

Endocrinology: phaeochromocytoma

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Aetiology/pathophysiology

Originating from the chromaffin cells of the sympathetic nervous system, most phaeochromocytomas arise within the adrenal medulla, with a smaller number derived from sympathetic ganglia. They commonly secrete norepinephrine (noradrenaline) and epinephrine (adrenaline), but in some cases significant amounts of dopamine may be released. As with many other endocrine tumours, the diagnosis of malignancy is dependent upon evidence of local infiltration or distant spread, since histological appearances do not reliably distinguish benign from malignant tumours.

Germline mutations in a number of different genes have been found to cause familial phaeochromocytomas (Table 1). Succinate dehydrogenase (SDH) mutations are a frequent cause of familial phaeochromocytoma and are important as patients with an *SDHB* mutation typically exhibit more aggressive disease with a high incidence of malignancy (Table 1). They are usually extra-adrenal, mainly occurring as paragangliomas in the head, chest and abdomen. *SDHD* mutations are maternally imprinted; thus only carriers who have inherited the mutation from the father develop the disease.

Epidemiology

Rare, accounting for 0.1–0.6% of all cases of hypertension in general outpatient clinics. Many remain occult and are only diagnosed at post-mortem.

Clinical presentation

Cases may come to light during the investigation of poorly controlled hypertension, when direct questioning reveals an array of other manifestations of catecholamine excess. These are frequently reported to occur in an episodic or paroxysmal fashion. Occasional cases present with pregnancy-associated hypertension, myocardial infarction, cardiac dysrhythmias or a dilated catecholamine cardiomyopathy. The incidence in normotensive asymptomatic subjects is 'rising' due to increased use of high-resolution imaging and screening for phaeochromocytoma in subjects with predisposing genetic mutations. About 5% of all adrenal 'incidentalomas' are phaeochromocytomas, with about

25% of all phaeochromocytomas now discovered incidentally during imaging for unrelated disorders.

Physical signs

Features of increased sympathetic activity are often present during a paroxysm, eg tachycardia, sweating, pallor (not flushing). Hypertension may be sustained or episodic and approximately 50% of cases exhibit orthostatic hypotension (the latter reflecting intravascular depletion in response to long-standing hypertension).

Investigations

This should be approached in two stages:

- > confirm catecholamine excess – through the measurement of their metabolites
- > localise the tumour.

Confirm catecholamine excess

Urinary metanephrines

Urinary-fractionated metanephrines (ie normetanephrine and metanephrine measured separately) offer a highly sensitive and specific screening test for the detection of phaeochromocytoma and paraganglioma.

Key point

An update on 'well-known facts' about phaeochromocytoma

In adults, phaeochromocytomas were known as the '10% tumour' reflecting approximately:

- > 10% extra-adrenal
- > 10% bilateral/multiple
- > 10% malignant
- > 10% familial.

This no longer holds true with, for example, many more cases now identified with an underlying genetic basis (Table 1). In addition, the prevalence of bilateral tumours is greater than 10% in certain familial syndromes (eg multiple endocrine neoplasia type 2 (MEN-2) and von Hippel–Lindau syndrome (VHL)), while in childhood a higher proportion are extra-adrenal and malignancy is more common.

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Key point

Commonly reported symptoms of pheochromocytoma

- > headache
- > sweating
- > palpitations / forceful heartbeat
- > anxiety
- > tremor
- > nausea and vomiting
- > chest and abdominal pain / dyspnoea.

Note that the triad of headache, sweating and palpitations is considered to be highly suggestive of a diagnosis of pheochromocytoma.

Plasma metanephrines

Plasma free metanephrines (normetanephrine and metanephrine) are a convenient (and slightly more sensitive) alternative to 24-hour urinary collections.

3-Methoxytyramine (a metabolite of dopamine, and measured in urine or plasma) is a potential marker of malignancy.

False positives

There are many causes of false positive biochemical screening. These fall into two groups:

1 true catecholamine excess, due to:

- > drugs (tricyclic antidepressants, phenoxybenzamine, monoamine oxidase inhibitors, levodopa, alpha-methyldopa, sympathomimetics, calcium channel blockers)
- > stimulants (eg coffee, nicotine)
- > anxiety
- > disease states (eg myocardial infarction (MI), heart failure, cardiogenic shock, obstructive sleep apnoea)

2 interference with analytical method (different depending on assay but including coffee, labetalol, levodopa, alpha-methyldopa, paracetamol and sympathomimetics).

