

Pheochromocytoma – revisited

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ABSTRACT

Pheochromocytomas are rare neuroendocrine tumours with a highly variable clinical presentation but most commonly presenting with episodes of headaches, sweating, palpitations, and hypertension. The serious and potentially lethal cardiovascular complications of these tumours are due to the potent effects of secreted catecholamines. Biochemical testing for pheochromocytoma is indicated not only in symptomatic patients, but also in patients with adrenal incidentalomas or identified genetic predispositions (eg, multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, neurofibromatosis type 1, and mutations of the succinate dehydrogenase genes). Imaging techniques such as CT or MRI and functional ligands such as ¹²³I-MIBG are used to localise biochemically proven tumours. After the use of appropriate preoperative treatment to block the effects of secreted catecholamines, laparoscopic tumour removal is the preferred procedure. If removal of pheochromocytoma is timely, prognosis is excellent. However, prognosis is poor in patients with metastases, which especially occur in patients with large, extra-adrenal tumours. [IJEM 2007;(3&4):23-29]

Key words: Pheochromocytoma, catecholamines, VMA, MIBG, secondary hypertension

INTRODUCTION

Pheochromocytomas are rare catecholamine secreting tumours that if missed invariably prove fatal(1). These tumours arise from chromaffin cells derived from neural crest tissue and appear brown on fixation with dichromate due to oxidation and polymerisation of catecholamines in the storage granules. Most chromaffin cells degenerate after birth, largest collection is in the adrenal medulla (site for 85% cases of pheochromocytoma), rest of the tumours arise from parasympathetic associated or sympathetic associated chromaffin tissue usually from collection of chromaffin tissue near the aortic bifurcation (organ of Zuckerkandl). Less common sites are mediastinum (2%) and neck (1%)(1).

Adrenal Gland

The adrenal glands are bilateral retroperitoneal organs located on the superior medial aspect of upper pole of each kidney weighing approximately 4 grams. The right adrenal is pyramid shaped, in relation to inferior vena cava and segment VII of liver, the left adrenal is flatter and lies posterior to

stomach and pancreas along left crus of diaphragm. Adrenal glands are supplied by branches from inferior phrenic, aorta and renal artery. Right adrenal vein is short (3 mm) and drains into inferior vena cava, rarely into right hepatic vein while as vein on left side empties into renal vein often after joining the inferior phrenic.

Adrenal mass

Although majority of adrenal masses are benign, malignant are not uncommon. Various types of adrenal tumours are shown in table 1.

Table 1: Various adrenal tumours

I.	Cortical tumors	Adenoma Carcinoma Functional Non-functional Myelolipoma Adrenal oncocytoma Non-functional Myelolipoma Adrenal oncocytoma
II.	Medullary tumors	Pheochromocytoma Neuroblastoma
III.	Others (including metastases)	

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Pheochromocytoma

The name pheochromocytoma proposed by Pick (1912) is derived from Greek words phalo (dusky) and chroma (colour). The first description of pheochromocytoma is credited to Frenkel (1886) who reported bilateral tumour in an 18 year old girl. Extra adrenal pheochromocytoma was first reported by Alezais and Pevon (1908). Roux and Mayo independently reported the first successful resection of pheochromocytoma in 1926 and 1927 respectively. In 1929 Rabin reported excess of normal vasopressor agent in pheochromocytoma. Epinephrine was isolated by Kelly and colleagues (1936) while Holton (1949) demonstrated the presence of norepinephrine in pheochromocytoma(2). Pheochromocytoma accounts for approximately 0.05%-0.1% of patients with any degree of hypertension(1). In western population the prevalence of pheochromocytoma is between 1:4500 and 1:1700 with an annual incidence of 8 cases per 1 million per year(3). The most common age group affected is fourth and fifth decade with equal incidence in both sexes. Significant numbers of pheochromocytomas remain undiagnosed, first seen at autopsy and contribute to the mortality in 60-75% of cases(4). It has been referred as '10% tumour' (because 10% are malignant, bilateral, extra adrenal, multiple, occur in children, familial) but recent reports have challenged this concept with upto 24% being familial(5).

Clinical features

Pheochromocytomas secrete excessive amounts of catecholamines, dopamine, norepinephrine and epinephrine; these also produce other hormones including ACTH, calcitonin, somatostatin, oxytocin, vasopressin and vasoactive intestinal peptide (VIP). The symptoms and signs of pheochromocytoma (table 2) are due to these compounds that are secreted(6).

