Recognition and management of phaeochromocytoma and paraganglioma

Henry Wang
Chandran Jepegnanam

Learning objectives

After reading this article, you should be able to:

- describe the pathophysiology of phaeochromocytomas
- describe the preoperative management of patients with phaeochromocytomas
- describe the intraoperative anaesthetic management of the tumour resection
- explain the immediate and long-term postoperative complications

Abstract

Phaeochromocytomas and paragangliomas (PPGL) are catecholamine-secreting neuroendocrine tumours arising from the chromaffin cells in the adrenal medulla. These tumours may be identified incidentally, as part of a work-up for multiple endocrine neoplasia or following haemodynamic surges during unrelated procedures. Advances in perioperative management and improved management of intraoperative haemodynamic instability have significantly reduced surgical mortality from around 40% to less than 3%. Surgery is the definitive treatment in most cases and laparoscopic resection where possible is associated with improved outcomes. Anaesthetic management of PPGL cases represents a unique haemodynamic challenge both before and after tumour resection. In this article we describe the physiology of these tumours, their diagnosis, preoperative optimization methods, intraoperative anaesthetic management and management of postoperative complications.

Keywords Alpha blockers; beta blockers; calcium channel blockers; catecholamine; laparoscopic; metanephrine; metyrosine; paraganglioma; phaeochromocytoma; PPGL

Royal College of Anaesthetists CPD Matrix: 1A01, 1A02, 2A03, 2A04, 2A05, 2A06, 2A07, 3A03

Background

Phaeochromocytomas are neuroendocrine tumours arising from the chromaffin tissue derived from the neural crest. Around 80% arise from the adrenal gland, the other 20% found in the paraaortic region, pelvis, chest and rarely the heart, are termed paragangliomas. Collectively they are referred to as phaeochromocytoma and paraganglioma (PPGL).

PPGL has an annual incidence of approximately 1–8/million in the general population. It is diagnosed in approximately 5% of patients presenting with an incidental adrenal gland mass. Approximately 10% of adrenal tumours are malignant, rising to 25% in larger and extra-adrenal tumours. Although there are no known risk factors for this tumour, nearly a third of cases are of an inherited nature. This includes syndromes such as multiple endocrine neoplasia types 2A and 2B as well as hereditary paraganglioma syndrome, in which specifically affected genes are identified. Other conditions associated with PPGL include von Hippel-Lindau disease and neurofibromatosis type 1. It has been shown that at least 32% of PPGL cases are familial with ten different genes having been found to be associated with the development of these tumours.[1,2]

Clinical features

The most common presenting complaint leading to a diagnosis of PPGL is hypertension, which found in up to 95% of patients. The classical triad of headache, palpitations and diaphoresis is highly specific (93.8%) and sensitive (90.9%) for PPGL. Unexplained hypertension, tachycardia and arrhythmia during uncomplicated diagnostic procedures such as colonoscopies, induction of anaesthesia and unrelated surgeries have also lead to a diagnosis of PPGL.

Less commonly patients with PPGL experience weight loss, orthostatic hypotension and cardiomyopathy. PPGL patients can present with associated metabolic disorders such as diabetes, hypercalcaemia, diarrhoea and fluid and electrolyte imbalance. Some present with non-specific symptoms such as abdominal or chest pain, nausea, anxiety, lethargy, tremor. A minority (around 13%) of patients are asymptomatic, possibly due to receptor down-regulation.[2]

PPGL can present as hypertensive crises either with or without a background of sustained hypertension. Severe cases may present as a medical emergency characterised by multiple organ failure, encephalopathy, hypertension or hypotension. In addition to urgent intensive medical therapy, emergency tumour removal may be indicated.

Pathophysiology

Metabolism of catecholamines

The initial step in catecholamine synthesis is the conversion of tyrosine into L-2,4-dihydroxyphenylalanine (DOPA) which then undergoes decarboxylation into dopamine. Dopamine then undergoes hydroxylation into noradrenaline which is then converted into adrenaline in the cytoplasm of the chromaffin cells. Catecholamines are removed from plasma either by re-uptake into neuronal cells or by enzymatic breakdown and subsequent renal

Henry Wang *FRCA is a Specialty Registrar in Anaesthesia in the Northwest Deanery, UK. Conflict of interest: none declared.*

Chandran Jepegnanam *FRCA is Consultant Anaesthetist at the Central Manchester University Hospitals Foundation Trust and an Honorary Senior Lecturer, Manchester Medical School, University of Manchester, UK. Conflicts of interest: none declared.*

excretion. Adrenaline is converted to metanephrine, and noradrenaline to normetanephrine by the enzyme catechol-O-methyltransferase (COMT). Metanephrine and normetanephrine are converted into vanillylmandelic acid by the enzyme monoamine oxidase. Monoamine oxidase can also directly metabolize adrenaline or noradrenaline into dihydroxymandelic acid which is then converted into vanillylmandelic acid by COMT.[2]

Figure 1 shows the synthesis and metabolism of catecholamines.

PPGL tumours secrete an excess of catecholamines and therefore enhances the sympathetic nervous system resulting in symptoms such as hypertension and palpitations.

Within sympathetic nerves, the pre-synaptic vesicles are overloaded with catecholamines due to increased production, resulting in an increased frequency of neuronal impulse. When the neurons are stimulated, they release an excess of noradrenaline due to selective desensitization of pre-synaptic $\alpha 2$-adrenergic receptors resulting in an exaggerated response. This dual mechanism explains how severe hypertension can result from relatively small increments in circulating noradrenaline as well as the paroxysmal nature of the hypertension that is triggered by stressful stimuli such as pain, intubation or surgical stimulus.

