

PHAECHROMOCYTOMA

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Phaeochromocytomas are uncommon tumours which are important because of their life-threatening metabolic effects. Surgical treatment is usually highly successful, but unfortunately approximately one third of cases are not diagnosed in life and nearly half of the deaths in undiagnosed patients are associated with general anaesthesia for some other surgical procedure.^{1,2}

The word phaeochromocytoma is derived from the Greek *phaeos* meaning dusky and *chromos* meaning colour because the tumour cells of the adrenal medulla stain dark brown with chromium salts. The first accurate clinical description linked to autopsy findings was by Fränkel of Freiburg, Germany, in 1886. The first diagnosis in life was achieved in Paris in 1922 by Labbé, Tinel and Doumer, but the patient died without surgery being attempted. The first successful surgical operations were performed independently by Roux in Lausanne, Switzerland, and Mayo in Rochester, Minnesota, USA in 1926.³

The incidence of phaeochromocytomas is approximately 1.5-2/10⁶ population per year.^{1,2} The tumours are often referred to as the '10% tumours' because approximately 10% are bilateral, or extra-adrenal, or malignant, or occur in children or the multiple endocrine neoplasia type II syndrome.

The symptoms are usually intermittent and may vary greatly in individual patients according to the relative secretion of adrenaline and noradrenaline⁴ and probably also dopamine.⁵ Hypertension is the most consistent finding with about half the patients having paroxysmal hypertension and half having sustained hypertension. Only recently have members of multiple endocrine neoplasia type II families been discovered to have phaeochromocytomas at a stage before even paroxysms of hypertension have been noted. It is probably not cost-effective to screen all patients with only hypertension because less than 1% will prove to have phaeochromocytomas.² The combination of hypertension and

any one of the additional features noted below should lead to measurement of catecholamine levels. Hypertension, plus all three of the other 'classic' symptoms of headache, sweating, or palpitations, has a sensitivity and specificity of approximately 90% for phaeochromocytoma in a patient with sustained hypertension.⁶ Hypertension which is difficult to control or occurring in children, young adults, pregnancy, or in association with glucose intolerance, neurofibromatosis or medullary carcinoma of the thyroid should also lead to investigation. Cardiovascular crises occurring under anaesthesia, in particular hypertension, tachyarrhythmias, pulmonary oedema, or shock should always raise suspicion of phaeochromocytoma.

Diagnosis is achieved by measurement of plasma and/or urinary catecholamines and their metabolites. Dopamine is occasionally an important secretory product, particularly of malignant tumours,⁵ but it is sufficient in nearly all cases to measure adrenaline and noradrenaline and their metabolites.⁷ There is a continuing controversy over the choice of the most appropriate test although there is more consensus that high pressure liquid chromatographic methods are more sensitive and specific than earlier techniques.^{8,9} However, fluorometric urinary catecholamine analysis is still widely used in clinical laboratories. A number of commonly used drugs including α -methyl-dopa interfere with fluorometric analysis and it is imperative to cease them several weeks before testing to avoid false positive results. These drugs, however, do not interfere with radio-enzymatic assays for plasma catecholamines. It would be advantageous from a cost-efficiency perspective to be able to rely on a single test, but this is not possible. Although there are advocates for plasma catecholamines and the urinary metabolites metanephrine and vanillylmandelic acid, no test is sufficiently reliable to be relied upon exclusively.¹⁰⁻¹³ In a clinical situation where the suspicion of phaeochromocytoma is high, a single negative test result should not be accepted and repeated testing of several catecholamines would be appropriate. Provocative tests should not be performed but suppression tests using clonidine may be useful in patients with only slightly elevated plasma catecholamine levels.^{9,10}

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Imaging investigations are instituted after the diagnosis has been firmly established biochemically. Computerized tomographic (CT) scanning has a sensitivity of approximately 90% in detecting intra-adrenal phaeochromocytomas.¹² Magnetic resonance imaging is probably no more sensitive than CT, but is proving to be more specific because it can distinguish phaeochromocytomas from other adrenal masses such as cortical neoplasms and metastases.^{14,15} Malignant phaeochromocytomas, however, have the same magnetic resonance appearance as benign phaeochromocytomas.¹⁵ Neither technique, when used routinely, is as reliable in detecting extra-adrenal phaeochromocytomas unless directed at a specific anatomical area.