Table 2: Symptoms and signs in pheochromocytoma

Symptoms	Signs
Headache	Hypertension
Palpitations	Tachycardia/ reflex bradycardia
Sweating	Postural hypotension
Anxiety/nervousness	Weight loss
Tremulousness	Pallor
Nausea/vomiting	Hypermetabolism
Pain in chest	Hyperglycemia
Weakness/fatigue	Tremor
Dizziness	Increased respiratory rate

The classical triad of symptoms include headache (90%), palpitations and excessive generalised sweating (60-70%)(1,6). Persistent hypertension is seen in only 50%(1). Differential diagnosis is given in table 3. Approximately 75% deaths associated with untreated pheochromocytomas are due to myocardial infarction or cerebrovascular accident(4, 7).

Initial Biochemical Testing

Missing a pheochromocytoma can have deadly consequences. Catecholamine secretion by pheochromocytoma can be episodic or in patients who are asymptomatic, negligible in nature so measurement of

Table 3: Differential diagnosis of pheochromocytoma (based on symptoms)

Neuroblastoma/ganglioneuroma	Paroxysmal tachycardia
Adrenal medullary hyperplasia	Angina pectoris/ myocardial infarction
Hyperadrenergic essential hypertension	Mitral valve prolapse
Baroreflex failure	Aortic dissection
Thyrotoxicosis	Hypoglycemia/ insulin reaction
Anxiety/panic attack	Renal parenchymal/vascular disease
Migraine/cluster headache	Intracranial lesions
Autonomic epilepsy	Toxemia of pregnancy
Abrupt clonidine withdrawal	Acute intermittent porphyria
Amphetamines/cocaine/ alcoholism	Menopausal syndrome

catecholamine metabolites in initial screening is a better practice as metanephrines are produced continuously within pheochromocytoma cells independent of catecholamine release, obviating the need for measurement during hypertensive spells. Measurement of plasma-free metanephrines and urinary fractionated metanephrine is the most sensitive diagnostic test(8) followed by intermediate sensitivity of urinary and plasma catecholamine levels, whereas, urinary total metanephrines and VMA offered least sensitivity(8). Spectrophotometric measurement of total metanephrines has been replaced by newer chromatographic methods that allow fractionated measurement of normetanephrine and metanephrine (fractionated metanephrines)(9). The urinary excretion or plasma concentrations of metanephrines show strong correlation with tumour size as compared to the catecholamine level(10,11).

Sampling procedures

Blood should be collected with patient supine for 20 minutes before sampling. Patient should have refrained from nicotine and alcohol for 12 hrs and preferably fasting overnight. The sample is collected into tubes containing heparin or ethylenediamine tetracetic acid (EDTA) stored in ice at 4°C before centrifuge.

24 hour urine collection is preferred over blood sampling as it avoids rigid sampling condition and is easy to implement Urine collected is preserved in containers with 20 ml of 6N HCl or 25 ml of 50% acetic acid. For prolonged storage, aliquots of blood or urine are stored at -80°C.

Pharmacologic tests

These are used to improve diagnostic accuracy for pheochromocytoma. However provocative tests are

inherently dangerous, suppression tests may be useful due to low risk.

Clonidine suppression test: Most often used suppression test(12). Blood is drawn before and three hours after the oral administration of clonidine 0.3 mg/70kg body weight, a decrease of plasma levels of normetanephrine more than 40% or to below upper reference limit has a diagnostic sensitivity of 98% compared to 67% sensitivity for norepinephrine alone(12).

Glucagon is the safest and most specific of provocative tests(13) and can be used in patients receiving β -blockers(13). It is given in a dose of 1mg intravenous bolus and blood for plasma catecholamines drawn before and 2 minutes after drug is injected while monitoring blood pressure & heart rate. An increase in plasma norepinephrine of greater than three fold or to more than 2000 pg/ml is considered a positive test(13).

Localization

Attempt to locate a pheochromocytoma should only be done after biochemical studies have established the presence of tumour. Overall pheochromocytoma in adrenal are more easily identified than those at extra adrenal sites. For localization two imaging studies one anatomical and one functional should be performed to locate primary recurrent or metastatic tumour.

CT scan

With or without contrast is the initial method used in most institutions(Figure 1). It is easy, widely available and relatively inexpensive. CT scan has 95% sensitivity and 70% specificity in localizing adrenal tumours of 1 cm or more in size and extra adrenal tumours of greater than 2 cm size(14,15). Administration of intravenous contrast media for CT scanning may evoke catecholamine release from tumours, though iohexol has not been shown to cause any hypertensive paroxysms(16). β -blockade prior to administration of contrast agent is a precautionary measure.



