Phaeochromocytoma

What is a phaeochromocytoma?

A phaeochromocytoma (PCC) is a rare tumour that secretes catecholamines. It is derived from chromaffin cells, usually in the adrenal medulla; however, occasionally extra-adrenal phaeochromocytomas or paragangliomas (PGLs) occur.[1] Many - but not all - authors define phaeochromocytoma as coming from the adrenal medulla and if the tumour is similar but located elsewhere, it is called a paraganglioma.

Subclinical phaeochromocytomas are often discovered as incidentalomas during radiological procedures or during routine screening for phaeochromocytoma in carriers of mutations.[2]

The excessive production of catecholamines may cause life-threatening hypertension or cardiac arrhythmias. Undiagnosed phaeochromocytomas, whether or not subclinical and even if biologically benign, may cause extremely deleterious consequences or even death, following abrupt release of catecholamines.[2]

Up to one third of all symptomatic presentations of phaeochromocytoma or paraganglioma are due to germline mutations in one of six genes defining multiple endocrine neoplasia (MEN) type 2, von Hippel-Lindau (VHL) disease, neurofibromatosis type 1 and the paraganglioma syndromes types 1, 3 and 4.[3]

About 10% of all phaeochromocytoma and paraganglioma are metastatic, with higher metastatic potential of PGLs compared to PCCs.[4]

Background

The name is of Greek etymology. *Phios* means *dusky, chroma* means *colour* and *cytoma* means *tumour*. This refers to the colour of tumour cells when stained with chromium salts.

A normal adrenal medulla secretes adrenaline (epinephrine) in response to neural control whereas the tumours are not innervated and the stimulus for secretion is unknown. They may secrete constantly or intermittently. The familial type tends to produce mostly noradrenaline (norepinephrine) but the sporadic type produces mostly adrenaline (epinephrine). Dopamine may also be produced.

Phaeochromocytoma epidemiology[5]

- Phaeochromocytomas are rare tumours, with an annual incidence of 2 to 9.1 per 1 million adults and may correspond up to 60% of all adrenal incidentalomas (epinephromas).
- The majority are benign but up to 25% may be malignant.
- Males and females are affected equally.
- Phaeochromocytomas can appear in any age, however, more commonly in the 3rd to 5th decade of life.
- Hereditary disease is more likely to present in younger patients.
- In children presenting with apparently sporadic phaeochromocytomas, up to 70% of cases are due to hereditary disease.
- Phaeochromocytomas are responsible for 0.2–0.6 of both systolic and diastolic hypertensions and rarely in isolated cases of systolic hypertension.
- However, about 50% of phaeochromocytomas are diagnosed only at autopsy because many of these tumours remain clinically silent during life.
- In MEN 2A patients, cancer develops between second and third decade of the life.
- Genetics
- Phaeochromocytomas may be either sporadic or a manifestation of hereditary (familial) syndromes, which are transmitted in autosomal dominant fashion.
- Up to 70% of phaeochromocytomas/EAPs carry germline or somatic mutations in one of the numerous predisposing genes.

Inherited forms

- Phaeochromocytomas occur in certain familial syndromes, including:
    - Multiple endocrine neoplasia 2 (MEN2) which is associated with RET mutations.
    - von Hippel-Lindau syndrome (VHL), which is due to VHL gene mutations.
    - Neurofibromatosis type 1 (NF1) which is due to NF1 gene mutations.
- It was thought that 10% of cases represent inherited syndromes but this figure may be up to 30%.
- Phaeochromocytomas occur bilaterally in 70% of MEN syndromes.
- Neurofibromatosis has a 1% incidence of phaeochromocytoma.
- VHL disease is associated with phaeochromocytomas, cerebellar haemangioblastomas and renal cell carcinoma.

History[5]

Symptoms are intermittent and may vary from once a month to several times a day with duration from seconds to hours. With time they tend to become more frequent and more severe.

