

Review Article

Phaeochromocytoma: diagnosis and management

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Introduction

In their working lifetime, most doctors will meet only one patient with a phaeochromocytoma, and a large general hospital will admit on average one such individual per year. However, despite its rarity, phaeochromocytoma attracts more than usual interest and awareness amongst physicians because, in common with a few other conditions such as infective endocarditis and Addison's disease, it combines lethal potential if untreated with possible cure in the majority if diagnosed. The need for maintaining a high index of suspicion is emphasized by the continuing small number of deaths attributable to undiagnosed tumours which occur annually in anaesthetic and obstetric practice.

Catecholamine metabolism

In outline, catecholamine metabolism begins with the rate-limiting action of tyrosine hydroxylase to give L-DOPA from tyrosine; this is followed by decarboxylation to produce dopamine, then hydroxylation yielding noradrenaline, and finally adrenaline is produced by *N*-methylation. This last step usually occurs only in the adrenal medulla (and some hindbrain nuclei) because the cortisol required for its induction is provided by the portocapillary circulation. Thus it is rare for extra-adrenal phaeochromocytomas to produce adrenaline. The metabolism of catecholamines by catechol-*O*-methyl transferase and/or monoamine oxidase results in the formation of normetanephrine and metanephrine and/or vanillylmandelic acid (VMA), the absolute amounts of these metabolites in blood and urine being higher than those of the parent catecholamines. Under normal circumstances the reuptake mechanism at the sympathetic nerve ending means that only small amounts are found in the circulation whereas in phaeochromocytoma, increased catecholamine

production leads to a greater proportion being released directly into the bloodstream.

Clinical aspects

Clinical features of catecholamine excess include hypertension, headache, sweating, palpitations, pallor, feelings of impending doom, paraesthesiae and heart failure. Large tumours secreting noradrenaline may give rise to episodes of bradycardia. Occasionally patients present more dramatically with haemorrhage and infarction of their tumour, or at the other extreme, with no symptoms at all despite dangerous hypertension. It is therefore worthwhile screening all patients with hypertension, or who present with unexplained heart failure or evidence of multiple endocrine neoplasia (MEN) syndromes. However, clinical features are usually less impressive than expected, possibly because of chronic downregulation of adrenoceptors. Conversely, symptoms attributable to catecholamine excess, if occurring in the absence of hypertension, carry a vanishingly small risk of being due to phaeochromocytoma.

Making the diagnosis

Once the possibility of phaeochromocytoma is entertained, diagnosis is not usually difficult but excluding the condition in patients presenting with symptoms of sympathetic overactivity due to other causes may present problems. There are two distinct stages to the diagnostic pathway. These answer the questions 'does this individual have a phaeochromocytoma?' and 'where is the tumour?'. To avoid false positives and negatives, unnecessary investigations and even operations, it should be a golden rule to answer the first question before proceeding to the second.

The tests required are mainly biochemical for the first, and radiological for the second, though no single radiological investigation is sufficiently accurate (or cost-effective!) to detect more than

80–90% of phaeochromocytomas. Computed tomography (CT) scanning in particular is oversensitive to the presence of non-functioning adenomas and should not therefore lead to further investigations in the absence of biochemical abnormalities.

For biochemical screening, there is unfortunately no single perfect or 'best' test. In contrast with most standard endocrine tests, many analyses are in use,¹ with the added difficulty of obtaining an entirely reliable method in routine laboratories. Measurement of metabolites is the commonest method. Our preference is to use 24-hour urinary VMA estimation as the initial screen in most patients. The advantages of this method over metanephrine or single plasma measurements are that it is much less likely to miss the occasional phaeochromocytoma exhibiting truly episodic secretion, and it is the least prone to interference by drugs (which only occurs if L-DOPA is being taken). In addition, an entirely normal result effectively excludes the diagnosis. Although patients are conventionally asked to avoid vanilla-containing foods at the time of the test, and to provide three separate samples, these precautions are unnecessary as a routine. The dietary contribution is small compared to that derived from endogenous noradrenaline and alone is unlikely to produce an abnormal result; and a several-fold rise in catecholamine levels is necessary to produce hypertension in patients with tumours. A three-fold elevation of VMA levels is almost always diagnostic, and most patients with levels more than two-fold elevation eventually prove to have tumours.

Those with less than two-fold elevation in VMA excretion therefore require further biochemical analysis, although only about 5% will have a phaeochromocytoma. Here the single most helpful investigation is measurement of plasma catecholamine levels, usually by high-performance liquid chromatographic separation followed by electrochemical or fluorimetric detection. Whilst generally reliable, occasional interference, particularly with the adrenaline peak, should give rise to suspicion if the results show a higher adrenaline than noradrenaline level. A few centres still undertake the 'gold-standard' radioenzymatic assay. Plasma noradrenaline is usually elevated at least two-fold in phaeochromocytoma.

It is useful to measure plasma catecholamine levels even in those with unequivocally elevated VMA excretion, since the adrenaline level provides a useful clue to tumour location. An elevated plasma adrenaline concentration suggests an adrenal phaeochromocytoma, but patients with large adrenal tumours may occasionally have normal levels because disruption of the adrenal portocapillary circulation by the tumour progressively removes cortisol supply.

