Phaeochromocytoma—investigation and management of 10 cases

J E Deal, P S Sever, T M Barratt, M J Dillon

Abstract

Since 1960 we have diagnosed phaeochromocytoma (paraganglioma) in 10 children. The cases include a 15 year old girl who over a three year period presented with multiple paragangliomata and an associated malignant carotid body tumour. All children were hypertensive, eight of 10 presenting with severe headaches. Diagnosis was based on finding a raised urinary vanillylmandelic acid excretion and plasma noradrenaline concentration. In addition six of eight children were hypercalcaemic with raised plasma calcitonin concentrations; plasma parathyroid hormone concentrations were high in two of seven and four out of eight children had raised plasma renin activities on presentation. No child, however, was found to have a multiple endocrine neoplasia syndrome. Despite the introduction of newer techniques for the detection of catecholamine producing tumours we found that selective arteriography and venous catecholamine sampling were superior for tumour localisation compared with ultrasound scanning, computed tomography, and meta-iodo-benzyl-guanidine (MIBG) scanning.

Phaeochromocytoma is a rare but treatable cause of hypertension in childhood.¹ At the Hospital for Sick Children, Great Ormond Street, London, which is a tertiary referral centre for childhood hypertension, 1.3% of cases referred over a 10 year period, for investigation of high blood pressure, were found to have a phaeochromocytoma (table 1). In children there is a higher incidence (32%) of multiple tumours and an increased occurrence of the multiple endocrine neoplasia syndromes when compared with that reported in adults.¹ The incidence of malignancy is 2.4%, compared with a malignancy rate of 10% in adults.²

Table 1 Diagnoses of 454 cases of hypertension admitted to the renal unit at the Hospital for Sick Children, 1975–85, including six of the children reported here

Diagnosis	No (%) of children
Coarse renal scarring:	
Reflux nephropathy	84 (19)
Obstructive uropathy	72 (16)
Glomerular disease	123 (27)
Renovascular disease	38 (8)
Haemolytic uraemic syndrome	32 (7)
Polycystic kidney disease	22 (5)
Idiopathic (essential)	18 (4)
Renal dysplasia	13 (3)
Wilms' tumour	9 (2)
Coarctation	7 (<2)
Phaeochromocytoma	6 (<2)
Renal vein thrombosis	4 (1)
Miscellaneous	26 (6)

A system for the classification of tumours of the autonomic nervous system was proposed by Glenner and Grimley in 1974 and is now widely accepted.³ Under this classification a tumour arising from the adrenal medulla is termed a phaeochromocytoma and chromaffin tumours arising outside the adrenals of paraganglionic origin are termed paragangliomata. Paragangliomata are more commonly found at extra-adrenal sites in children than in adults and can occur anywhere in the autonomic nervous system. Tumours of the carotid body, in association with phaeochromocytoma, have been frequently reported in adults,^{4 5} but there is only one report in the literature of an affected child, that of a 12 year old boy.¹ We report here 10 cases of paragangliomata, including one child with multiple lesions and a malignant carotid body tumour, that have been seen at the Hospital for Sick Children since 1960.

Patients

REVIEW OF CASES

Clinical details of all 10 children are summarised in table 2; the cases are tabulated in chronological order of presentation. They ranged in age from 3.5 months to 16 years, mean age 10.3 years. Only three children were less than 10 years old at presentation.

The commonest presentation in the present series was severe headaches; varying in duration from 11 days to 2.5 years. The youngest child (case 3) presented with episodes of diarrhoea and sweating and two generalised fits, presumed to be due to her hypertension, at the age of 3 months. All children were hypertensive; in eight children it was sustained and in only two was the blood pressure labile. One girl (case 10) was diagnosed fortuitously: although asymptomatic she was found to be hypertensive at an outpatient clinic visit where she was being followed up for a stage IV Wilms' tumour that had been diagnosed and treated seven years previously by chemotherapy, radiotherapy, and a right nephrectomy.

Another girl (case 7) who presented with headaches, pallor, and tachycardia, was initially found to have two para-aortic paragangliomata. After surgical removal of these she presented over the subsequent three years with two further extra-adrenal tumours, bilateral intra-adrenal tumours, and a malignant carotid body tumour, which were all surgically removed.

