*Phaeochromocytoma*

A phaeochromocytoma 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 occurMany - 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.

The excessive production of catecholamines may cause life-threatening hypertension or cardiac arrhythmias. If the diagnosis is overlooked, the result can be disastrous or fatal but, if this rare tumour is diagnosed, it is curable.

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 type 2, von Hippel-Lindau (VHL) disease, neurofibromatosis type 1 and the paraganglioma syndromes types 1, 3 and

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 in response to neural control and produces about 85% adrenaline (epinephrine) 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.

Epidemiology

They occur in between 0.5 and 2 in 1,000 patients with hypertension but patients may be normotensive or have a labile blood pressure.

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There is no sex difference in incidence or any particular racial predisposition.

Diagnosis is usually made between the third and the fifth decades.

Approximately 10% occur in children.

In children, 50% are solitary adrenal tumours, 25% are bilateral and 25% are extra-adrenal. They are more likely to be familial than those presenting in adult

Inherited forms

Phaeochromocytomas occur in certain familial syndromes, including:

Multiple endocrine neoplasia (MEN) syndrome.

Neurofibromatosis.

Von Hippel-LIndau (VHL) disease.

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

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].

Examination

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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

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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[A recent consensus guideline stated that plasma free metanephrines were the blood test of choice].

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.

Imaging

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

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].

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]. The molecular structure of MIBG is similar to noradrenaline (norepinephrine) and concentrates within adrenal or extra-adrenal phaeochromocytomas.

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Genetic testing

Differential diagnosis

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Anxiety disorder.

Carcinoid tumour.

Alcohol withdrawal.

Labile hypertension.

Drug abuse.

Factitious phaeochromocytoma - has been described

Management

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 usefu].

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].

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].

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 adrenalectom]. In one study of 201 patients with incidentalomas, 30% were found to have a phaeochromocytoma].

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]....