¹³¹I-*m*-iodobenzylguanidine (¹³¹I-MIBG) scintigraphy was introduced at the University of Michigan Hospitals in 1980 and has since been used there in evaluating over 200 patients with proven phaeochromocytoma. This technique is currently being used in major hospitals around the world. It has a similar overall sensitivity to that of CT but has greater specificity and is also superior to CT in the detection of phaeochromocytomas in extra-adrenal sites.¹³ ¹³¹I-MIBG is also particularly useful in identifying malignant metastases in sites such as bone, liver, and lungs.¹⁶ ¹³¹I-MIBG has located mediastinal phaeochromocytomas which escaped detection by previous investigations but which were then able to have their exact anatomical relationships further defined by dynamic contrasted CT imaging.¹⁷ At the University of Michigan, 13 patients with middle mediastinal phaeochromocytoma have been identified initially by ¹³¹I-MIBG scintigraphy. CT and ¹³¹I-MIBG scans are complementary and should be done in all cases pre-operatively because together they will correctly locate at least 95% of tumours.¹⁸ The identification of an extra-adrenal phaeochromocytoma and/or the finding of normal plasma adrenaline levels when other catecholamines are elevated should raise the suspicion that the tumour may be malignant.⁷ Invasive investigations such as arteriography or adrenal venous sampling should now rarely, if ever, be necessary for the location of a phaeochromocytoma. Since the introduction of ¹³¹I-MIBG, neither technique has been used by the authors.

Pre-operative preparation with α -adrenergic receptor blockade is essential and is one of the main reasons for the relative safety of surgery on phaeochromocytomas in the modern era.¹³ Induction of general anaesthesia and manipulation of the tumour provoke the release of large amounts of catecholamines and prior receptor blockade is very important. Most patients have some reduction of intravascular volume and α blockade for 7 to 10 days allows volume re-expansion. The most commonly used drug is phenoxybenzamine which is given

orally in gradually increasing amounts, if necessary up to 300 mg day, until postural hypotension develops. After α -blockade is established, a β -blocking agent such as propranolol may be added for the last few days pre-operatively. The administration of a β -blocker is not always necessary but β -blockers are useful if there is tachycardia, particularly during the operation itself. The use of β -blockers is also recommended in patients whose catecholamine profile indicates an excessive secretion of adrenaline. In other rare circumstances, drugs such as the α -blocker phentolamine or the enzyme inhibitor α -methyl-*p*-tyrosine may be helpful.⁴

During surgery, monitoring of intra-arterial blood pressure is essential and monitoring of central venous pressure is also advisable. Although some have advocated routine use of a Swan-Ganz catheter for measurement of pulmonary wedge pressure, its insertion may provoke cardiac arrhythmias in the sensitized myocardium. It is recommended, therefore, that it should be used, with caution, in patients who have been in congestive heart failure. Blood pressure fluctuations should be expected even in a well-prepared patient. The α - and β -blocking agents previously mentioned may be used to manage blood pressure and arrhythmias during surgery, but for the control of hypertension many anaesthetists prefer to use rapidly acting direct vasodilating agents such as sodium nitroprusside or adenosine.^{19,20} Intravenous nitroprusside has been used routinely when the systolic blood pressure exceeds 160 mmHg, with titration of the rate of infusion to control the blood pressure at this level or lower. After removal of the tumour there may be a substantial increase in the intravascular capacity and this is better managed by intravenous fluid replacement rather than by vasopressor drugs. Rarely, in the well-prepared patient, an intravenous infusion of noradrenaline may be required while volume is being restored.