Two children had a positive family history: one (case 10) had an uncle who had been diagnosed some years before her presentation and the other (case 9) had a 17 year old sister

Renal Unit,
Hospital for Sick
Children and Department
of Paediatric Nephrology,
Institute of Child Health,
London
J E Deal
T M Barratt
M J Dillon

Department of Clinical
Pharmacology,
St Mary's Hospital,
London
P S Sever

Correspondence to:
Dr J E Deal, Department of
Paediatric Nephrology,
Institute of Child Health,
30 Guilford Street,
London WC1N 1EH.
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Table 2 Clinical details of the 10 children with phaeochromocytoma in chronological order of presentation

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at presentation (years)	13.3	12.6	0.3	7.5	10.1	10.4
Sex	Male	Female	Female	Female	Male	Female
Presenting symptoms	Headaches, convulsion	Headaches, pallor, abdominal pain	Diarrhoea, sweating	Headaches	Headaches, convulsion	Headaches, sweating
Investigations:						
Urinary vanillylmandelic acid	↑	↑	↑	↑	↑	↑
Plasma noradrenaline (pg/ml)*	—	—	1371	5130	18 345	27 700
Plasma renin activity	—	—	N	N	↑	N
Calcitonin	—	—	↑	↑	↑	↑
Parathyroid hormone	—	—	↑	N	—	N
Plasma calcium (mmol/l)	—	—	2.7	2.64	2.75	2.64
Preoperative treatment	Phentolamine	Phenoxybenzamine, propranolol	Phenoxybenzamine, propranolol	Phenoxybenzamine, propranolol	Phenoxybenzamine	Labetalol, phenoxybenzamine, propranolol
Site and size of tumour (cm)	Right adrenal 5×4	Right adrenal 7×6	Left adrenal 0.3×0.3	Right adrenal 5×3	Left adrenal 5×5	Right adrenal 3×2.5
Other features						

N, normal; ↑, concentration raised.
*To convert pg/ml to nmol/l: ×0.005988.

who was diagnosed at the same time as he was being investigated. There were no positive family histories of multiple endocrine neoplasia syndromes.

At presentation all 10 children had raised 24 hour urinary vanillylmandelic acid concentrations. Plasma noradrenaline concentrations were also raised in the eight children measured. Case 7, the child with multiple paragangliomata, had repeatedly normal urinary vanillylmandelic acid concentrations after the removal of her first two tumours but raised plasma noradrenaline concentrations.

Plasma renin activity was raised in four out of eight patients on presentation and six of the eight had raised plasma calcitonin concentrations (normal <0.08 µg/l), but these were normal when repeated postoperatively. Associated with a raised plasma calcitonin concentration, the six patients were noted to be hypercalcaemic at presentation (normal <2.6 mmol/l corrected); postoperatively they were normocalcaemic. Plasma concentrations of parathyroid hormone were high in two of seven children at presentation but fell to normal after removal of their phaeochromocytoma.

Table 3 shows the localisation techniques that were used in our patients. Case 1, who presented in 1960 for investigation, had a phaeochromocytoma clinically diagnosed and underwent

intravenous pyelography, which failed to localise the tumour, and then proceeded to an exploratory laparotomy.

MANAGEMENT

All patients required treatment for their hypertension on presentation as shown in table 2. Six children were successfully treated with a combination of phenoxybenzamine (1–4 mg/kg/day) and propranolol (1–10 mg/kg/day) alone. Case 1 was prepared for surgery with phentolamine (100 µg/kg intravenously). Treatment with labetalol alone in cases 6, 8, and 10 did not produce adequate α blockade and so their treatment was changed. Four of the present series were treated with nifedipine (0.5–4 mg/kg/day). In one child (case 8) nifedipine was added to the regime of propranolol and phenoxybenzamine to achieve adequate catecholamine blockade. In case 10 nifedipine alone was insufficient to block the patient's symptoms and control the blood pressure, this was only achieved when phenoxybenzamine and labetalol were introduced. In two patients (cases 7 and 9) adequate preoperative control of blood pressure was achieved with nifedipine alone.

All 10 children were successfully treated by surgical removal of their paragangliomata. There were no operative complications and no

Table 3 Radiological techniques used to localise catecholamine secreting tumours in the 10 patients

	Case No									
	1	2	3	4	5	6	7	8	9	10
Intravenous pyelography	—	+	—	—	—	+	—	+	±	+
Ultrasound				—	—		—		+	
Computed tomography							+		±	+
¹²³ I-MIBG scan							+	+	±	+
Selective arteriography		+	+	+	+	+	+	+	+	+
Serial catecholamine sampling				+	+	+	+	+	±	

+, Technique helped localise the tumour; —, technique failed to localise the tumour; ±, equivocal result; * MIBG scan localised the tumours present at initial presentation only but was unhelpful when subsequent tumours were investigated.