If resting plasma noradrenaline does not resolve the questionable diagnosis, two further methods are available, the commoner of which is the pharmacological suppression test. Either the ganglion-blocking agent pentolinium or the centrally acting α_2 -agonist clonidine is administered in an attempt to suppress noradrenaline release. Pentolinium is preferable for most patients.² It has a plasma half-life of only 20 minutes, so that the test can be carried out in the outpatient setting. Secondly, it is better than clonidine at suppressing adrenaline release from the adrenal medulla; and, thirdly, ganglion blockade is particularly effective in suppressing noradrenaline release when sympathetic nerve discharge is high, as is likely in 'problem' patients with symptoms ultimately attributable to sympathetic overactivity. Clonidine is of use in those being screened for phaeochromocytoma because of associated tumours in the MEN syndrome (usually medullary carcinoma of the thyroid), whose noradrenaline levels may be normal, since it will suppress even normal levels. Renal function should be ascertained prior to a pentolinium test, as the drug is entirely excreted by the kidney. The other method in questionable cases involves determination of the ratio in plasma of noradrenaline to its deaminated metabolite dihydroxyphenylglycol (DHPG), usually about 1.5:1. The latter is mainly found in sympathetic nerve endings, and reversal of the ratio is strongly suggestive of a tumour.

Tumour imaging

The next step is to localize the tumour, which has been much less problematic since the advent of CT scanning. Adrenal images usually differ (in attenuation and localization) between phaeochromocytoma and other tumours. For extra-adrenal phaeochromocytomas, however, CT scanning should be withheld until the radiologist can be given some clue where to concentrate. In about 85% of patients this can be achieved by radiotope scanning using meta-iodobenzylguanidine (MIBG) which is an ¹²³I- or ¹²⁵I-labelled analogue of noradrenaline. MIBG is taken up diffusely by chromaffin tissue but is visible only when a bulk of such tissue is present, that is, tumour or sometimes the normal adrenal.³

In some centres magnetic resonance imaging may be tried before more invasive methods; however, the semi-infarcted state of some tumours may make interpretation difficult and in our hands this technique has helped only with a few head and neck phaeochromocytomas which eluded detection by CT or MIBG scanning.

Venous sampling

These investigations still leave a small number of phaeochromocytomas unlocated and here the problem is solved by undertaking selective venous sampling.⁴ This procedure involves collection and subsequent assay for catecholamine concentration of about 25 samples of blood under fluoroscopic guidance from various sites in the vena cava and veins draining into it. It is an extremely low-risk procedure, as long as the temptation to undertake a venogram of the phaeochromocytoma is resisted; this can cause immediate infarction of the tumour and cataclysmic release of stored catecholamines. An arterial sample is taken at the end of the procedure. The procedure is more helpful in investigation of phaeochromocytoma than of other endocrine tumours, because the very short plasma half-life of catecholamines (about one minute) means that most is removed during one passage round the circulation, the venous levels being due to release of noradrenaline from peripheral nerve endings. The site of tumour secretion therefore shows a marked step-up in arterial concentration relative to venous. For adrenal phaeochromocytomas (which should not nowadays pose a diagnostic problem) venous sampling can be less helpful as the normal adrenal vein catecholamine concentration is much higher than peripheral levels, and the increased release from the tumour occurs through increased blood flow rather than concentration.

There is now little place for arteriography except where CT scan of the adrenals produces equivocal results. Arteriography should be approached with caution, the patient being α -blocked prior to and closely monitored during the procedure, with boluses of phentolamine on hand.

Management

Once the diagnosis is made, all patients should have their blood glucose and electrolytes checked; the former is frequently raised due to α -receptor mediated inhibition of insulin release, while the latter may rarely be affected by co-secretion of ACTH. Additionally, all patients should be

screened for medullary carcinoma of the thyroid by measurement of plasma calcitonin.

The definitive treatment is surgical, even where metastatic spread has already occurred; the physician's task is to make surgery safe for the patient. The mainstays of treatment are α -blockade and intravascular volume expansion. The α -blocker of choice is phenoxybenzamine, which acts irreversibly by alkylating both α_1 - and α_2 -receptors so that it cannot be overcome by a catecholamine surge from the tumour. With a starting dose of 10 mg once daily, dose increments each take several days to reach maximum effect, and should be continued several days pre-operatively on an in-patients basis until there is at least a 10 mmHg postural drop in blood pressure. A need for β_1 -blockade may be indicated by tachycardia, with the caveat that immediately postoperatively one should beware of hypotension caused by the removal of α -mediated vasoconstriction combined with the inability to mount a reflex tachycardia. If this occurs, the correct management is volume expansion, β -agonist administration, and if all else fails, administration of angiotensin.

It is fortunate that 90% of phaeochromocytomas are benign, as the treatment of malignant disease remains uncertain and unsatisfactory, with poor sensitivity to both chemotherapy and radiotherapy, and variable progression. Primary tumours should be removed or debulked, and some patients have responded well to high-dose MIBG (used as a means of targeting radioactivity).

It can sometimes be difficult to distinguish benign tumours which appear to have invaded their capsule on the one hand, and malignant growths in which no mitoses can be seen histologically because of their very slow division rate. Because of these occasional histological diagnostic difficulties, all patients should be followed up annually with measurement of catecholamine secretion and blood pressure. Always asking the diagnostic questions in the right order will simplify the management of this intriguing condition.

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