Most false positive levels are significantly lower than in pheochromocytoma. Repeat the test having stopped any interfering medication, and consider an alternative screening method.

Clonidine suppression test

Clonidine acts via presynaptic alpha-adrenoreceptors to block catecholamine secretion and can be used to distinguish increased norepinephrine release due to sympathetic activation from autonomous tumoral secretion. Failure to adequately suppress plasma norepinephrine in response to clonidine is highly predictive of pheochromocytoma (97%), but a normal test result does not exclude pheochromocytoma (negative predictive value only 75%). Use of plasma normetanephrine increases the positive and negative predictive values to 100 and 96%, respectively.

Localise the tumour

CT/MRI

CTs of the abdomen and pelvis are commonly used (Figs 1 and 2). T2-weighted MRI with gadolinium enhancement has similar

Table 1. Hereditary syndromes associated with pheochromocytoma and/or paraganglioma

Von Hippel–Lindau syndrome (VHL)

VHL (tumour suppressor gene) mutations

Pheochromocytomas in ~20%; higher percentage in some kindreds (type 2) ~5% are malignant

Multiple endocrine neoplasia (type 2) syndrome

RET (proto-oncogene) mutations

Type 2a (Type 2) – medullary thyroid carcinoma, pheochromocytomas, hyperparathyroidism

Type 2b (Type 3) – medullary thyroid carcinoma, pheochromocytomas, marfanoid habitus, mucosal neuromas

Neurofibromatosis (type 1)

NF gene mutations

Pheochromocytomas in <5% of cases (20% bilateral)

Hereditary paragangliomas

Mutations identified in succinate dehydrogenase complex subunits B, D, C, A, AF2 (ie SDHB, SDHD, SDHC, SDHA, SDHAF2)

Paraganglioma and/or pheochromocytoma (PPGL), rare renal cancers, gastrointestinal stromal tumours (GIST); head and neck paragangliomas may occur in addition to, or independent of, abdominal/thoracic PPGL

Familial pheochromocytomas

TMEM27 mutations – pheochromocytomas and rare renal cancers

MAX mutations – mainly PPGL

KIF1B – pheochromocytoma and neuroblastoma

EGLN1 – pheochromocytoma and congenital erythrocytosis

MDH2 – pheochromocytoma and paraganglioma

Polycythaemia-paraganglioma syndrome

EPAS (HIF2A) mutations – polycythaemia, PPGL, somatostatinoma

Leiomyomatosis and renal cell cancer

Fumarate hydratase (FH) mutations – cutaneous and uterine leiomyomas, type 2 papillary renal carcinoma, rare PPGL

sensitivity and specificity to CT. The tumour typically exhibits a distinctive 'bright white' signal on T2-weighted images.

Radioiodine-labelled metaiodobenzylguanidine scintigraphy / single-photon emission CT (SPECT)

Metaiodobenzylguanidine (¹²³I-MIBG), which is taken up by chromaffin cells, is useful in localising both adrenal and extra-adrenal tumours (Fig 3) and is the first-line nuclear imaging method. Pretreating with potassium iodide blocks thyroidal uptake.

PET-CT

¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET, ¹⁸F-fluorodopa PET and ¹⁸F-fluorodopamine PET all offer the higher spatial resolution of PET scanning and may allow detection of smaller lesions not

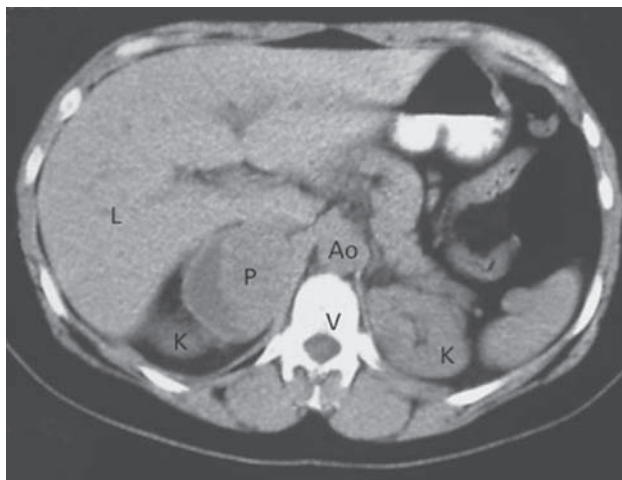


Fig 1. Pheochromocytoma. Abdominal CT showing a right-sided phaeochromocytoma (P). Ao = aorta; K = kidney; L = liver; V = vertebral body.

readily visualised with ^{123}I -MIBG. ^{18}F -FDG PET has particular use in malignant disease.