Case 7	Case 8	Case 9	Case 10
15.7 Female Headaches, pallor	8.9 Male Headaches, sweating	11.6 Male Headaches	12 Female Found hypertensive at routine clinic visit
↑	↑	↑	↑
4147 N ↑ —	12 975 ↑ N N	22 039 ↑ ↑ ↑	5243 ↑ N N
2.65 Phenoxylbenzamine, propranolol, nifedipine	2.56 Labetalol, Phenoxylbenzamine, propranolol, nifedipine	2.87 Nifedipine	2.56 Nifedipine, labetalol, phenoxylbenzamine
Bilateral adrenal + 4 extra-adrenal + carotid body tumour	Right adrenal 3.5×4.5	Bilateral adrenal 1.3×1.0 (left) 2.3×2.3 (right)	Left adrenal 7×5.5
		Family history positive	Family history positive, history of right nephrectomy for Wilms' tumour

deaths. Two patients underwent bilateral adrenalectomies (cases 7 and 9). Both subsequently required adrenal replacement treatment with hydrocortisone and fludrocortisone. Case 9 underwent reimplantation of adrenal cortex into his forearm musculature but four months after operation there were no signs of cortisol release with adrenocorticotrophic hormone stimulation. One child (case 10), who had had previous surgery for a stage IV Wilms' tumour involving nephrectomy and adrenalectomy, and had a subsequent adrenalectomy for her phaeochromocytoma, is also on adrenal replacement treatment.

Our children have been followed up for 1.3–10 years (mean 5.3 years), they are all well, none has any evidence of a recurrence, and no patient has developed a multiple endocrine neoplasia syndrome.

Discussion

Paragangliomata are reported to occur more commonly in boys before adolescence^{1 6 7}: Stackpole *et al*, in their review of 100 cases in childhood, reported a male:female ratio of 2:1.¹ In adults the reverse is true with paragangliomata in women being seen more commonly after adolescence.⁸ In the 10 children discussed here there was a preponderance of girls with a ratio boys:girls of 4:6.

Extra-adrenal and multiple paragangliomata are reported to be more common in childhood than in adults. Stackpole *et al* reported, an incidence of 31% and 32% respectively,¹ compared with an incidence of 10% extra-adrenal and 4% bilateral adrenal tumours reported by Melicow in adults.⁸ Eight out of 10 of our children, however, had solitary tumours, which were all intra-adrenal (five right and three left). One child (case 9) had bilateral adrenal tumours and case 7 had multiple extra-adrenal and bilateral adrenal paragangliomata.

In 1974 Glenner and Grimley proposed a system for the classification of paraganglia.³ They recommended that the term phaeochromocytoma be limited to paragangliomata arising in the adrenal medulla. Paraganglia and the paragangliomata arising from them are, in their classification, divided into four 'families' on the basis of anatomical location, histochemical features, and innervation. (1) *Branchiomeric (chemodectomas)*—associated with arterial vessels and cranial nerves of the ontogenetic branchial arches. (a) Intercarotid (carotid body); (b) jugulotympanic (glomus jugulare, glomus tympanicum); (c) orbital; (d) laryngeal; (e) subclavian; (f) aorticopulmonary; (g) coronary; and (h) pulmonary. (2) *Intravagal*. (3) *Aortico-sympathetic*—associated with the sympathetic chain and the retroperitoneal ganglia. In the abdomen (including the organ of Zuckerkandl), thorax, and neck. (4) *Visceral-autonomic*—(a) atria of the heart; (b) urinary bladder; (c) liver hilum; and (d) mesenteric vessels.

The older classification based on chromaffin staining is unsatisfactory because staining is frequently unpredictable and chromaffin positivity of a paraganglioma does not correlate reliably with catecholamine production.^{3 9}

Branchiomeric paraganglia, which are more commonly chromaffin negative and non-functioning, are rare in childhood. In the series of Stackpole *et al* only one in 100 children had an associated non-chromaffin positive paraganglioma in addition to a phaeochromocytoma. This was in a 12 year old boy who seven years after removal of an intra-abdominal and a thoracic paraganglioma, at the age of 19 years, was found to have a carotid body tumour.¹ Revak *et al* reported a 36 year old man with bilateral carotid body tumours who had had a phaeochromocytoma resected at the age of 11 years.¹⁰ Carotid body tumours in isolation occur commonly in the third to sixth decades of life and are only rarely reported in children—in a 1986 review of carotid body tumours by Dickinson *et al* only one of 32 cases was less than 16 years old.¹¹