Figure 1: CT scan of abdomen with right adrenal pheochromocytoma

MRI (Figure 2)

MRI with or without gadolinium enhancement is a reliable method in identifying more than 95% of tumours(17). It is superior to CT in assessment of relationship between the tumour and the surrounding vessels especially great vessels, rendering MRI important in ruling out vascular invasion(15,17). Chemical shift MRI differentiates benign adenomas from pheochromocytoma, metastatic, hemorrhage pseudocysts or malignant tumours. On T2 sequence pheochromocytoma appears characteristically bright with high signal with no signal loss on opposed phase images due to hypervascularity(17). MRI is a good imaging modality for detection of intracardiac, juxtacardiac and juxtavascular pheochromocytoma because it reduces cardiac and respiratory motion induced artifacts. The advantage MRI offers is lack of radiation exposure and it doesn't cause release of catecholamines necessary but, MRI is costlier. MRI is the initial imaging for pheochromocytoma in pregnancy and in those who are allergic to contrast material used in CT(2).



Figure 2: MRI of abdomen with left adrenal pheochromocytoma

USG is not usually recommended except in case of children and pregnant women when MRI is not available(2).

Functional Imaging

Functional imaging studies are performed as there is presence of cell membrane and vesicular catecholamine transport system in pheochromocytoma cells. Functional imaging include ^{123}I or ^{131}I MIBG scintigraphy, 6-18F-fluorodopamine, 18F dihydroxyphenylalanine (18F-dopa), 11C-hydroxyephedrine and 11C-epinephrine positron emission tomography (PET).

MIBG

MIBG yields nearly 100% specificity for this tumour(18). MIBG labeled with ^{131}I has a false negative rate of 15% in patients with pheochromocytoma; MIBG labeled with ^{123}I has much better sensitivity. Another advantage of ^{123}I

over ^{131}I labeled MIBG is the additional ability for imaging by single photon emission computed tomography (SPECT)(19) and also that ^{123}I has shorter half life than ^{131}I -MIBG (13 hrs vs. 8.2 days) so higher doses can be given. ^{123}I can however be used as a modality of treatment in malignant pheochromocytoma(19). In order to block uptake of free $^{123/131}\text{I}$ by thyroid gland, potassium iodide (100 mg twice a day) for 4 days in ^{123}I MIBG and for 7 days in ^{131}I MIBG is given to the patient. Patients are usually scanned at 24 hours and again at either 48 or 72 hours to differentiate the images appearing on earlier scan from being physiological or from tumour (which persist or increase in later scans).

Positron Emission Tomography

PET imaging is done using short lived positron emitting agents. Most PET radiopharmaceuticals used for detection of pheochromocytoma enter the pheochromocytoma cells using the cell membrane norepinephrine transporter. Labeled analogue of dopamine is a useful scintigraphic agent as dopamine is a better substrate for this transporter than most other amines, including norepinephrine. 6-18F-fluorodopamine, sympathoneuronal imaging agent is a positron emitting analogue of dopamine PET scan has been shown to have 100% sensitivity(20) and is superior to ^{131}I MIBG scintigraphy in patients with metastatic pheochromocytoma, with upto 100% sensitivity in most cases(21).

Few cases of pheochromocytoma that are negative to even 6-18F-fluorodopamine PET scans have also been identified, which were negative on ^{131}I or ^{123}I MIBG scintigraphy also(2).

PET 11C-hydroxy ephedrine, 11C-epinephrine or 18F-fluorodopa are other PET imaging agents. These agents have limited diagnostic yield due to limited affinity for norepinephrine transporter system and shorter half life of 11C radiopharmaceuticals (~20 minutes) rendering whole body scans difficult(22).

Increased glucose metabolism characterizes various malignant tumours and thus the uptake of glucose labeled with 18F-fluoride is useful in imaging these tumours. FDG PET reveals more metastasis than MIBG scintigraphy in metastatic pheochromocytoma but it cannot distinguish benign from malignant disease(23).

Advantages of PET scan is that it can be one within minutes to hours after injecting a short lived positron emitting agent. There is a low radiation exposure and a superior spatial resolution. Limited availability of radiopharmaceuticals and PET equipment are the drawbacks for its widespread use.

Octreoscan

Somatostatin receptor scintigraphy using octreotide has been used, its sensitivity is low especially in detecting solitary tumour but octreoscan is useful in metastatic pheochromocytoma especially those that express somatostatin receptors and are negative on MIBG

scintigraphy and 6-18F-fluorodopamine PET(24).

Other

Venacaval sampling for catecholamine and metanephrines is done when extra adrenal tumour has escaped removal during previous surgery and other techniques have failed to localize the tumour(25).

