Pheochromocytomas / Paragangliomas and two cases

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Abstract

Pheochromocytomas are catecholamine-producing neuroendocrine tumours that arise from the adrenal medulla or extra-medullary pheochromoblasts with highly variable clinical presentation, including episodes of headache, sweating, palpitations and hypertension. Due to the non-specificity of the symptoms there is usually a delay between the onset of symptoms and the final diagnosis. To make a firm diagnosis, biochemical testing of the blood (catecholamines) or urine (metanephrines and VMA) are mandatory. Many stimuli increase circulating catecholamines and metabolites and must receive due attention to prevent false-positive results. Therapeutically, surgery is the gold standard. To minimise complications during and post surgery the lesion(s) should be carefully localised via imaging studies. Adequate pre- and postoperative medical treatment is important. The history, diagnosis and therapy of two patients - the one with a paraganglioma of the organ of Zuckerkandl, the other with a intra thoracic paraganglioma are presented.

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Orientation

Pheochromocytomas are catecholamine-producing neuroendocrine tumours that arise from the adrenal medulla. Most commonly they present with episodes of headaches, sweating, palpitations and hypertension. These episodes may be serious and are potentially fatal due to cardiovascular complications. The episodes are the result of the sporadic release of excess catecholamines by the tumour. The non-specificity of symptoms and signs often delay a firm diagnosis. Paragangliomas are tumours that arise from extra-adrenal chromaffin cells.

Two patients each with a diagnosis of pheochromocytoma, were referred to the Department of Nuclear Medicine to localise the anatomical sites of the tumours.

Discussion

The adrenal medulla is formed from cells of the ectoderm of the neural tube. These cells give rise to sympathoblasts which form ganglion cells and pheochromoblasts. The latter cells are so-called chromaffin cells because they stain brown when exposed to potassium dichromate. These cells frequently produce catecholamines.

During embryonic development and cell migration, some of the chromoblasts/chromocytes may be diverted from their

Case 1

In July 2006, a 31-year-old white female who did not smoke or consume alcohol, but with a history of hypertension for the past 6 years, chronic sweating, episodes of flushing, a throbbing headache, pain in the right flank and 20 kg weight loss over the previous year, was referred to a cardiologist. Clinical examination of the patient was negative, the blood pressure was $^{130}/_{80}$ mm Hg, and an ultrasound study of the kidneys was negative.

Biochemistry of the blood showed high CRP and chromogranin levels. Biochemistry of the urine showed elevated levels of vanillylmandelic acid (VMA), homovanillic acid (HVA), VMA/creatinine ratio, HVA/creatinine ratio, metanephrine and normetaphrine. Thyroid function tests were normal. A diagnosis of pheochromocytoma, possibly a paraganglioma, was made; the patient was referred to the Department of Nuclear Medicine at the Pretoria Academic Hospital to localise the site of the tumour. A metaiodobenzylguanidine-^{123}I (^{123}I-MIBG) study was done. Planar and single photon emission computed tomography (SPECT) images were obtained 4 hr and 24 hr post-injection of the tracer, and a SPECT/CT scan 24 hr post-injection. These images showed intense concentration of the radiotracer on the right side antero-paravertebrally approximately at the level of L3 and a diagnosis of a paraganglioma of the gland of Zuckerkandl was made.

Surgery was performed and a 50 g encapsulated tumour removed – size 5 x 4.5 x 3.5 cm. Histological evaluation confirmed the diagnosis of paraganglioma showing significant cell pleomorphism and a rich blood capillary network. The cells were found to be strongly positive for chromogranin and synaptophism. Follow-up blood, urine and radioisotope studies were normal (see Figure 1A and 1B).

Figure 1 A: 24-hour conventional whole-body ^{123}I-MIBG study – a paraganglioma located in the gland of Zuckerlandl: (a) focus of intense ^{123}I-MIBG uptake, (b) urinary bladder containing some ^{131}I-MIBG