Familial phaeochromocytomata are well recognised. In the review of Stackpole *et al*, 9% of cases had a positive family history,¹ and in that of Kaufman *et al* in 1983 of phaeochromocytomata at the Mayo clinic, 31% of cases were familial.⁷ Familial occurrence may or may not be associated with multiple endocrine neoplasia syndromes or with neurocutaneous syndromes (neurofibromatosis, von-Hippel Lindau). In multiple endocrine neoplasia syndromes there is a high incidence of bilateral adrenal phaeochromocytomata.¹² Inheritance in familial cases is by mendelian dominant transmission with variable penetrance.¹³ No child in the present series had evidence of a multiple endocrine neoplasia syndrome.

Raised plasma renin activity in association with phaeochromocytomata has been previously described.^{6 14 15} Reports of the association of renal artery stenosis with phaeochromocytomata have appeared in the literature since 1963 when Rosenheim *et al* observed unilateral renal ischaemia due to compression of a renal artery by a phaeochromocytoma.¹⁴ Hiner *et al* in 1976

reported a raised plasma renin activity as well as catecholamines in an 11 year old girl¹⁵; an intra-adrenal tumour was removed, which was not found to be compressing the renal artery or the kidney. Both catecholamines and plasma renin activity fell to normal after surgery. Before surgery haemodynamic studies indicated that there was reduced renal cortical blood flow and fractional flow to the outer cortex consistent with the effects of catecholamines or with those of angiotensin. A 9.5 year old girl was reported by Robinson *et al* in 1973 who was found to have a renal artery stenosis independent of her phaeochromocytoma and not due to compression or haemodynamic effects.⁶ These reports suggest that high plasma renin activity in the presence of a phaeochromocytoma may be due to one or more of several factors: (i) ischaemia secondary to volume depletion caused by excess catecholamines, (ii) compression of a renal artery by the tumour, (iii) intrinsic renal artery diseases, and (iv) intrinsic renal parenchymal disease.⁸ Four children in the present series were found to have raised plasma renin activities at presentation. In one child (case 10) this was presumed to be due to the pressure of a large adrenal phaeochromocytoma on the upper pole of the kidney causing distortion of the upper pole artery on the arteriogram; in the other three cases the intra-adrenal tumours were felt to be too small to be causing a pressure effect. One of these patients did not have arteriography and so we cannot exclude a renal artery stenosis in him, but in all four children the plasma renin activity fell to normal after surgery.

Reliance on urinary determinations of vanillyl-mandelic acid excretion can be misleading in paragangliomata. The amounts of free catecholamines and their metabolites vary depending on the levels of synthesising and metabolising enzymes within the tumour and the excretory function of the kidneys.¹⁶ These factors may account for the false positive and negative results that are reported. In addition, in children, 24 hour urinary collections are difficult and cumbersome to obtain and are not always possible. Plasma catecholamine concentrations have the highest sensitivity for diagnosing paragangliomata; urinary vanillylmandelic acid concentrations are the least sensitive tests.¹⁷ Plasma catecholamines should be obtained under standardised, controlled conditions, however, which are often difficult to achieve in children. It has been suggested, in adults, that a raised plasma adrenaline may be used as a marker for distinguishing between adrenal and extra-adrenal tumours as the adrenal medulla is the principal source of adrenaline and so, theoretically, both plasma adrenaline and noradrenaline concentrations should be measured.¹⁸ In practice, however, we found that the seven children in our series with adrenal tumours whose plasma noradrenaline concentrations were measured, had appreciably raised values. Case 7 had raised noradrenaline concentrations before removal of both her intra-adrenal and extra-adrenal tumours.

We did not find it necessary to perform pharmacological tests on our patients to make the diagnosis of phaeochromocytoma and would

view them as being potentially dangerous procedures to undertake.

The localisation techniques that were used in our 10 cases have already been outlined in table 3. The current literature suggests that the use of computed tomography should all but eliminate the need for potentially hazardous arteriographic studies in the preoperative detection and localisation of paragangliomata.¹⁹ This has not been our experience nor that of others.²⁰ Ultrasound and computed tomography were only helpful in localising large tumours. In only three of the eight patients who had an ultrasound scan was the scan positive. For two patients, who initially had negative scans, when their tumours were localised by other means, repeating the ultrasound scan allowed the phaeochromocytomata to be visualised. Computed tomography was positive in two of five patients only and missed a 5 cm diameter tumour in one case.