Treatment of Pheochromocytoma

The optimal therapy for a pheochromocytoma is prompt surgical removal after diagnosis in order to prevent potentially lethal hypertensive crisis(6). Safe surgical removal involves a team effort comprising of an internist, an anesthesiologist and a surgeon with prior experience with pheochromocytoma.

Preparation for surgery

The medical treatment is directed at controlling hypertension (including hypertensive crisis during removal of tumour, at maintaining stable blood pressure during surgery and minimizing adverse effects of high catecholamine levels during anesthesia). Maintain adequate blood pressure control for two weeks prior to surgery. Treatment should be initiated by use of a non competitive adrenoceptor blocker phenoxybenzamine (1mg/kg/d). Other α -blocking drug with shorter duration of action are prazosin (2-5 mg q 6 to 8 hrs), terazocin (2-5 mg OD) and doxazosin (2-8 mg OD).

Labetalol(200-600mg q 12 hrs) has both α and β antagonistic activity and can be given orally as well as intravenously, but due to more of β antagonistic activity can cause more slowing of heart rather than control of BP.

Once BP is controlled, the patient is given normal to high salt diet to restore blood volume to normal and β blockers (propranolol, esmolol) are only needed when significant tachycardia or catecholamine induced arrhythmia occur. These should never be given in absence of α blockade as that might accelerate epinephrine induced vasoconstriction.

Metyrosine (1.5-4g/d) competitively inhibits tyrosine hydroxylase which is the rate limiting step in catecholamine biosynthesis. Calcium channel blockers have also been used to control BP. Hypertensive crises is treated with short acting agent like phentolamine (5 mg bolus or 100mg in 500 ml 5% dextrose as intravenous infusion). Alternatively, continuous infusion of sodium nitroprusside, nifedipine (10mg oral or sublingual) can be used. The main goals in the operating room are careful blood pressure monitoring, excellent venous access, rapid and smooth induction of anaesthesia and excellent exposure and minimal manipulation of the tumour. To achieve these, arterial lines are placed in large vessels, central venous line is put in, general anaesthesia induction is done with inhaled anaesthetic agents, muscle relaxants without hypertensive side effects (like vecuronium) used. A Swan-Ganz catheter may be used in elderly and those with cardiac dysfunction. Intraoperatively gentle handling of tumour and dissecting patient from tumour is done to prevent spillage and haemorrhage by tumour fracture(2).

Surgical Approach

Both operative techniques, laparoscopic (lateral transabdominal approach and posterior retroperitoneal approach) as well as open (transabdominal anterior approach, lateral approach and posterior approach), are being used.

Laparoscopic approach with its multiple advantages like reduced pain, smaller incision, more rapid recovery and fewer complications is preferred in small (<3cm) to medium(3-6cm) size tumours(26). For bilateral tumours posterior retroperitoneal laparoscopic approach is considered better over lateral transabdominal approach as the latter requires the patient to be repositioned. In case the patient has undergone previous abdominal operation posterior retroperitoneal poses no problem whereas lateral transabdominal approach may be difficult because of adhesions. Posterior retroperitoneal approach offers no abdominal explorations as compared to little exploration in lateral approach(27).

Open approach was classically used particularly in the case of familial pheochromocytoma. Open approach, as compared to laparoscopic approach, allows access to both adrenals and full explorations of intra abdominal, retroperitoneal and extra adrenal deposits of tumour. This approach is feasible for large tumour size (>6cm)(27,28). For bilateral tumours open transabdominal anterior approach is better than posterior approach but manipulation of tumour by posterior approach may exceed that by anterior approach(28). In cases of carcinomas open operations allows best exposure as against laparoscopic approach(27,28). In case the patient has under gone previous abdominal operations open approach is more difficult than laparoscopic one. (27,28) With growing expertise in advanced laparoscopic procedures, recent reports show increasing trend towards laparoscopic adrenalectomy in the past decade with special stress on adrenal sparing surgery(29,30).

Post operative Management

In case hypotension develops during or after surgery, volume replacement is the treatment of choice, dopamine infusion may be required. The volume of fluid required is often large during the first 24 – 48 hours due to decreased sympathetic tone.

Postoperative hypertension during first 24 hours may be done due to pain, volume overload or autonomic instability. In case hypertension persists, essential hypertension is still most likely diagnosis. Before discharge urine collection for biochemical testing should be done. Repeat measurement should be made if symptoms reappear or yearly for first 5 yrs if patients remains asymptomatic. Operative mortality in experienced hands is approximately 1.3 %(31). Long term survival of benign pheochromocytoma is same as age adjusted normal. Approximately 25% patients remain hypertensive but easily controlled with medications(32).