Increased circulating catecholamine causes persistent vasoconstriction leading to increase in afterload and myocardial work, which can result in hypertrophic cardiomyopathy or dilated cardiomyopathy. However there is evidence that these changes are reversible following tumour resection.

Chronic vasoconstriction in PPGL patients also leads to decreased vascular volume and it is not unusual for them to be severely fluid depleted.

Diagnosis

All symptomatic patients, those with adrenal 'incidentalomas' and those with hereditary risk of developing a catecholamine-secreting tumour should be investigated for PPGL. Diagnostic work-up of PPGL usually begins by gathering evidence for increased catecholamine production by the tumour followed by identifying the tumour's location.

The historic method of direct assay of plasma concentrations of catecholamines and catecholamine metabolites in the urine suffered from poor sensitivity and specificity. A large number of false negatives can arise as catecholamines are quickly metabolized to metanephrines in the tumour by COMT. Urinary and plasma metanephrine screening is a much more sensitive and specific test.

Blood sampling for biochemical markers should be performed with the patient supine, 15–20 minutes after venous cannulation. Patients should avoid food, caffeinated beverages, strenuous physical activity, or smoking for at least 8 hours before testing. False-positives can be generated by any physiological stress such as acute illness or medications affecting either catecholamine disposition (such as tricyclic antidepressants) or liquid chromatography measurement methods (paracetamol and sulphasalazine).[3] Metanephrine levels greater than four times the reference normal level is considered diagnostic of PPGL. The severity of increase also indicates the need for urgent management.

When diagnostic uncertainties remain (such as patients who present with features strongly suggestive of PPGL but found to have borderline metanephrine assay levels) the clonidine suppression test can be a useful tool. Plasma catecholamines are measured before and 3 hours after administration of 0.3 mg of oral clonidine. Cases in which clonidine fails to reduce catecholamine levels by more than 50% of baseline levels is strongly suggestive of PPGL.

CT and MRI scans are the initial tools for localization of the tumour. Contrasted CT currently has a sensitivity of 88–100% and is favoured for its excellent spatial resolution in imaging the chest, abdomen and pelvis. MRI is preferred in the detection of metastatic PPGL; it can be especially useful in detecting base of

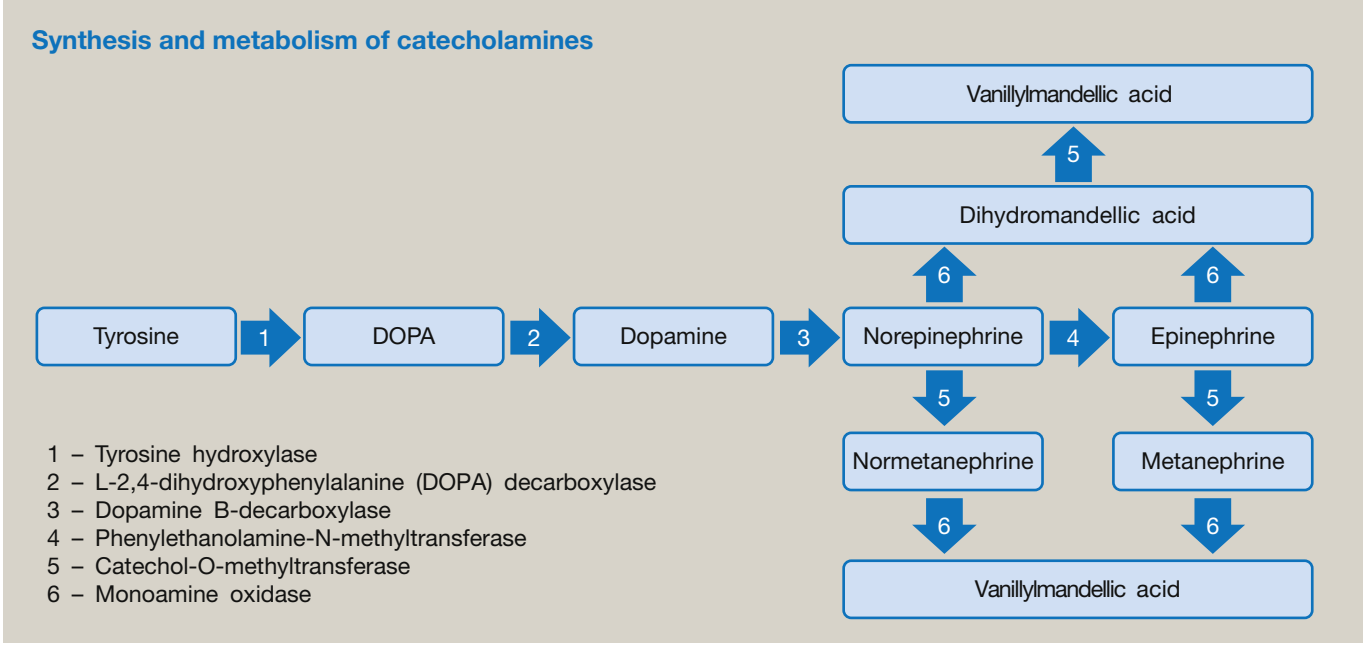

Figure 1