The operative approach will be influenced by the pre-operative imaging investigations. For intra-abdominal phaeochromocytomas a thorough laparotomy through an anterior approach is recommended to allow exploration of both adrenal glands and exploration for extra-adrenal phaeochromocytomas, particularly along the aorta and in the renal hila. Even after CT and ¹³¹I-MIBG have been performed, some tumours will not have been detected and such patients will not be cured unless a complete laparotomy is performed.²¹ Palpation of even small extra-adrenal tumours will cause blood pressure fluctuations despite pre-operative α -blockade, and the withholding of such preparation, as advocated by some, would subject the patient to a preventable increased risk of intra-operative hypertensive crisis.

The tumours should be approached cautiously

and handling of the tumour itself kept to a minimum. Interruption of the major effluent vein or veins is desirable at an early stage of dissection to reduce catecholamine discharge into the circulation. Access to the right adrenal is achieved by reflecting the duodenum and head of pancreas to the left after using Kocher's manoeuvre and mobilizing the inferior vena cava. There is often a short vein between the inferior vena cava and the right lobe of the liver and, if present, it should be divided before attempting to dissect around the pheochromocytoma. Access to the left adrenal is obtained either via the lesser sac or inferior to the transverse mesocolon and reflection of the pancreas superiorly. This approach leads directly to the left adrenal and minimizes the risk of splenic injury. The long left adrenal vein, draining into the left renal vein, is easily identified and secured before any manipulation of the tumour is required.

Postoperatively patients should be followed up for life with at least annual blood pressure measurement and catecholamine studies.²² At the University of Michigan, follow-up ¹³¹I-MIBG scans are done in any patient who has symptoms suggestive of recurrence. In several patients, tumour recurrence, or an occult tumour, has been detected in the presence of normal catecholamine levels. Recurrence may happen if benign tumour cells were seeded by rupture of the tumour at the first operation, or if the tumour was malignant, and of course a new primary tumour may develop in the opposite adrenal gland or elsewhere. The diagnosis of malignancy in the absence of metastases cannot be made on usual histological criteria because nuclear pleomorphism, giant cells, frequent mitotic figures, and capsular invasion may all occur in tumours which subsequently follow a benign course. Recently, measurement of nuclear DNA ploidy has shown promise of providing useful additional prognostic information in pheochromocytomas.²³

Malignant pheochromocytomas are best treated surgically if the tissue is resectable. External beam radiotherapy is sometimes helpful for unresectable tumours, particularly in bone, when pain relief is needed. Its use in other areas is limited because of the relative radioresistance of the tumours which require approximately 6000–9000 rad for effect. Widespread systemic metastases may be managed with high therapeutic doses of ¹³¹I-MIBG¹⁷ although only about one third of metastases take up sufficient isotope to achieve adequate tumour irradiation. It is currently estimated that 9000 rad is necessary to demonstrate reduction in tumour size and decreased secretion of catecholamines, and this would usually require repeated doses of ¹³¹I-MIBG. Chemotherapy and interferon are other options which are currently undergoing evaluation with some partial tumour responses being noted. For

control of symptoms, phenoxybenzamine and α -methyl-*p*-tyrosine are particularly useful.¹⁶ It should be realized that metastatic pheochromocytoma may be relatively slow growing and some patients survive many years when their blood pressure is controlled with adequate therapy. Because of the inability to determine whether a pheochromocytoma is benign or malignant on standard histopathologic criteria, and the propensity for bone metastases to remain occult for long periods of time, careful life-time follow-up is further emphasized.

In summary, pheochromocytomas produce a variety of symptoms and a high index of suspicion is necessary before the diagnosis is likely to be made. In the hands of an experienced clinical team, the combination of accurate imaging investigations, careful pre-operative adrenergic blockade, expert anaesthesia, and intelligent surgery should lead to a successful outcome in most patients.

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