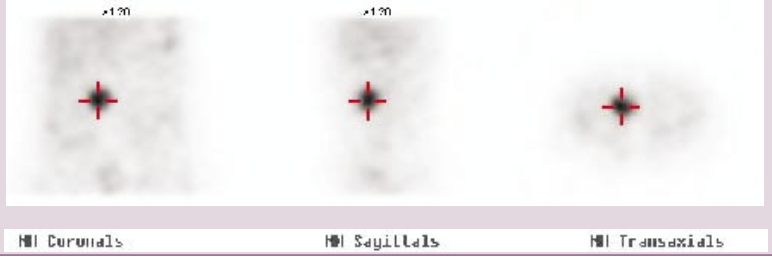
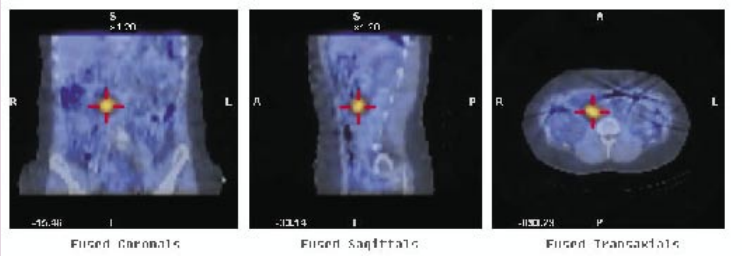


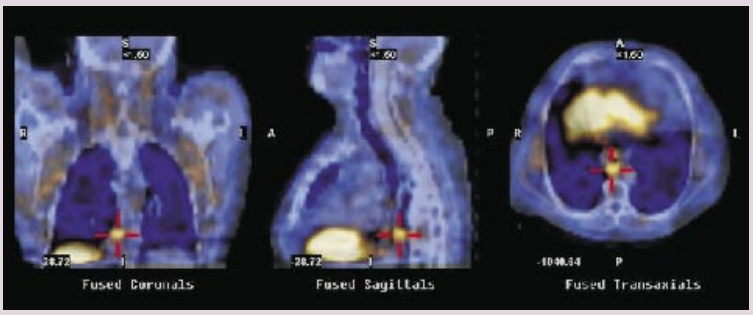
Figure 1 B: Fused SPECT/CT study



Case 2

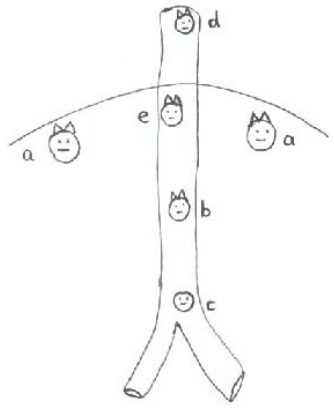
On October 17, 2006 a 63-year-old moderately overweight white man with an 8 year history of excessive sweating, cardiac arrhythmia, panic attacks, no alcohol abuse, no smoking, and a normal blood pressure but with elevated blood and urine biochemical markers for pheochromocytoma, arrived at the department. A ^{123}I-MIBG study identified a paraganglioma in the thoracic paravertebral space (see Figure 2).

Figure. 2: A fused SPECT CT. Paraganglioma located in the thoracic paravertebral space.



course and become associated with groups of extramedullary neuroendocrine cells called paraganglia. These cell groups or ganglia are usually located prevertebrally. The most common locations of paraganglia are near the right or left adrenal gland, in the lumbar paravertebral spaces, anterior to the large vessels of the abdomen, at the origin of the inferior mesenteric artery from the aorta (organ of Zuckerkandl), in the left thoracic paravertebral space, and in the coeliac ganglia, in this order of frequency (fig 3). Some of the chromoblasts may become associated with parasympathic ganglia.

Figure 3: Most common locations of paraganglia. (a) Adrenals; (b) paravertebral lumbar space; (c) organ of Zuckerkandl; (d) paravertebral space left thorax; (e) anterior of large vessels.



Tumours that develop from the adrenal medulla are called pheochromocytomas. Tumours may also develop from the sympathetic or para-sympathetic paraganglia and are called paragangliomas – a term first applied by Kohn.[1]

Pheochromocytomas and sympathetic paragangliomas are chromaffin positive (meaning they stain brown when exposed to potassium dichromate), and usually produce catecholamines. Parasympathetic paragangliomas are usually chromaffin negative.[2] Around 80% of pheochromocytomas arise from the adrenal medulla; 20% arise from extra-adrenal chromaffin tissue and are usually found in the abdomen.[3] Pheochromocytomas are responsible for 0.1 - 0.6% of hypertensive cases. The incidence in autopsy studies is higher, suggesting that a significant number of tumours are missed resulting in premature death.[4]

Paragangliomas of the head and neck are usually chromaffin negative. Chromaffin-positive parasympathetic paragangliomas rarely produce catecholamines.[2, 5]