There are a number of symptoms that may present but the first four are in bold as they are almost invariably present:

- **Headache**
- **Profuse sweating**
- **Palpitations**
- **Tremor**
- Nausea
- Weakness
- Anxiety

- Sense of doom
- Epigastric pain
- Flank pain
- Constipation
- Weight loss

Persons with familial phaeochromocytoma may be asymptomatic.[6]

Examination[5]

Again, the most common features are in bold:

- **Hypertension** but it may be paroxysmal in 50%.
- **Postural hypotension**.
- **Tremor**.
- Hypertensive retinopathy.
- Pallor.
- Fever.
- Acute hypertension with a tumour that releases predominantly noradrenaline (norepinephrine) may cause reflex bradycardia.

Neurofibromas may be felt and café au lait patches may be seen.

Investigations[7]

Blood tests

- Blood glucose is often raised.
- Calcium may be elevated.
- Haemoglobin is elevated due to haemoconcentration from reduction in circulating volume.

- Plasma catecholamines and plasma metanephrines (the o-methylated metabolites of catecholamines) have both been used in diagnosis.[8] A recent consensus guideline stated that plasma free metanephrines were the blood test of choice.[9]

Urine

- 24-hour urine collection is required for creatinine (to assure full 24-hour specimen), total catecholamines, vanillylmandelic acid (VMA) and metanephrines.
- The bottle for collection should be dark and acidified and should be kept cold to avoid degradation of the catecholamines.
- Preferably collect urine immediately after a crisis.
- Physical stress and a number of drugs may interfere with the assay and cause false elevation of metanephrines. Drugs include tricyclic antidepressants, alcohol, levodopa, labetalol, sotalol, amfetamines, benzodiazepines and chlorpromazine.
- Urinary VMA has a false positive rate in excess of 15%. One study found that of all urine and blood tests, urine free metanephrines produced the best results.[8]

Imaging

After biochemical confirmation of a tumour, imaging is necessary to locate it.[10]

- Extra-adrenal phaeochromocytomas develop in chromaffin tissue of the sympathetic nervous system and can occur anywhere from the base of the brain to the urinary bladder.
- Common locations for extra-adrenal phaeochromocytomas include close to the origin of the inferior mesenteric artery, bladder wall, heart, mediastinum and carotid and glomus jugulare tumours.

Various techniques may be employed:

- CT is the initial imaging modality of choice - it is sensitive and detects around 85-95% of tumours in excess of 1 cm in diameter.
- CT provides excellent spatial resolution for the thorax, abdomen and pelvis.[9]

- MRI is particularly useful for locating metastatic disease.
- If phaeochromocytoma is confirmed biochemically but CT or MRI do not show a tumour, a scan with metaiodobenzylguanidine (MIBG) labelled with ^{131} iodine or ^{123} iodine may be performed.[11] The molecular structure of MIBG is similar to noradrenaline (norepinephrine) and concentrates within adrenal or extra-adrenal phaeochromocytomas.
- A somatostatin receptor analogue called pentetreotide, labelled with ^{111} indium is less sensitive than MIBG but may be used to detect phaeochromocytomas that do not concentrate MIBG.[12]
- Positron emission tomography (PET) scanning appears promising but is still in fairly early stages of assessment.[13]

Genetic testing

All patients should be involved in shared decision-making for genetic testing.[9] Tumour location and number, age, gender and family history will point to the need for genetic testing. Such testing forms the basis of early diagnosis and follow-up including management of relatives.[3]

Histology

Histological assessment of tissue removed after surgery using certain criteria (the PASS system) can help to differentiate benign from malignant tumours. A PASS score of <4 is predictive of benign phaeochromocytomas, whereas a score greater than 6 is characteristic of malignant tumours. Such patients should be followed closely for recurrence.[14]

Risk factors[5]

'Phaeochromocytoma crisis', presents with severe hypertension, circulatory failure and shock, with subsequent involvement of multiple organ systems, including the cardiovascular, pulmonary, neurological, gastrointestinal, renal, hepatic and endocrine systems. Any of the following may precipitate a hypertensive crisis:

- Induction of anaesthesia.
- Opiates.
- Dopamine antagonists.

- Decongestants such as pseudoephedrine.
- Drugs that inhibit the reuptake of catecholamines, including tricyclic antidepressants and cocaine.
- X-ray contrast media.
- Pregnancy and childbirth.

