Phaeochromocytoma

Jacques W M Lenders, Graeme Eisenhofer, Massimo Mannelli, Karel Pacak

Phaeochromocytomas are rare neuroendocrine tumours with a highly variable clinical presentation but most commonly presenting with episodes of headaches, sweating, palpitations, and hypertension. The serious and potentially lethal cardiovascular complications of these tumours are due to the potent effects of secreted catecholamines. Biochemical testing for phaeochromocytoma is indicated not only in symptomatic patients, but also in patients with adrenal incidentalomas or identified genetic predispositions (eg, multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, neurofibromatosis type 1, and mutations of the succinate dehydrogenase genes). Imaging techniques such as CT or MRI and functional ligands such as ^{123}I-MIBG are used to localise biochemically proven tumours. After the use of appropriate preoperative treatment to block the effects of secreted catecholamines, laparoscopic tumour removal is the preferred procedure. If removal of phaeochromocytoma is timely, prognosis is excellent. However, prognosis is poor in patients with metastases, which especially occur in patients with large, extra-adrenal tumours.

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Department of Internal Medicine, Division of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen 6525GA, Netherlands (Prof J W M Lenders MD); **Department of Clinical Pathophysiology, University of Florence, Italy** (Prof M Mannelli MD); **Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development** (Prof K Pacak MD); **and Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke** (G Eisenhofer PhD) **National Institutes of Health, Bethesda, Maryland, USA**

Correspondence to:
Prof Jacques W M Lenders
j.lenders@aig.umcn.nl

Phaeochromocytomas are catecholamine-producing neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. Tumours from extra-adrenal chromaffin tissue are referred to as extra-adrenal phaeochromocytomas or paragangliomas. The term paraganglioma is also used for tumours derived from parasympathetic tissue in the head and neck, most of which do not produce catecholamines. Nearly 80–85% of phaeochromocytomas arise from the adrenal medulla, whereas about 15–20% are from extra-adrenal chromaffin tissue.[1,2] Catecholamine-producing extra-adrenal paragangliomas are usually found in the abdomen.[3,4]

In general outpatient clinics, the prevalence of phaeochromocytoma in patients with hypertension is 0·1–0·6%.[5–7] Although these tumours are frequently searched for, they are rarely found. The relatively high prevalence of phaeochromocytoma in autopsy studies (about 0·05%) also indicates that many tumours are missed, resulting in premature mortality.[8–11]

Hereditary phaeochromocytomas occur in multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, neurofibromatosis type 1, and the familial paragangliomas.[12–14] Sporadic forms of phaeochromocytoma are usually diagnosed in individuals aged 40–50 years, whereas hereditary forms are diagnosed earlier, most often before age 40 years.[15–17] Phaeochromocytoma is rare in children, but when found it is often extra-adrenal, multifocal, and associated with hereditary syndromes.[1,18,19]

Clinical presentation of phaeochromocytoma can vary greatly, with similar signs and symptoms produced by many other clinical conditions (panel 1). Phaeochromocytoma is therefore often referred to as the great mimic. Most but not all the clinical signs and symptoms of phaeochromocytoma are due to the direct actions of secreted catecholamines. Hypertension, tachycardia, pallor, headache, and feelings of panic or anxiety, usually dominate the clinical presentation (table 1).[17,20,21] Metabolic effects include hyperglycaemia, lactic acidosis, and weight loss.[22] Less common signs and symptoms are nausea, fever, and flushing. Hypertension is often paroxysmal in nature, in some patients occurring on a background of sustained hypertension, whereas others can have normal blood pressure between paroxysms. Hypertensive episodes can be severe and result in hypertensive emergencies. Blood pressure can also be consistently normal, especially in patients with adrenal incidentalomas, in those screened for an identified familial syndrome, or in those with a very small tumour.[23] Because of increasing use of advanced imaging techniques and improved recognition of genetic causes of phaeochromocytoma, where routine screening is becoming mandatory, the numbers of normotensive and asymptomatic patients diagnosed with the disease have steadily risen.[23–26] About 5% of all incidentalomas are phaeochromocytomas, with about 25% of all phaeochromocytomas now being discovered incidentally during imaging studies for unrelated disorders.[23,26,27]

Normal blood pressure or even hypotension is also common in patients with dopamine-producing paragangliomas, in whom diagnosis is often based on the space-occupying complications of tumours.[28,29] Presumably as a consequence of their asymptomatic nature, these tumours tend to be large; most present with metastases.

Some patients also present with unexplained orthostatic hypotension that, on a background of hypertension, provides an important diagnostic clue for the presence of a phaeochromocytoma. Occasionally,

Search strategy and selection criteria

We searched the databases PubMed and EMBASE (Jan 1, 2000, to May 1, 2005) using the following keywords: "phaeochromocytoma", "paraganglioma", and "extra-adrenal". We also included review articles, book chapters, or commonly referenced older publications. We reviewed the reference lists of articles identified by the search strategy and selected those we judged relevant. The search was restricted to papers published in English.