Genetic testing

All patients with a phaeochromocytoma/paraganglioma should be considered for genetic testing, first to allow early diagnosis and treatment of other features of the associated hereditary syndrome; secondly to prompt more stringent, lifelong clinical follow-up, as recurrences are more likely in familial phaeochromocytoma/paraganglioma; and thirdly to prompt appropriate family screening. Presently, cost-effective genetic



Fig 2. Pheochromocytoma. Abdominal T2-weighted MRI showing a large left-sided phaeochromocytoma (heterogeneous high signal mass) indenting and compressing the adjacent kidney.

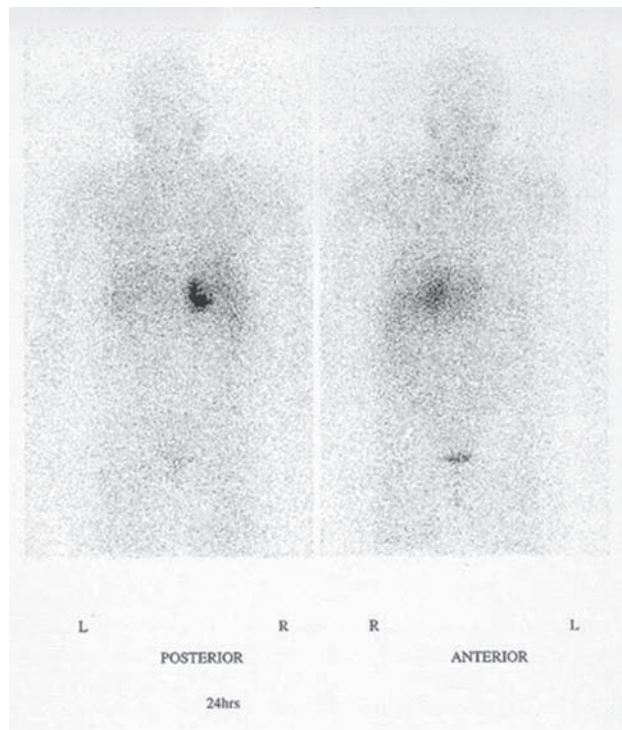


Fig 3. Pheochromocytoma: ^{123}I -MIBG scan. The right-sided phaeochromocytoma shown in Fig 1 demonstrates avid uptake of MIBG.

screening is recommended to those with a positive family history or those under 50 years, especially children. Other clues that should be regarded as an indication for genetic testing include bilateral adrenal or multifocal extra-adrenal disease or the association of phaeochromocytoma with other tumours. The clinical picture may direct genetic testing to one of the suspected genes.

Differential diagnosis

Several conditions may present with features of sympathetic overactivity and thus mimic phaeochromocytoma.

Treatment

Medical therapy

Prior to considering surgical removal, medical treatment must be instituted with the aims of:

- > ameliorating symptoms
- > normalising BP
- > correcting intravascular depletion.

Hazard

Alpha-blockade before beta-blockade

Beta-blockers must not be given to patients with suspected or proven phaeochromocytoma until alpha-blockade has been established, since there is a significant risk of precipitating a life-threatening hypertensive crisis due to unopposed alpha-adrenoceptor activity.

Alpha-blockade

The non-competitive alpha-antagonist phenoxybenzamine is the initial treatment of choice, with escalating dose titration (start with 10 mg twice daily and increase gradually until BP is normalised; most cases require 0.5–2 mg/kg per day in divided doses). The alpha1-antagonist doxazosin provides an alternative for those intolerant of phenoxybenzamine.

Beta-blockade

The non-selective agent propranolol (20–80 mg every 8 hours) is generally preferred, but may not be required in all patients (eg those with a pure noradrenaline-secreting paraganglioma).

Surgical excision

Both traditional and laparoscopic approaches can be used for tumour removal.

Adjunctive therapy for malignant tumours

Options include:

- > alpha-methylparatyrosine – which ameliorates symptoms through inhibition of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthetic process
- > radioiodine (^{131}I)-labelled MIBG – although large and repeated doses may be necessary.

Prognosis

Even those with malignant tumours frequently survive for many years. The extent of end-organ damage is often a key factor in determining long-term outcome. ■

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