Differential diagnosis

If the urine tests for total catecholamines, VMA and metanephrines are positive, the main differential diagnosis is to decide if is it is part of a familial condition.

- There may be a family history.
- Bilateral tumours suggest MEN.
- There may be features of neurofibromatosis including café au lait spots.
- VHL disease is associated with phaeochromocytomas, cerebellar haemangioblastomas and renal cell carcinoma.

Other considerations include:

- Anxiety disorder.
- Carcinoid tumour.
- Alcohol withdrawal.
- Labile hypertension.
- Drug abuse.
- Factitious phaeochromocytoma - has been described.

Phaeochromocytoma treatment and management[7]

Associated conditions must be sought and, if found, appropriate management includes genetic counselling.

Surgical resection of the tumour is the treatment of choice and usually results in cure of the hypertension. Pre-operative treatment with alpha-blockers and beta-blockers is required to control blood pressure and prevent intraoperative hypertensive crises.

- Alpha blockade with phenoxybenzamine is started at least 7 to 10 days before operation to allow for expansion of blood volume.
- Only once this is achieved is beta blockade considered. If beta blockade is started too soon, unopposed alpha stimulation can precipitate a hypertensive crisis.
- Calcium-channel blockers are also useful.
- Complete resection of the tumour is usually possible and surgical mortality rates are less than 2% or 3% with an experienced anaesthetist and surgeon.
- Laparoscopic surgery is being used more often for tumours smaller than 6 cm but for larger tumours, an open operation is probably safer.[15]

After surgery, a 24-hour urine collection for total catecholamines, metanephrines and VMA is required two weeks after operation. If results are normal, the prognosis is excellent. It is important to ensure that hypertension is controlled or resolved. Lifelong annual biochemical testing is recommended to detect recurrent or metastatic disease.[9]

Sometimes, when a patient is being investigated for hypertension, a mass may be found in an adrenal gland. This may represent phaeochromocytoma, glucocorticoid excess or primary aldosteronism. The mass may even be irrelevant and misleading. Such findings are called 'incidentalomas'. If the clinical history or physical examination of a patient with unilateral incidentaloma suggests glucocorticoid, mineralocorticoid, adrenal sex hormone or catecholamine excess, which is confirmed biochemically, the treatment of choice is often adrenalectomy.[16] In one study of 201 patients with incidentalomas, 30% were found to have a phaeochromocytoma.[17]

In the rare malignant cases, palliative care may be achieved with radiotherapy and chemotherapy. New emerging therapies, such as the tyrosine kinase inhibitor sunitinib, which rectifies the results of genetic abnormalities, may revolutionise the treatment of malignancy in the future. [18]

Prognosis

The five-year survival rate for non-malignant phaeochromocytoma is over 95% but for malignant phaeochromocytomas it is less than 50%. The risk of malignancy is rather higher when children are affected. [19]

Most paragangliomas arise from chromaffin tissue, along the para-aortic sympathetic chain, or within the organs of Zuckerkandl at the origin of the inferior mesenteric artery, the wall of the urinary bladder and the sympathetic chain in the neck or mediastinum. They are usually benign and amenable to surgical resection. Around half are hereditary and so genetic testing should be considered. [20] They can recur many years after initial presentation, so long-term follow-up is important. [1]

Phaeochromocytoma and pregnancy

Pre-eclampsia is fairly common, whilst phaeochromocytoma is very rare and only a few hundred cases in pregnancy have been reported in the literature.

- If phaeochromocytoma is diagnosed for the first time in pregnancy, there are special concerns with a maternal and fetal mortality rate of 48% and 55% respectively.
- If diagnosis precedes pregnancy, the outcome is vastly better. Alpha-adrenergic blockade with phenoxybenzamine is required as soon as the diagnosis is made.
- If surgery is performed in the first or second trimester, the pregnancy need not be terminated but fetal loss is high.
- In the third trimester, as soon as fetal lung maturity is confirmed, lower segment caesarean section (LSCS) followed by surgical removal of the tumour are required. [21]

- Conservative management during pregnancy has been described. [22]

Further reading

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