***Panel 1:* Differential diagnosis of phaeochromocytoma**

Endocrine
Hyperthyroidism
Carcinoid
Hypoglycaemia
Medullary thyroid carcinoma
Mastocytosis
Menopausal syndrome

Cardiovascular
Heart failure
Arrhythmias
Ischaemic heart disease
Baroreflex failure

Neurological
Migraine
Stroke
Diencephalic epilepsia
Meningioma
Postural orthostatic tachycardia syndrome (POTS)

Miscellaneous
Porphyria
Panic disorder or anxiety
Factitious disorders (eg, from use of sympathomimetic drugs such as ephedrine)
Drug treatment (eg, monoamine oxidase inhibitors, sympathomimetic drugs, withdrawal of clonidine)
Illegal drugs (eg, cocaine)

	Frequency
Headache	60–90%
Palpitations	50–70%
Sweating	55–75%
Pallor	40–45%
Nausea	20–40%
Flushing	10–20%
Weight loss	20–40%
Tiredness	25–40%
Psychological symptoms (anxiety, panic)	20–40%
Sustained hypertension	50–60%
Paroxysmal hypertension	30%
Orthostatic hypotension	10–50%
Hyperglycaemia	40%

Table adapted from references 17, 20, and 21. *Frequency in patients tested because of signs and symptoms.

Table 1:* Frequency of signs and symptoms (%) of phaeochromocytoma

patients with predominantly epinephrine-secreting tumours present with hypotension or even shock.[30] Pathophysiological factors contributing to hypotension and shock, include intravascular volume depletion, abrupt cessation of catecholamine secretion due to tumour necrosis, desensitisation of adrenergic receptors, or hypocalcaemia.[31] Shock can also be caused by a complicating cardiovascular emergency, such as myocardial infarction, cardiac arrhythmias, or a dissecting aortic aneurysm. Other cardiovascular complications of phaeochromocytoma include sudden death, heart failure due to toxic cardiomyopathy, hypertensive encephalopathy, a cerebrovascular accident, or neurogenic pulmonary oedema.[32–34] Since these disorders, when occurring without phaeochromocytoma, are often accompanied by strong increments in plasma catecholamines, the exclusion or confirmation of an eventual underlying phaeochromocytoma in these patients is especially difficult.

Paroxysmal signs and symptoms, a consequence of episodic secretion of catecholamines, provide compelling clues for a phaeochromocytoma.[17,20,21] Anaesthesia and tumour manipulation are the most well-known stimuli to elicit a catecholaminergic crisis. Food, micturition (urinary bladder phaeochromocytoma), and various chemical compounds or drugs (eg, glucagon, radiographic contrast substances, tyramine, metoclopramide, and tricyclic antidepressants) might also induce paroxysms. Such spells are usually unpredictable. For most patients they last between several minutes and 1 h.[35,36]

Despite improved diagnostic techniques that can bring about an earlier diagnosis of phaeochromocytoma, there still usually remains a delay of 3 years between initial symptoms and a final diagnosis.[18,27] The most obvious reason for this delay is that in daily clinical patient care, the individual symptoms are quite non-specific—especially headaches, palpitations, and sweating, which are the most frequent. Nevertheless, if all three symptoms present together, the specificity of this combination is reported to be more than 90%.[37] Hypertension from a phaeochromocytoma during pregnancy can mimic pre-eclampsia, so that the diagnosis is delayed or even missed entirely.

Advances in diagnosis and genetics now challenge the traditional rule of 10 for phaeochromocytomas (10% bilateral, 10% extra-adrenal, 10% familial, 10% malignant). Prevalence of bilateral adrenal tumours is higher than 10% in some familial phaeochromocytoma syndromes such as multiple endocrine neoplasia type 2 and von Hippel-Lindau syndrome.[38] Prevalence of extra-adrenal tumours can reach 20%,[1,19] and up to a quarter or more are hereditary.[12–14,24] Finally, although metastases might be rare for adrenal phaeochromocytomas (up to 5%), the prevalence of malignant disease is about 33% for extra-adrenal phaeochromocytomas and even higher in patients with specific mutations such as those causing some forms of familial paragangliomas (eg, *SDHB*, a gene that encodes the B subunit of mitochondrial succinate dehydrogenase).[1,15,18,19,39]

We further review here the advances in genetics, biochemical diagnosis, and tumour imaging techniques and how these advances affect the spectrum of disease presentations that must now be considered and the available options for disease management and treatment.