Hereditary Pheochromocytoma

Upto 24% pheochromocytomas are inherited (in

autosomal dominant pattern)(5). Hereditary pheochromocytoma is associated with multiple endocrine neoplasia type 2, von Reckling Hausen's neurofibromatosis type 1, von Hippel-Lindau (VHL) syndrome and succinate dehydrogenase gene family(5,33).

Pathology

Sporadic pheochromocytomas are generally solitary, well circumscribed, encapsulated tumours. These may still be considered adrenal in origin if the cortex of the adrenal is found in close relationship to the tumour. There is no histopathological feature to distinguish malignant from benign pheochromocytoma. Only the tumour invasion of tissues and presence of metastatic lesions (most commonly in liver, lungs, lymphatic nodes and bones) are consistent with the diagnosis of malignancy(6,34). Most pheochromocytoma range from 3 to 5 cm in size. Largest tumour reported was 20 cm in diameter(35).

Malignant Pheochromocytoma

Frequency of malignant pheochromocytoma ranges from 13 to 34% with slight male predominance with half occurring at presentation(36). The overall 5 yr survival rate varies from 34% to 60%(37). Clinical manifestations of malignant pheochromocytoma are similar to benign counterpart. There is increased dopamine excretion and its metabolites due to intraneuronal loss of dopamine hydroxylase as a consequence of cell dedifferentiation. Non diploid DNA pattern is associated with an increased likelihood of malignancy(38).

First line systematic therapy is targeted radiotherapy using ¹³¹I-MIBG (50mCi to 900mCi), with this one third of patients show partial response (50% reduction in tumour mass) and improvement in symptoms(39). In rapidly progressive metastatic tumour chemotherapy is recommended using combination of cyclophosphamide (750mg/m²) Vincristine (1.4 mg/m²) and dacarbazine 600 mg/m²(CVD) administered I/V in 21 day cycles, with 57% having complete or partial response. (40) External beam radiotherapy is used in palliation of chronic pain and symptoms of local compression(41).

Pheochromocytoma in Children

About 5 -10% of all pheochromocytoma occur in children with an incidence of 2 per million, it is the most common endocrine tumour in paediatric age group(42,43). These are commonly familial (9-50%), extra adrenal (8-43%), bilateral adrenal (7-53%) and multifocal with peak at 10 to 13 yrs of age. Less than 10% of paediatric pheochromocytoma are malignant with a 5 yr survival of 40-50%(42).

In contrast to adults 70-90% of children present with sustained hypertension. MRI is preferred over CT due to lack of radiation exposure. MIBG can be used to localize tumour. Treatment is similar to that in adults.

Pheochromocytoma in Pregnancy

Pheochromocytoma remains unrecognized antepartum in 47% to 65% of patients and it carries a high morbidity and

mortality (40.3% maternal and 56% fetal)(44). Localization is best done by MRI and/or ultrasonography(2). In case of hypertensive crisis in pregnancy phentolamine (1-5 mg bolus or 1 mg/min infusion) or sodium nitropruside (1 mg/kg/min) can be use. In first two trimesters, the tumour should be removed after adequate preoperative α -blockade while in third trimester patient should be treated with α -blockers till fetal maturity is reached followed by cesarean section. Labour and vaginal delivery should be avoided(6,45).

CONCLUSION

Pheochromocytomas are rare, mostly benign catecholamine-producing tumors of chromaffin cells of the adrenal medulla or of a paraganglion. Typical clinical manifestations are sustained or paroxysmal hypertension, severe headaches, palpitations and sweating resulting from hormone excess. However, their presentation is highly variable and can mimic many other diseases. If remaining unrecognized or untreated, they can be a life-threatening condition. Therefore, the most important message of this review is to think of them. Physicians commonly treating hypertension should evaluate such patients for a possible correctable cause. The diagnosis of pheochromocytomas depends mainly upon the demonstration of catecholamine excess by 24-h urinary catecholamines and metanephrines or plasma metanephrines. They are localized by a computed tomography scan and magnetic resonance imaging of the adrenal glands and abdomen; complementary ^{123}I -metaiodobenzylguanidine scintigraphy and ^{18}F -dihydroxyphenylalanine-positron emission tomography are available. Because approximately one out of four pheochromocytomas turn out to be hereditary entities, screening for genetic alterations is important. Laparoscopic and adrenal sparing surgical intervention following preoperative α -blockade is the treatment of choice.

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