The recently introduced meta-iodo-benzyl guanidine (MIBG) scanning for localising catecholamine producing tumours was not the most sensitive investigation in our patients. We used ¹²³I instead of ¹³¹I labelled MIBG as this decreases radiation exposure and increases the sensitivity of the scan.²¹ Using ¹²³I-MIBG, however, normal adrenal glands are visualised and in our patients it has been difficult to distinguish increased MIBG uptake in an abnormal gland from normal adrenal MIBG uptake particularly in one child (case 9) who had bilateral adrenal phaeochromocytomata. Case 7 had a positive MIBG scan at presentation (fig 1) but subsequently MIBG scanning was unhelpful because her paragangliomata were either intra-adrenal or anatomically situated very near her adrenals. The MIBG scan was unable to distinguish these tumours from normal adrenal glands. A review of the use of MIBG scanning in 400 cases concluded that, in the case of sporadic intra-adrenal lesions MIBG scanning is probably no better than a computed tomogram but is superior for localising extra-adrenal, recurrent, and malignant lesions.²¹

Although invasive and time consuming we

Figure 1 Case 7: MIBG scan showing the presence of two para-aortic paragangliomata.

found arteriography and venous catecholamine sampling to be the most helpful investigations for localising tumours. In all eight children who underwent arteriography the tumours were localised. Sampling was very helpful and localised the tumours in six out of seven children studied. In one child (case 9) sampling was positive but because he had bilateral adrenal phaeochromocytomata it was difficult to localise precisely the sources of catecholamine production. In another (case 7) sampling was particularly helpful in localising her multiple tumours (figs 2 and 3). In one child (case 3) arteriography and sampling enabled us to identify a 0.3 cm intra-adrenal phaeochromocytoma that had not been identified by other means.

Preoperative control of the hypertension in patients with phaeochromocytomata is very important, both for definitive surgery and arteriography. Perioperative deaths have usually resulted from inadequate preoperative preparation and blood pressure control.²² The treatment for phaeochromocytomata has traditionally involved the use of α and β sympathomimetic blocking agents: usually phenoxybenzamine and propranolol. Five of our children have been

Figure 2 Case 7: noradrenaline sampling data showing high concentrations from the main right renal vein. A tumour was subsequently removed from the right para-adrenal region. Results are in pg/ml; to convert to nmol/l, $\times 0.005988$.

Figure 3 Case 7: noradrenaline sampling data showing high concentrations from the left adrenal vein. A left intra-adrenal phaeochromocytoma was removed subsequently. Results are in pg/ml; to convert to nmol/l, $\times 0.005988$.

successfully treated with this combination alone preoperatively. More recently labetalol, which has both α and β blocking activity, has been used in the management of phaeochromocytomata.²³ Oral labetalol was used in three of our children but did not produce adequate α blockade and so their treatment was changed. Recently interest has grown in the use of nifedipine in the management of catecholamine excess states. Serfas *et al* first reported the suppression of symptoms by nifedipine in a patient with hypertrophic cardiomyopathy and a phaeochromocytoma.²⁴ Symptom relief was associated with a fall in plasma noradrenaline concentrations suggesting that nifedipine blocked the release of noradrenaline from phaeochromocytomata. A second report by Lenders *et al* postulated that nifedipine blocked the peripheral action of noradrenaline by exhaustion of intracellular calcium stores after chronic noradrenaline stimulation in a patient with a bladder paraganglioma.²⁵ Four of the present series were treated with nifedipine; however, in only two of the children was adequate preoperative control of their blood pressures achieved with nifedipine alone.

Paragangliomata are rare in childhood and

hence experience in any one institution is limited. Our experience of 10 cases differs in some respects from that previously reported with a lower incidence of extra-adrenal and multiple tumours. Despite recent advances in radiological techniques for localising tumours we have continued to find arteriography and catecholamine venous sampling to be the most sensitive techniques for localising tumours and for providing important preoperative surgical information regarding the vascular supply of a tumour. The use of nifedipine in the preoperative preparation of our most recent cases has been encouraging, although in most cases phenoxybenzamine and propranolol remain the drugs of first choice for catecholamine blockade. Case 7 illustrates the importance of close follow up for further tumours and the association of other tumours of the paraganglia system in the same patients.

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