Phaeochromocytoma

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Key points

Phaeochromocytomas are uncommon but crises may be fatal.

Optimal medical pre-operative treatment significantly decreases peri-operative mortality.

Intensive peri-operative monitoring and care is essential.

Close collaboration of surgeon, endocrinologist, anaesthetist and intensivist is the key to success.

Emergency undiagnosed presentations still have a high mortality.

Phaeochromocytomas are functionally active catecholamine tumours of chromaffin cells typically found in the adrenal medulla. Although not commonly encountered in medical practice, they are responsible for 0.5% of hypertensive conditions and have been documented in 0.1% of routine autopsies. This condition could present to the physician, anaesthetist or intensivist in a dramatic fashion. It requires a high level of diagnostic acumen and thorough understanding of the underlying pathophysiology to reduce the associated high morbidity and mortality of 50% in unexpected emergency situations to < 2% for elective surgery.

Pathology

Chromaffinomas, derived from the embryonal neuro-ectodermal crest, are so named because of their affinity for chromate salt solutions. While 90% of phaeochromocytomas occur in the adrenal medulla, the rest may be found in the neck, thorax, abdomen or pelvis having originated from chromaffin cells of the ubiquitous sympathoadrenal system. These are often called paragangliomas. Phaeochromocytomas are often referred to as the '10% tumour' as approximately 10% are familial, 10% bilateral, 10% extra-adrenal and 10% malignant. They present most frequently in the fourth decade with an equal sex incidence but occur more commonly in boys prior to puberty. At this age, up to 35% may be extra-adrenal and 30% of the latter may be malignant.

These tumours are biochemically very active being responsible for the production and secretion of biogenic amines, mainly norepinephrine and epinephrine. Methylation of norepinephrine to epinephrine only occurs in the adrenal medulla and depends on cortisol delivered by an intact portocapillary circulation which can be disrupted by tumour. Thus, in contrast with the normal medulla which largely secretes epinephrine, paragangliomas and most phaeochromocytomas mainly produce norepinephrine. Chromaffinomas have also been noted to secrete opioid peptides, VIP, ACTH, calcitonin, somatostatin and neuropeptide Y and this may play a part in the varied symptomatology associated with phaeochromocytomas.

Associated syndromes

In addition to the clinical picture and complications of excess catecholamine secretion, this tumour can also present with one of the uncommon clinical syndromes associated with the majority of familial chromaffinomas. They are autosomal dominant inherited conditions:

1. **Multiple endocrine neoplasia (MEN) type 2 syndrome** or Sipple's syndrome refers to the triad of phaeochromocytoma or adrenal medullary hyperplasia, medullary thyroid carcinoma and hyperparathyroidism.
2. **MEN type 3 syndrome** is characterized by phaeochromocytoma, medullary thyroid carcinoma, mucosal neuromas, ganglioneuromas of the gastrointestinal tract, thickened corneal nerves and Marfanoid body habitus. These associated tumours are also derived from the neuro-ectoderm and familial phaeochromocytomas are rarely malignant or extra-adrenal.
3. **Neurofibromatosis** is an autosomal dominant condition with a 1% incidence of phaeochromocytoma, although other causes of hypertension may be associated with this condition.
4. **Von Hippel Lindau disease** is the co-existence of cerebellar haemangioblastoma and retinal angiomas; it has a 14% incidence of phaeochromocytoma.

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Cardiovascular pathophysiology

The predominant feature of this condition is undoubtedly severe hypertension which may be sustained, paroxysmal or both. As a marked discrepancy exists between the degree of hypertension and plasma catecholamine concentration, other factors such as receptor sensitivity, inherent reactivity of vascular smooth muscle and sympathetic activity must be involved also. Down-regulation of the adrenergic receptors is thought to occur via reduced numbers of α_1- and β_1-receptors while impaired occupancy-response coupling also involves α_2-receptors. On the other hand, β_2-receptor activity remains intact, being markedly less responsive to raised norepinephrine concentrations.