Genetics of phaeochromocytoma

Advances in genetics and recognition of the high prevalence of phaeochromocytoma in certain familial syndromes led to mandatory routine screening in patients with identified mutations, even in the absence of typical clinical signs and symptoms.[40] Accumulating evidence also suggests that a hereditary basis for phaeochromocytoma is more frequent than previously thought, accounting for up to 24% of patients with the tumour with no obvious initial evidence of a syndrome or family history.[13,24,41]

So far, germline mutations in five genes have been identified to be responsible for familial phaeochromocytomas: the von Hippel-Lindau gene (*VHL*), which causes von Hippel-Lindau syndrome; the *RET* gene leading to multiple endocrine neoplasia type 2; the neurofibromatosis type 1 gene (*NF1*), which is associated with von Recklinghausen's disease; and the genes encoding the B and D subunits of mitochondrial succinate dehydrogenase (*SDHB* and *SDHD*), which are associated with familial paragangliomas and phaeochromocytomas (table 2).[14] Phaeochromocytomas are not always present and usually are not the first clinical manifestation of syndromes due to mutations of *VHL*, *RET*, and *NF1* genes. Phaeochromocytomas in these three syndromes are usually associated with other benign or malignant neoplasms (panel 2).

	Chromosome	Exons	Protein	Frequency of germline mutations in apparent sporadic phaeochromocytoma*	Frequency of malignant disease*
VHL	3p25-26	3	pVHL19 and pVHL30	2–11%	5%
RET	10q11.2	21	Tyrosine-kinase receptor	<5%	3%
NF1	17q11.2	59	Neurofibromin	Unknown	11%
SDHB	1p36.13	8	Catalytic iron-sulfur protein	3–10%	50%
SDHD	11q23	4	CybS (membrane-spanning subunit)	4–7%	<3%

VHL=von Hippel-Lindau syndrome. *Data from references 13, 24, and 42–45.

Table 2: **Characteristics of genes associated with familial forms of phaeochromocytoma**

Panel 2: Main clinical features of syndromes associated to phaeochromocytoma

Von Hippel-Lindau syndrome

Type 1 (no phaeochromocytoma)
- Renal-cell cysts and carcinomas
- Retinal and CNS haemangioblastomas
- Pancreatic neoplasms and cysts
- Endolymphatic sac tumours
- Epididymal cystadenomas

Type 2 (with phaeochromocytoma)

A: Retinal and CNS haemangioblastomas
- Phaeochromocytomas
- Endolymphatic sac tumours
- Epididymal cystadenomas

B: Renal-cell cysts and carcinomas
- Retinal and CNS haemangioblastomas
- Pancreatic neoplasms and cysts
- Phaeochromocytomas
- Endolymphatic sac tumours
- Epididymal cystadenomas

C: Phaeochromocytomas only

Multiple endocrine neoplasia type 2

A: Medullary thyroid carcinoma
- Phaeochromocytoma
- Hyperparathyroidism
- Cutaneous lichen amyloidosis

FMTC: Familial medullary thyroid carcinoma only

B: Medullary thyroid carcinoma
- Phaeochromocytoma
- Multiple neuromas
- Marfanoid habitus

Neurofibromatosis type 1
- Multiple fibromas on skin and mucosae
- "Cafè au lait" skin spots
- Phaeochromocytomas

Paraganglioma syndromes
- Head and neck tumours (carotid-body tumours; vagal, jugular, and tympanic paragangliomas)
- Phaeochromocytomas
- Abdominal or thoracic paragangliomas (or both)

Von Hippel-Lindau syndrome

Renal clear-cell carcinomas and cysts, CNS and retinal hemiangioblastomas, phaeochromocytomas, pancreatic tumours and cysts, endolymphatic tumours, and epididymal cysts occur in von Hippel-Lindau syndrome, which affects about one in 36 000 livebirths.[46–48] Presentation of these clinical manifestations can vary, with two broad types (1 and 2) depending on the presence or absence of a family history of phaeochromocytoma.[47] Overall, phaeochromocytoma is present in 10–20% of patients with the syndrome, with a mean age at presentation of 30 years.[47] Phaeochromocytomas in von Hippel-Lindau syndrome produce norepinephrine but not epinephrine. These tumours often have a bilateral adrenal presentation, and occasionally are multifocal with abdominal or thoracic localisations.[24,49–51] Malignant disease is rare, at about 5% or lower.[42]

Multiple endocrine neoplasia type 2

In multiple endocrine neoplasia type 2, phaeochromocytoma is the first clinical manifestation in 10–30% of patients, but penetrance is ultimately about 50%.[52] Phaeochromocytomas in these patients produce both epinephrine and norepinephrine, with production of epinephrine occasionally predominating.[51] Most patients (50–80%) develop bilateral adrenal tumours, either simultaneously or at different times. Extra-adrenal localisation or malignant disease are very rare (<5%).[16,24]

Neurofibromatosis type 1 syndrome

In neurofibromatosis type 1, phaeochromocytoma is relatively rare (<5%). Because of this, routine screening for the tumour is not generally recommended. Genetic testing in members of an affected family is possible.[24] Phaeochromocytomas in affected individuals usually produce both epinephrine and norepinephrine.

