is preferable has not yet been established. The major adverse effect of prazosin is postural hypotension, which is usually most marked after the first dose, and appears dose-related.<sup>7</sup> The pregnant woman, case 7, had a significant hypotensive episode following the first dose of prazosin 2 mg. This effect can probably be prevented by giving a small dose (< 1 mg) of the drug at bedtime. It has been suggested by several authors that a dramatic and prolonged hypotensive response to prazosin may suggest underlying phaeochromocytoma.<sup>8-10</sup> Another aspect of prazosin therapy, the management of symptomatic hypertensive crises in several of these patients, is worthy of mention.

In 3 instances, using a dose of 2 mg of prazosin, symptoms were abolished and blood pressures were reduced as follows: from 210/140 mmHg to 125/90 mmHg in 1 hour; from 280/130 mmHg to 160/80 mmHg in 1 hour, from 180/150 mmHg to 122/86 mmHg in 2 hours.

No untoward effects were noted. If access to an intensive care unit is not readily available, prazosin offers an effective method of control of these crises in the ward situation.

The rationale for the use of magnesium sulphate to control the peri-operative pressor crises in phaeochromocytoma has been described previously.<sup>11-13</sup> In short, magnesium appears to inhibit the release of catecholamines from the adrenal medulla, to reduce the sensitivity of  $\alpha$ -adrenergic receptors to catecholamines, and to exert a direct vasodilatory effect. In this series it was the sole agent used for blood pressure control during 5 tumour removals. It proved extremely effective and safe if given in adequate dosage: boluses of 2 - 4 g plus infusions of 1-2 g/h to achieve blood magnesium levels of 2,5 - 4,0 mmol/l.

The development of a phaeochromocytoma crisis in case 10, characterised by hypotension and pulmonary oedema with a normal wedge pressure, is intriguing. On the previous day, this patient had been well with a normal blood pressure and was being treated with prazosin and propranolol. Hypotension in this context has been described previously<sup>14,15</sup> and may reflect a predominant adrenaline secretion by the tumour. However, before this episode the patient's plasma catecholamine levels had shown a predominant nor-adrenaline secretion.

The pulmonary oedema with normal wedge pressure may be akin to neurogenic pulmonary oedema in which an increased sympathetic discharge leads to redistribution of blood volume from the systemic to the pulmonary circulation together with an increase in capillary permeability induced by the catecholamines.<sup>16</sup> Another explanation for the pulmonary oedema is the development of a catecholamine-induced cardiomyopathy, which may be reversible with therapy.<sup>17,18</sup> Whatever the mechanism involved, this complication is indicative of the diversity of presentations of this tumour.

Phaeochromocytoma does not appear to have any racial predilection, and this report serves to emphasise this point. This tumour should be considered as a secondary cause of hypertension in both blacks and whites.

There is no doubt that phaeochromocytomas will continue to confuse, confound and indeed fascinate, but, with a high index of suspicion, detection of most of these tumours is possible and surgical removal offers the chance of cure.

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