Clinical presentation

Although early diagnosis (approximately 0.5% of all hypertensive patients) and treatment minimizes the morbidity associated with phaeochromocytomas, routine screening of all hypertensives is not feasible. It is, therefore, considered fortunate that the majority of chromaffinomas present early and dramatically. The hallmark of the condition is the paroxysmal crisis presenting with marked hypertension, severe headache, drenching perspiration, palpitations, facial pallor, anxiety, tremor, weakness, chest pain, faintness and paraesthesia. True paroxysmal hypertension is only seen in 35% of cases; sustained hypertension, with or without discrete paroxysms, is more frequent. The latter presentation may also be associated with weight loss, dyspnoea, visual disturbance, carbohydrate intolerance, hypercalcaemia, polycythaemia and heat intolerance.

Triggers of paroxysms are occasionally identified and may be physiological or iatrogenic. The former include changing position, abdominal pressure, coitus, sneezing, voiding, defaecation, exercise, anxiety and certain alcoholic beverages. Iatrogenic factors include anaesthetic agents, histamine-releasing drugs, succinylcholine, metoclopramide, nicotine, naloxone, β-blockade, phenothiazines, tricyclic antidepressants and glucagon. Certain hospital procedures, particularly induction of anaesthesia, endotracheal intubation, arteriograms, lumbar puncture and labour may also lead to a crisis.

Complications of a hypertensive crisis include myocardial ischaemia, cardiac failure, arrhythmias, neurogenic pulmonary oedema, cerebrovascular events and acute abdominal pain with shock (haemorrhage into a tumour). Consequently, the differential diagnosis is extensive as conditions associated with severe hypertension include chronic anxiety with panic attacks, cerebrovascular events, thyroid crisis, severe migraine, dissecting aneurysm, carcinoid, hypertensive encephalopathy, pre-eclampsia, malignant hyperthermia and cardiovascular events due to cocaine, amphetamine or catecholamine abuse.

Therefore, the diagnosis of phaeochromocytoma may be suggested by a paroxysmal crisis, subacute illness, family history, MEN syndrome or other inherited condition, unexpected cardiovascular manifestations in response to iatrogenic factors or an incidental suprarenal mass detected on imaging.

Diagnosis

Firm diagnosis of this tumour is essential to enable appropriate management. The mortality for emergency presentation is approximately 50% but only 2% for elective surgery.

Biochemical investigations

Colorimetric urinary measurement of free catecholamines and the main metabolites vanillylmandelic acid (VMA) and metanephrine are adequate for diagnosis in most patients. Urine is collected over 24 h or by random 1-h samples. Until recently, these tests formed the basis of the diagnosis but assay of urinary catecholamines by high-performance liquid chromatography with electrochemical detection (HPLC-ED) is now used because of its superior sensitivity.

However, sole reliance on urinary indices can be misleading because renal excretory function may be altered and catecholamine enzyme activity within chromaffinomas may be unpredictable. This leads to changes in the ratio of free plasma catecholamine and urinary metabolites. Consequently, both plasma catecholamines and urinary metabolites should always be measured.

Other laboratory tests may be performed but they are less popular because of the reliability of catecholamine measurements. Measurement of plasma chromagranin A (a neuropeptide co-released with norepinephrine) has a low specificity, as does measurement of platelet catecholamine content. Also, an increased ratio of urinary norepinephrine to 3,4-dihydroxyphenylglycol (DHPG) is not more sensitive than the absolute value of the former alone.

Pharmacological suppression and provocation and the invasive technique of selective venous sampling have now been abandoned.

Radiological investigations

This is a vital investigation as it reveals multifocal or locally invasive tumour. It confirms a biochemically established diagnosis and suggests a firm diagnosis if laboratory results are equivocal. Abdominal-pelvic CT or MRI identifies 97% of phaeochromocytomas. MRI is preferred to CT imaging because of reduced

exposure to ionizing radiation, improved differentiation between benign adrenal adenomas and chromaffinomas, and reduced requirement for intravenous contrast which is associated with complications.

M-iodobenzylguanidine (MIBG) radioisotope studies are useful when no tumour is visualized. MIBG is an iodinated analogue of norepinephrine which is actively taken up by tissues involved in catecholamine synthesis. This test has a specificity and sensitivity of 90% and is performed routinely in some centres to identify latent multifocal tumour. Of the two isotopes available, 123-MIBG produces better images than 131-MIBG enabling single photon emission tomography. However, it is more expensive. Isotope tumour uptake is impaired by medications such as labetalol and tricyclic drugs. MIBG can also be used if surgery is contra-indicated.