Paraganglioma syndromes

The germline mutations of the succinate dehydrogenase gene family are the most recently identified hereditary causes of phaeochromocytoma.[43,53] Mutations of each of the *SDHB* and *SDHD* genes have been seen in about 3–11% of patients with non-syndromic phaeochromocytoma, mainly occurring as paragangliomas in the head, chest, and abdomen (panel 2).[43,44] Head and neck paragangliomas are more commonly associated with *SDHD* than with *SDHB* mutations.[43,53] Penetrance seems slightly higher and multifocal disease seems to be more frequently associated with *SDHD* than with *SDHB* mutations, but *SDHB* mutations are associated with an increased rate of malignant disease (up to 50%).[44,45] The chromaffin tumours due to mutations of both genes produce predominantly norepinephrine. Whether other malignant diseases are associated with *SDHB* mutations such as renal-cell carcinoma and thyroid papillary carcinoma is not currently clear.[44] *SDHD* mutations are maternally imprinted; thus, only carriers who have inherited the mutation from the father develop the disease and those who inherit from the mother are disease-free.[54]

Genetic testing

Should genetic testing be propagated in all patients with a phaeochromocytoma? It has been suggested that all patients with a phaeochromocytoma should be considered for genetic testing.[44,55] The reasons are twofold. First, the syndromic hereditary forms of phaeochromocytoma are associated with other neoplasms, so an early diagnosis of a hereditary syndrome might lead to regular surveillance and eventual treatment and thus improve the prognosis; this could extend to other family members with similar benefits. Second, in patients with proven germline mutations, multiple phaeochromocytomas and recurrences are highly probable, so that a more stringent clinical follow-up is recommended throughout life. Presently, the indication for cost-effective genetic testing is recommended to those patients who have a positive family history or those who are younger than 50 years, especially children.[24] However, other clues that should be regarded as an indication for genetic testing include the presence of bilateral phaeochromocytomas or multifocal extra-adrenal disease, or the association of phaeochromocytomas with other tumours. Direction of genetic testing to one of the suspected genes can benefit from consideration of the clinical picture and biochemical phenotype of the tumour: bilateral epinephrine-producing tumours or the association of phaeochromocytoma with medullary thyroid carcinoma indicate the need for *RET* analysis; predominantly norepinephine-producing phaeochromocytomas—especially if bilateral or in association with renal-cell carcinoma or cysts, retinal or cerebrospinal haemangioblastomas, or pancreatic tumours—indicate *VHL* testing; and the association between chromaffin tumours and head or neck paragangliomas indicates analysis of *SDHB* or *SDHD* genes.

If genetic testing is negative in a patient with phaeochromocytoma, only biochemical testing for recurrence of the tumour after surgery is needed. When genetic testing is negative in a family member of a patient with a hereditary form of phaeochromocytoma, no additional biochemical or imaging tests are necessary.

Biochemical diagnosis and localisation

Biochemical testing

All patients with suspected phaeochromocytoma should undergo biochemical testing. These include patients with paroxysmal signs or symptoms suggestive of a phaeochromocytoma; patients with recent, therapy-resistant, or volatile hypertension; patients with a paradoxical blood pressure response during surgery and anaesthesia; patients with a hereditary predisposition for a phaeochromocytoma; asymptomatic patients with an adrenal incidentaloma; and patients with sudden attacks of anxiety. Because of the low prevalence of phaeochromocytoma, biochemical screening for the tumour in asymptomatic patients with hypertension is not indicated.

Biochemical presentation of excessive production of catecholamines is an essential step for the diagnosis of phaeochromocytoma. Traditional biochemical tests include measurements of urinary and plasma catecholamines, urinary metanephrines (normetanephrine and metanephrine), and urinary vanillylmandelic acid (VMA). Measurements of plasma-free metanephrines (normetanephrine and metanephrine) represent a more recently available test.[56] Because of insufficient sensitivity and specificity, chromogranin A has no additional benefit over the use of catecholamines or their metabolites for initial diagnosis of phaeochromocytoma.[57–59]

The potentially fatal consequences of a missed diagnosis justify the need for a high level of reliability of a positive test result in that rare patient with the tumour. This conversely also provides confidence that a negative test result reliably excludes the tumour. The initial examination of a patient with suspected phaeochromocytoma should therefore include a suitably sensitive biochemical test. Either blood or urine testing can be used, with each test having its own advantages and disadvantages. Accumulating evidence suggests that

measurements of plasma-free metanephrines or urinary-fractionated metanephrines (normetanephrine and metanephrine separately) are the most sensitive tests for diagnosis, and are the most suitable for reliable exclusion of phaeochromocytoma (table 3).[50,60–66] Increased sensitivity of metanephrines compared with catecholamines is due to the continuous production of O-methylated metabolites in tumours from catecholamines leaking from chomaffin stores. The production of O-methylated metabolites is independent of the highly variable release of catecholamines.[67,68] Although tumours produce and metabolise catecholamines, they do not always release catecholamines. Provided appropriate reference intervals are used, the high diagnostic sensitivities of plasma-free or urinary-fractionated metanephrines mean that negative test results exclude the presence of virtually all phaeochromocytomas. Exceptions include asymptomatic small tumours that produce and metabolise negligible amounts of norepinephrine or epinephrine.