Eight known major hereditary forms of pheochromocytoma and paraganglioma have been identified - in ***multiple endocrine neoplasia type 2***, in ***von Hippel-Lindau syndrome***, and in ***familial paragangliomas, etc.*** [2,6] Hereditary forms are usually diagnosed before the age of 40 years, and sporadic forms after 40. Pheochromocytoma is rare in children.[7]

Clinical presentation

Hypertension, tachycardia, pallor, headache, and feelings of panic or anxiety are the clinical symptoms and signs that usually dominate. Most of these symptoms and signs are the result of excessive secretion of catecholamines. The hypertension is typically paroxysmal in nature with a normal blood pressure between episodes. Episodes can be severe and result in hypertensive emergencies. In some patients the episodes are superimposed on a background of sustained hypertension. The blood pressure can also be consistently normal, especially in those with a very small tumour, and in patients with adrenal incidentalomas. About 5% of all incidentalomas are pheochromocytomas.[5, 8] Normal blood pressure, or even hypotension is not uncommon in patients with dopamine-producing paraganglioma.[9] A patient may present with unexplained orthostatic hypotension on a background of hypertension. Paroxysmal signs and symptoms provide compelling clues for a pheochromocytoma. Stimuli that elicit episodic catecholamine secretion and a paroxysm, even a crisis, include anaesthesia, tumour manipulation, food, micturition, and various drugs (glucagon, tyramine, tricylic antidepressants, etc). Paroxysms usually last minutes to an hour.

Note. Many of the symptoms and signs associated with pheochromocytoma are fairly typical of many other clinical conditions (table 1). Pheochromocytoma is therefore often referred to as "the great mimic".[5]

Table 1: Differential diagnosis of phaeochromocytoma

Endocrine
Hyperthyroidism
Carcinoid
Hypoglycaemia
Medullary thyroid carcinoma
Mastocytosis
Menopausal syndrome

Cardiovascular
Heart failure
Arrhythmias
Ischaemic heart disease
Baroreflex failure

Neurological
Migraine
Stroke
Diencephalic epilepsy
Meningioma
Postural orthostatic tachycardia syndrome (POTS)

Miscellaneous
Porphyria
Panic disorder or anxiety
Factitious disorders (eg, from use of sympathomimetic drugs such as ephedrine)
Drug treatment (eg, monoamine oxidase inhibitors, sympathomimetic drugs, withdrawal of clonidine)
Illegal drugs (eg, cocaine)

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Diagnosis

Despite diagnostic progress, there still usually remains a delay of about 3 years between the onset of symptoms and the final diagnosis.[10] The reason for the diagnostic delay is the non-specific symptoms – especially headaches, palpitations and sweating. If all three of these symptoms are present, the diagnostic specificity is said to be > 90%.

Diagnostic progress and genetics now challenge the traditional rule of 10 for pheochromocytomas (10% bilateral, 10% extra-adrenal, 10% familial, 10% malignant). The incidence of bilateral tumours is higher than 10% in familial phaechromocytomas. About 25% of the extra-adrenal tumours are hereditary.[6] The incidence of metastases is around 5% for adrenal phaechromocytomas but may be 33% for extra-adrenal phaeochromocytomas.

Since the clinical presentation of phaeochromocytomas varies greatly, biochemical testing and imaging procedures are mandatory.

Biochemical tests

All patients with suspected phaeochromocytoma should undergo biochemical testing. Traditional tests include measurement of urinary and plasma catecholamines, urinary metanephrines (normetanephrine and metanephrine) and urinary vanillylmandelic acid (VMA). Biochemical presentation of excessive production of catecholamines is an essential step for the diagnosis of phaeochromocytoma-blood or urine can be used. Accumulating evidence suggests that measurements of plasma free metanephrines or urinary fractionated metanephrines are the most sensitive tests for diagnosis, and are the most suitable for reliable exclusion of phaeochromocytomas.[11]

Provided appropriate reference intervals are used, the high diagnostic sensitivities of plasma-free or urinary fractionated metanephrines mean that negative test results exclude the presence of virtually all phaeochromocytomas. Exceptions include asymptomatic small tumours that produce and metabolise negligible amounts of norepinephrine or epinephrine. Another problem is that a positive plasma or urinary metanephrine test does not always reliably indicate a pheochromocytoma. Many physiological stimuli, drugs, and clinical conditions (eg, hypertension, heart failure, stroke, baroreflux failure, etc.) increase the circulating catecholamines and metabolites, and compound the problems.[5] Having said this, most true-positive results can be distinguished from false-positives by the magnitude of increases in test results – well above the false-positives.