Pre-operative preparation

Anaesthetic evaluation and management should commence as soon as the operation is scheduled to facilitate interdisciplinary co-operation and optimize management. Clinical assessment must include a detailed history to elucidate symptoms of cardiac origin as catecholamine cardiomyopathy has been diagnosed in up to 50% of patients. On examination, evidence of hypertensive end-organ damage to kidneys, eyes and myocardium and the presence of familial conditions are identified. ECG may reveal ventricular hypertrophy, arrhythmias and myocardial ischaemia and echocardiography can give some indication of myocardial function. Full blood investigations may reveal an elevated haematocrit (intravascular volume depletion), hyperglycaemia, hyperparathyroidism or raised plasma calcitonin concentrations (MEN syndrome).

The targets of pre-operative preparation are good blood pressure control, treatment of significant dysrrhythmias, blood volume repletion and amelioration of any end-organ damage. Criteria for optimal pre-operative control often quoted are: (i) BP consistently < 160/90 mmHg; (ii) postural hypotension not < 80/45 mmHg; (iii) absence of ST-T changes in ECG for 7 days; (iv) no more than one premature ventricular contraction every 5 min; and (v) nasal congestion.

Treatment of hypertension

Phenoxybenzamine has been the main-stay of pre-operative control for decades and still plays a major role in most centres. It is a non-selective irreversible α-adrenergic antagonist known to alkylate α-receptors permanently and prevent the clinical response to catecholamine release. However, phenoxybenzamine also blocks α_2-receptors causing tachyarrhythmias (disinhibition of cardiac sympathetic neurons). Therefore, β-blockade is required. Some believe that α_2-blockade is also beneficial as a minor degree of the peripheral vasoconstriction is dependent upon α_2-receptor activity. Phenoxybenzamine has a long half-life (24 h); the duration of action is even longer because of its irreversible action. This may be the explanation for postoperative hypotension in some patients. It has been argued that complete α-blockade obscures intra-operative haemodynamic changes which may be the first signs of inadvertent manipulation of latent tumour or incomplete excision. However, this has not been the authors' experience.

Phenoxybenzamine is commonly started at least 14 days before surgery and continued until 1–2 days before surgery. It is thought that α-blockade is required for a minimum of 2 weeks in order to restore normovolaemia and myocardial function. Therefore, some advise treatment for months; stopping the drug a couple of days before surgery reduces the risk of postoperative hypotension. Starting dose is 10 mg twice daily and increased, depending on BP control, postural hypotension and nasal stuffiness, to 60–200 mg daily.

The introduction of selective α_1-receptor antagonists has been encouraged because, unlike phenoxybenzamine, they are not associated with tachyarrhythmias and sedation. Prazosin, terazosin and doxazosin are competitive, selective α_1-antagonists that may be preferred to phenoxybenzamine because of their shorter duration of action and no requirement for β-blockade. In addition, doxazosin requires only once daily administration (1 mg daily, slowly increased up to 16 mg as required, not omitted the day before surgery). Postural hypotension is still a common adverse effect and can be severe in hypovolaemic patients at the start of therapy. Pre-operative control of blood pressure is comparable to phenoxybenzamine but it is not as effective during surgery when massive plasma catecholamine concentrations can competitively displace the α_1-receptor antagonist from its receptor.

Pre-operative β-blockade has always been controversial. Therapy should never be started prior to established α-blockade, as the hypertensive action of catecholamines on α-receptors is then unopposed by the vasodilator effect of peripheral β_2-receptor stimulation while the negatively inotropic effect of β-blockade further compromises a dysfunctional myocardium. Administration of α_1-selective antagonists limits the use of β-blockers to predominantly epinephrine-secreting tumours, once echocardiography has excluded significant myocardial impairment. Even then, only low doses of β_1-specific antagonists are indicated.

Anaesthetic management

Pre-operative assessment and investigations should be reviewed to ensure adequate preparation, including cover with glucocorticoids and mineralocorticoids if bilateral adrenalectomy is possible. Benzodiazepine premedication is often prescribed.