As with all biochemical tests of catecholamine excess, a remaining difficulty is that a positive result for plasma or urinary metanephrines does not always reliably indicate a phaeochromocytoma. The many physiological stimuli, drugs, and clinical conditions that cause increases in circulating catecholamines and metabolites compound this problem. The rarity of the tumour in tested patients, many of whom have symptoms associated with increased sympathetic activity and circulating catecholamines (eg, hypertension, heart failure, stroke, baroreflex failure, cardiogenic shock), also means that false-positive results exceed true-positive results.

Most true-positive results can be distinguished from false-positive test results from the magnitude of increases in test results above reference intervals (table 4). Most patients with phaeochromocytoma have increases well above even the highest false-positive results. In these patients, diagnosis is straightforward. Further confirmation can be achieved by the demonstration of similar patterns of increased plasma and urinary normetanephrine and metanephrine or repeat testing with an alternative method.

The major remaining difficulties are patients with smaller increases (less than two to three times the upper reference limits), most of whom will not have phaeochromocytoma. Drugs, dietary interferences, or inappropriate sampling conditions are causes of false-positive results. False-positive results could arise either due to direct interference with analytical methods or pharmacological effects on the disposition of catecholamines (table 5). Interference with analytical methods is highly variable from method to method. Avoidance of such interference needs intimate knowledge of the procedures used and how various drugs can affect them. Pharmacological effects on the disposition of catecholamines are independent of the measurement method and can be avoided by the withdrawal or substitution of drugs known to cause increases in catecholamines and their metabolites. Phenoxybenzamine (used to treat patients with suspected phaeochromocytoma) and tricyclic antidepressants are major causes of false-positive results, in one study accounting for up to 45% of false-positive increments of urinary and plasma normetanephrine and norepinephrine.[69] Sampling of blood after overnight fasting and in the supine position can easily avoid the effects of diet and physical activity on plasma measurements. For urine measurements, timed or overnight urine samples or volume correction using additional measurements of creatinine can avoid difficulties with incomplete or overzealous collection of urine.[66]

Use of clonidine to suppress catecholamine release from the sympathoadrenal system provides a dynamic

	Sensitivity	Specificity
Plasma-free metanephrines	99%	89%
Plasma catecholamines	84%	81%
Urinary catecholamines	86%	88%
Urinary-fractionated metanephrines	97%	69%
Urinary total metanephrines	77%	93%
VMA	64%	95%

Sensitivity values of all tests for familial phaeochromocytoma are lower than that for sporadic phaeochromocytomas; the reverse is the case for specificity values. Table adapted from reference 64.

Table 3: **Sensitivity and specificity of biochemical tests for diagnosis of phaeochromocytoma**

	Presence of phaeochromocytoma		
	Unlikely*	Possible	Likely†
Urine tests			
Catecholamines (HPLC)			
Norepinephrine (nmol/24 h)	<500	500–1180	>1180
Epinephrine (nmol/24 h)	<100	100–170	>170
Fractionated metanephrines (HPLC)			
Normetanephrine (nmol/24 h)	<3000	3000–6550	>6550
Metanephrine (nmol/24 h)	<1000	1000–2880	>2880
Total metanephrines (spectrophotometry)			
Total of normetanephrine and metanephrine (μmol/24 h)	<6	6–12·7	>12·7
VMA (spectrophotometry)			
VMA (μmol/24 h)	<40	40–55	>55
Blood tests			
Catecholamines (HPLC)			
Noradrenaline (nmol/L)	<3·00	3·00–7·70	>7·70
Adrenaline (nmol/L)	<0·45	0·45–1·20	>1·20
Free metanephrines (HPLC)			
Normetanephrine (nmol/L)	<0·60	0·60–1·40	>1·40
Metanephrine (nmol/L)	<0·30	0·30–0·42	>0·42

HPLC=high-pressure liquid chromatography. Unlikely=number of true-negative results>>number of false-negative results; possible=false-positive results>true-positive results; likely=true-positive results>>false-positive results. *Cut-off points represent upper reference limits used for estimation of sensitivity and specificity in table 3; therefore, the negative predictive value (ie, likelihood that phaeochromocytoma is not present) varies for every test, depending on differences in the test characteristics in table 3. †Cut-off points are calculated from 99th percentile in a reference group of 644 patients who had no phaechromocytoma. Table adapted from reference 64.