Pharmacological impacts on catecholamine levels can be avoided by withdrawing or substituting drugs known to cause increases in catecholamine and their metabolites. Phenoxybenzanine and cyclic antidepressants are major causes of false-positive results.[5]

Sampling of blood after overnight fasting and in the sitting position can easily avoid the effects of diet and physical activity on plasma measurements.[12]

Genetic testing

Jimenez ***et al*** recommended genetic testing for all patients under the age of 20 years with a family history suggestive of hereditary pheochromocytoma with an apparently sporadic pheochromocytoma.[2]

Imaging procedures

Tumour localisation should ideally be undertaken once there is unequivocal biochemical evidence for pheochromocytoma.[5]

- *CT Imaging* of the entire abdomen and pelvis, with or without contrast, are most often used.[13] Patients should be protected from a hypertensive crisis or cardiac arrhythmia by blocking the α- and β-adrenoreceptors.

- *MRI* with gadolinium enhancement has similar diagnostic sensitivity (90-100%) and specificity (70-80%) to CT, is the preferred procedure for localisation of extra-adrenal tumours, during pregnancy, in children, and in patients allergic to contrast – no adrenergic blockade needed.[5]

Radioscintigraphy

A ^{123}I-metaiodobenzylguanidine (MIBG) study is indicated to increase specificity (95-100%), to evaluate the mass of the detected tumour, to rule-in/rule-out multiple involvement, and as a prelude to MIBG-therapy. If ^{123}I-MIBG is not available, ^{131}I-MIBG could be used but has poorer imaging qualities. Coupling of functional (MIBG) with anatomical imaging (CT or MRI) might also be of value for the detection of additional multifocal tumours. Several drugs (labetalol, tricyclic antidepressants and calcium antagonists) can interfere with tumour uptake or retention of ^{123}I-MIBG. Hence their withdrawal (5x their t½) is indicated.[5] Small recurrent tumours or metastases in the adrenal region can be detected intraoperatively by a gamma-detector probe after the isotope is given a few hours before surgery.[14, 15, 16]

PET imaging studies, using ^{18}F-fluorodopamine, ^{18}F-fluorodopa or ^{18}Fluorodeoxy-glucose

^{18}F-fluoro-deoxyglucose, the only PET imaging compound widely available, is not recommended for initial diagnostic localisation, since it is non-specific for pheochromocytoma and sensitivity is restricted. However, ^{18}F-fluoro-dopamine PET offers better diagnostic sensitivity than ^{131}I-MIBG, especially in metastatic pheochromocytoma - can localise far more foci than can ^{131}I-MIBG.[17, 18]

Management of phaeochromocytoma

Once a phaeochromocytoma is located, complications during surgery must be kept to the minimum, and this is realised through adequate preoperative management. The major aim of preoperative medical treatment is to prevent catecholamine-induced serious and potentially life-threatening complications during surgery, (a hypertensive crisis, cardiac arrhythmias, pulmonary oedema, cardiac ischaemia, etc).[19]

Traditional preoperative medical regimens include blockade of α-adreno-receptors with phenoxybenzanine, prazozin, doxazosin, or urapid.[5, 19] Phenobenzamine is often preferred because it blocks α-adrenoreceptors non-competively. Others advocate pretreatment with doxazosin, based on a presumed increased risk of post-operative hypotension due to extended non-competitive α-adrenergic blockade.

Other drugs used for preoperative management are labetalol or calcium-channel blockers, either alone or in combination with α-adrenergic receptor blockers.[20] Criteria used to assess effective preoperative preparation include a blood pressure below 160/90mm Hg for more than 24 hr, orthostatic hypotension but blood pressure should not fall below 80/45 in upright position, or not more than one ventricular extrasystole/min, no S-T segment changes, etc.

Risk of excessive orthostatic hypotension can be kept to a minimum by increasing salt and fluid intake. After surgery, patients must be under close surveillance for the first 24 hr; major postoperative complications are hypotension and hypoglycaemia.[5]

Malignant pheochromocytoma

Despite molecular diagnostic and prognostic markers, it remains impossible to predict subsequent malignant degeneration of pheochromocytomas. There is still no effective treatment for malignant pheochromocytomas. Radical surgery is considered the gold standard to improve symptoms and survival. ^{131}MIBG therapy is disappointing - there are indications that increased doses may give better results.[5, 21-23]

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