Technique

Large calibre intravenous cannulae and an arterial catheter are sited under local anaesthesia. A central venous catheter should be inserted but a pulmonary artery flotation catheter (PAFC) is indicated only in the presence of a significantly impaired myocardium. Isoflurane-fentanyl based anaesthesia is an accepted standard technique, minimizing negative inotropic effects and catecholamine-induced arrhythmias.

Haemodynamic compromise is most likely during: (i) induction of anaesthesia; (ii) endotracheal intubation; (iii) tumour manipulation; and (iv) ligation of the tumour's venous drainage. The first three can lead to plasma catecholamines concentrations up to 200 times normal and lethal consequences. Adequate pre-operative care aims to limit the severity of these episodes but vasodilators must be prepared and close at hand. Such agents include boluses of phentolamine 1–5 mg and labetalol 5–10 mg or sodium nitroprusside, GTN and nicardipine infusions. Sodium nitroprusside has a rapid onset and offset of action; it is not associated with toxicity when used in recommended doses. Nicardipine is a calcium channel blocker which has been used as an infusion for fast titration of blood pressure. The use of isoflurane as an antihypertensive agent is a practical alternative. Magnesium sulphate infusions have recently been described (inhibits catecholamine release, exerts a direct vasodilator effect and reduces α-receptor sensitivity).

The detrimental myocardial effects of catecholamine surges result from greatly increased myocardial oxygen requirements in the presence of coronary vasospasm. Acute pulmonary oedema may follow intense pulmonary vasoconstriction and increased capillary permeability. Tachyarrhythmias are often controlled with esmolol (bolus or infusion). Lidocaine and amiodarone are required very infrequently for ventricular arrhythmias.

Final ligation of the tumour's venous supply is associated with a sudden drop in plasma catecholamine concentrations, often precipitating rapid refractory hypotension. Other factors causing hypotension include down-regulation of α-receptors, suppression of the contralateral adrenal medulla, persistence of pre-operative adrenergic-receptor blockade, relative hypovolaemia and catecholamine-induced cardiomyopathy. Initially, this should be treated with fluids as directed by CVP or PAFC measurements. When fluids are not fully effective, vasopressors are required. Angiotensin may be more useful than the commonly used α-agonists as a consequence of α-receptor down-regulation.

A large retrospective audit demonstrated a 30% incidence of such adverse haemodynamic episodes with negligible mortality in the well-prepared patient. There was a greater risk with large tumours, prolonged surgery and high pre-operative plasma catecholamine concentrations.

Postoperative management

Initially, patients should be managed on a high dependency or intensive care unit to ensure cardiovascular stability in the presence of hypovolaemia, refractory hypotension, persistent hypertension (occasionally after incomplete primary tumour resection or metastasis) and care of epidural analgesia. Hypoglycaemia may occur as a result of the abrupt cessation of α_2-mediated pancreatic β-cell inhibition. Persisting β-blockade may mask hypoglycaemic symptoms.

Surgical factors

The surgical techniques available include open retroperitoneal, open transabdominal or laparoscopic surgery. Minimally invasive procedures diminish the stress response, reduce blood loss and are associated with a significantly faster recovery, shorter hospital stay and, according to some advocates, a lower incidence of postoperative adverse events. The latter is not universally accepted. A specific complication of laparoscopic surgery is the dramatic catecholamine response during initial gas insufflation; this is often more severe than the intubation response.

Obstetric management

Management of the obstetric patient depends on the time of diagnosis. Labour is a known precipitant of hypertensive crises and must be avoided by elective Caesarean section, preferably under regional anaesthesia. Unexpected presentation at delivery may closely resemble pre-eclampsia, apart from the absence of oedema and proteinuria, and treatment with magnesium sulphate infusion is fortunately appropriate in either case. If phaeochromocytoma is diagnosed before 24 weeks gestation, the tumour is often resected immediately, even though there is a possibility of fetal compromise. After 24 weeks, the pregnancy is often allowed to continue under constant α-blockade. Antenatal diagnosis improves maternal mortality from 17% to < 1% and fetal mortality from 26% to 15%.

Key references

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See multiple choice questions 17–19.