Table 4: **Likelihood of phaeochromocytoma at different cut-off points for biochemical tests of catecholamine excess**

	Nature of interference
Analytical methods	
Coffee (including decaffeinated coffee)	HPLC assays: plasma catecholamines
Labetalol	Spectrophotometric and fluorometric assays: urinary catecholamines and metanephrines;
Sotalol	HPLC assays: plasma catecholamines
Buspirone	HPLC assays: urinary metanephrines
Paracetamol	HPLC assays: plasma-free metanephrines
Levodopa	HPLC assays: catecholamines and metabolites
α-methyldopa	HPLC assays: catecholamines
Sympathomimetics (eg, amfetamines, ephedrine)	Spectrophotometric and fluorometric assays: plasma and urinary catecholamines
Pharmacodynamic or pharmacokinetic interference	
Tricyclic antidepressants	Blocks norepinephrine reuptake, causing rises in plasma and urinary norepinephrine, normetanephrine, and VMA
Phenoxybenzamine	Blocks presynaptic α2 adrenoceptors, causing increases in plasma and urinary norepinephrine, normetanephrine, and VMA
Monoamine oxidase inhibitors	Blocks deamination, causing up to five-fold increases in plasma and urinary metanephrines
Levodopa	Metabolised by enzymes that also convert catecholamines
α-methyldopa	Metabolised by enzymes that also convert catecholamines
Stimulants (eg, caffeine, nicotine)	Increased plasma and urinary catecholamines
Sympathomimetics (eg, amfetamines, ephedrine)	Increased plasma and urinary catecholamines
Calcium-channel blockers (dihydropyridines)	Increased plasma catecholamines due to sympathetic activation

HPLC=high-pressure liquid chromatography.

Table 5: **Sources of variable interference with measurements of catecholamines and catecholamine metabolites**

pharmacological test to distinguish increased catecholamine release due to sympathetic activation from increased release due to phaeochromocytomas.[70] Failure to suppress plasma norepinephrine (ie, a reduction of <50% from basal or consistently raised basal plasma concentrations of >3 nmol/L) after clonidine is highly predictive for phaeochromocytoma (97%). By contrast, the negative predictive value of a normal test result is only 75%. If plasma normetanephrine is used (of which a failure to suppress is a reduction of less than 40% from basal or consistently raised basal concentrations of plasma normetanephrine of more than 0·60 nmol/L) instead of plasma norepinephrine, the positive and negative predictive values of this test improve to 100% and 96%, respectively.[69] Thus, although absence of suppression of plasma norepinephrine or normetanephrine both provide strong evidence for phaeochromocytoma, only the suppression of normetanephrine provides reasonable evidence that a phaeochromocytoma is not present.

Imaging procedures

Tumour localisation should ideally only be initiated once there is unequivocal biochemical evidence for phaeochromocytoma. CT scans of the entire abdomen (including pelvis), with and without contrast, are most often used for initial localisation of adrenal or possible extra-adrenal abdominal phaeochromocytomas.[71] Evidence from one small study indicates that contrast-enhancement with iohexol has no effect on plasma catecholamines.[72] Until this finding is confirmed, patients should be protected from a hypertensive crisis or cardiac arrhythmia by combined blockade by α and β adrenoceptors. Although T2-weighted MRI with gadolinium enhancement has a similar diagnostic sensitivity to CT scanning, it is preferred for the localisation of extra-adrenal tumours or tumours during pregnancy, in children, or in patients with allergies to contrast.[1,73,74] No adrenergic blockade is needed.[71] Since CT scanning and MRI have similar sensitivities (90–100%) and specificities (70–80%), MRI is the preferred procedure.[2,71]

Because of the restricted specificities of CT and MRI, identification of a mass detected by these techniques can be achieved by use of the increased specificity (95–100%) of ^{123}I-metaiodobenzylguanidine (MIBG) scanning.[2,75] If ^{123}I-MIBG is not available, ^{131}I-MIBG could be used as an alternative, but has poorer imaging qualities than ^{123}I-MIBG.[76] The coupling of functional with anatomical imaging might also be valuable for the detection of additional multifocal or metastatic tumours, which can be important for appropriate guiding of subsequent management and treatment. However, ^{123}I-MIBG scanning might not be warranted before surgery in all patients with biochemically proven phaeochromocytomas. Such imaging is most relevant in patients with extra-adrenal or large (>5 cm) adrenal tumours with increased risk of malignant disease,[77] or in patients with high suspicion of the presence of multifocal disease.

Several drugs (eg, labetalol, tricyclic antidepressants, and specific calcium antagonists) can interfere with tumour uptake or retention of ^{123}I-MIBG.[78] Temporary withdrawal of these interfering drugs (five times their half-lives) or use of other drugs can avoid false-negative test results. In patients whose ^{123}I-MIBG scans are negative, ^{111}In-octreotide scanning might be useful in case no other functional imaging techniques are available.[79,80] Small recurrent tumours or metastases in the adrenal region can be detected intraoperatively by a γ-detector probe after the isotope is given a few hours before surgery.[81]

PET with ^{18}F-fluorodopamine, ^{18}F-fluorodopa, ^{18}F-fluorodeoxyglucose, or ^{11}C-hydroxyephedrine are other functional imaging methods that can be used as alternatives to ^{123}I-MIBG or as additional procedures if ^{123}I-MIBG scanning is negative.[82–85] ^{18}F-fluorodeoxyglucose, the only PET imaging compound that is widely available, is not recommended for initial diagnostic localisation, since it is non-specific for phaeochromocytoma and sensitivity is restricted.[82] However, the compound can be useful if other imaging procedures are negative, often in more rapidly growing dedifferentiated tumours that have lost the ability to accumulate more specific drugs.[82,86] ^{18}F-fluorodopamine PET offers better diagnostic sensitivity than ^{131}I-MIBG scintigraphy, especially in metastatic phaeochromocytomas where the compound

can localise far more foci than can ^{131}I-MIBG.[86,87] ^{18}F-fluorodopa and ^{11}C-hydroxyephedrine have also been reported to offer excellent sensitivity and specificity, but how useful these drugs are for metastatic phaeochromocytomas is unclear.[83,84]

Management of phaeochromocytoma

Preoperative management

Once a phaeochromocytoma is located, complications during surgery need to be kept to a minimum by appropriate preoperative medical treatment. With adequate pretreatment, perioperative mortality has fallen to less than 3%, which emphasises the importance for adequate preoperative management.[12,88,89] The major aim of medical pretreatment is to prevent catecholamine-induced, serious, and potentially life-threatening complications during surgery, including hypertensive crises, cardiac arrhythmias, pulmonary oedema, and cardiac ischaemia.[89–91] Even if a diagnosis is considered in very rare life-threatening conditions (eg, shock due to a haemorrhagic necrosis or rupture of a phaeochromocytoma), stabilisation with subsequent medical pretreatment and elective surgery is preferred, since emergency tumour resection without proper preparation results in poor survival.[92]

There are no randomised prospective studies that are large enough to establish the most effective drug regimen before surgery. Traditional regimens include the blockade of α-adrenoceptors with phenoxybenzamine, prazosin, doxazosin, or urapidil.[93–95] Phenoxybenzamine is often preferred because it blocks α-adrenoceptors non-competitively. This type of blocking offers advantages over competitive blockade with compounds such as doxazosin, which avoids drug displacement from α-adrenoceptors by excessive increases in catecholamines during surgery. However, several groups have advocated pretreatment with doxazosin, based on a presumed increased risk of postoperative hypotension due to extended, non-competitive α-adrenergic blockade.[19,96] But several retrospective, non-randomised clinical trials comparing phenoxybenzamine with prazosin or doxazosin have provided conflicting results.[97–99]

Other alternative drugs for preoperative management are labetalol or calcium-channel blockers (dihydropyridines), either alone or in combination with α-adrenergic receptor blockers.[100] Labetalol is a combined α and β-adrenoceptor blocker with stronger actions on β than α-adrenoceptors. Therefore, this drug is less suitable for pretreatment than other α-adrenoceptor blockers. Calcium-channel blockers have the advantage of not causing orthostatic hypotension, but if used alone they do not prevent haemodynamic instability completely. α-methyl-paratyrosine (metirosine), which blocks catecholamine synthesis, is occasionally used for preoperative treatment. Two retrospective studies showed that use of metirosine as an adjunct to phenoxybenzamine needed less antihypertensive drug treatment during surgery than did the sole use of phenoxybenzamine, but this finding has not been verified by any prospective study.[101,102]

Pretreatment with an α-adrenergic blocker can usually be undertaken on an outpatient basis and is safe in most patients.[103] Treatment usually lasts for 10–14 days.[88] The initial dose of phenoxybenzamine is 10 mg twice a day. The dose is increased every 2–3 days by 10–20 mg to a total daily dose of 1 mg/kg, which is sufficient in most patients. Doxazosin is given in increasing doses from 1 to 16 mg once a day.[93] A β-adrenoceptor blocker (eg, propranolol 40 mg three times daily or atenolol 25–50 mg once daily) could be included after several days of α-adrenergic blockade. This addition is especially useful in patients who also have tachyarrhythmias. Blockade of β-adrenoceptors should never be initiated before blockade of α-adrenoceptors, since the loss of β-adrenoceptor-mediated vasodilatation leaves α-adrenoceptor stimulation unopposed, which could result in hypertensive crises.

To ensure adequate preoperative preparation, several criteria have been proposed: blood pressure should be reduced to below 160/90 mm Hg for at least 24 h; orthostatic hypotension should be present, but blood pressure in the upright position should not fall below 80/45 mm Hg; there should be no more than one ventricular extrasystole every 5 min; and the electrocardiogram should show no S-T segment changes and T-wave inversions for 1 week.[88]

Risk of excessive orthostatic hypotension can be kept to a minimum by the increase of salt and fluid intake. The additional advantage of this approach is that it reduces the risk of postoperative hypotension. Should substantial rises in blood pressure still take place during surgery, these can be controlled by bolus or by continuous infusion of phentolamine, sodium nitroprusside, or a shortacting calcium antagonist (eg, nicardipine); tachyarrhythmias can be treated by infusion of a shortacting β-adrenoceptor blocker (eg, esmolol).[93,96]

After surgery, patients need to be under close surveillance for the first 24 h in an intensive or intermediate care unit. The two major postoperative complications are hypotension and hypoglycaemia. Postoperative hypotension is due to the abrupt fall in circulating catecholamines after tumour removal in the continuing presence of α-adrenoceptor blockade (by phenoxybenzamine). Treatment consists of fluid replacement and occasionally intravenous ephedrine. If ephedrine infusion is ineffective, vasopressin might be used.[104] The risk of hypoglycaemia is related to rebound hyperinsulinaemia due to the recovery of insulin release after tumour removal.[93]

Surgical treatment

Laparoscopic removal of intra-adrenal and extra-adrenal phaeochromocytomas is now the preferred surgical

technique.[105] Data from observational studies clearly show that the laparoscopic procedure reduces postoperative morbidity, hospital stay, and expense compared with conventional laparotomy.[106–112] The complication rate of laparoscopic adrenalectomy (apart from intraoperative blood pressure derailments) is probably less than 8% with a conversion rate of 5%.[109,113,114] Some clinicians recommend a retroperitonal laparoscopic approach for suprarenal paragangliomas and a transperitoneal laparoscopic approach for infrarenal paragangliomas.[110]

Because of the high incidence of bilateral adrenal disease in familial phaeochromocytoma (eg, von Hippel-Lindau and multiple endocrine neoplasia type 2 syndromes), adrenal-cortex-sparing laparoscopic surgery (partial adrenalectomy) has been advocated to save the cortex and prevent permanent glucocorticoid deficiency.[115–121]

Currently, after adequate medical preparation, operative mortality is less than 1% if undertaken by an experienced anaesthesiologist and a skilful surgeon.[114,117,122] The long-term prognosis of patients after resection of a solitary sporadic phaeochromocytoma is excellent, although hypertension might persist after surgery in nearly 50% of patients.[123] Findings from a large study with a long-term follow-up showed a recurrence rate of 17%, with half the patients showing signs of malignant disease.[27] Recurrences occurred more often in patients with extra-adrenal disease (33%) than in those with adrenal disease (14%), and more often in the familial population (33%) than in the non-familial population (13%).[124] In patients who have undergone adrenal cortex-sparing surgery, a small piece of tumour could have been left behind or a new tumour could develop in the remnant because of a genetic predisposition. The risk of tumour recurrence in the remnant adrenal gland is 10%, but the metachronous tumour development in the contralateral adrenal gland is 30% in patients with hereditary forms of phaechromocytoma.[116,119,124] All patients should be followed up every year for at least 10 years after surgery. Patients with extra-adrenal or familial phaeochromocytoma should be followed up indefinitely.

Malignant phaeochromocytomas

Despite the increasing availability of molecular diagnostic and prognostic markers, it remains impossible to predict the subsequent development of malignant disease, based on histological findings in a resected tumour.[125,126] Not one histological feature predicts or provides unequivocal evidence of malignant derangement. Only the presence of metastases of chromaffin tissue at sites where no chromaffin tissue should be expected establishes a definite diagnosis of malignant phaeochromocytoma. The most common metastatic sites are the bones, lungs, liver, and lymph nodes. In general, tumours that are large (>5 cm) or have an extra-adrenal location have a higher risk for malignant disease than tumours that are small or have an adrenal location.[19] Paragangliomas in patients with *SDHB* mutations have a particularly high rate of malignant disease.[52,53] Increased plasma or urinary concentrations of dopamine and dihydroxyphenylalanine (dopa) arise more often in malignant than in benign phaeochromocytomas.[127–129] When malignant disease is confirmed, the natural clinical course is highly variable in patients with 5-year survival rates of 50%.[126]

There remains no effective treatment for malignant phaeochromocytoma. Radical surgical removal of tumour tissue is the mainstay to improve symptoms and survival, but there are no randomised studies that support this approach. Symptomatic treatment can be obtained with α-adrenergic blockers. α-methyl-paratyrosine can be useful in selected patients with very high concentrations of circulating catecholamines. Treatment with ^{131}I-MIBG or combination chemotherapy (cyclophosphamide, vincristine, and darcabazine) has shown disappointing results, with only shortlasting remissions.[130–132] Although nearly 80% of patients show symptomatic improvement after ^{131}I-MIBG treatment, less than 5% have a complete remission and 30% have a partial tumour remission.[131,132] Improved long-term survival has been shown with increased doses of ^{131}I-MIBG.[133] However, controlled studies need to confirm these results and establish whether combination treatment of ^{131}I-MIBG with myeloablative chemotherapy (and stem cell rescue) can improve prospects of patients with metastatic disease.

Conflict of interest statement

We declare that we have no conflict of interest.

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