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BMH Medical Journal 2016;3(2):43-50 **Review Article**

Pheochromocytoma: State of the Art and Guide to Evaluation and Management

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Pheochromocytoma is so called because it acquires a dusky color on staining with chromium salts. Roux in Switzerland and Charles Mayo in United States first performed excision of Pheochromocytoma. The excess circulating catecholamines have action on the adrenergic receptors. Approximately 0.5% of hypertensives are having pheochromocytoma of which 10% are accidentally detected. 85% of pheochromocytoma occur in adrenal medulla, 8% in the organ of Zuckerkandl. Ectopic sites are rarely involved like the chest (2%), neck (1%) and urinary bladder [1].

Among the extraadrenal pheochromocytomas 85% are located in the abdomen [1]. These locations can be superior para aortic region, inferior para aortic region or pelvic region. Extra adrenal pheochromocytomas secrete only noradrenaline. Paragangliomas of urinary bladder form < 0.5% of all bladder tumor. 10% of extra adrenal paragangliomas occur in the bladder. Zimmerman reported the first case of bladder pheochromocytoma (1953). Extra adrenal pheochromocytoma has higher incidence of malignancy. Incidence of malignancy in organ of Zuckerkandl is 22% and in bladder is 15%.

Pheochromocytoma may be associated with multiple endocrine neoplasia MEN 2A, MEN 2 B (Multifocal B/L adrenal tumor but benign). In VHL Type II (Von Hippel Lindau syndrome) which is associated with haemangioblastomas of cerebellum, brain stem, spinal cord and eyes along with tumors of pancreas and kidneys 20% may have pheochromocytoma [1,2]. Paraganglioma syndromes (PGL) are associated with phaeochromocytoma. There are 4 types of PGL syndromes. Neurofibromatosis Type I (1% incidence), tuberous sclerosis (Skin lesions + Angiofibroma), Sturge Weber syndrome (Facial angiomas along the trigeminal nerve), Carneys triad (Gastric leiomyosarcoma, pulmonary chondromas) are other rare conditions associated with a phaeochromocytoma.

Among all Pheochromocytoma 25% are associated with six syndromes MEN 2, VHL, NF, PGL 1, 3 and 4. Among the thoracic extra adrenal pheochromocytomas 30% are due to PGL and 3% VHL. Multifocal pheochromocytomas are most common with MEN 2, followed by VHL, PGL 1 and 4. Pheochromocytomas occur with equal frequency in males and females [1-3]. Commonly seen between the third and fourth decades of life. Presentation at younger age is seen in hereditary

conditions.

Metabolism and actions of Catecholamines on receptors

In a normal individual adrenal medulla predominantly secretes epinephrine (85%) however pheochromocytoma predominantly contains norepinephrine with the exception of familial pheochromocytoma. The metabolism of catecholamines and its end product are depicted in **Figure 1**. Alpha stimulation produces elevated blood pressure, glycogenolysis, gluconeogenesis, and intestinal smooth muscle relaxation. Beta Stimulation results in increase heart rate and contractility. **Figure 2** shows actions of catecholamines on the various receptors and also the drugs modifying these actions.

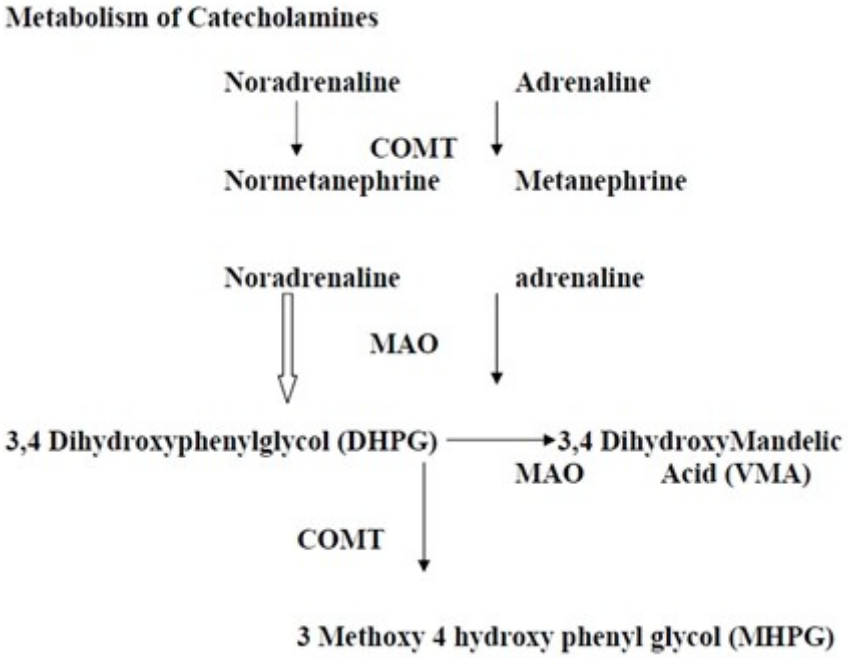

Figure 1: Metabolism of Catecholamines

Alpha 1	Post synaptic location Vasoconstiction Pupillary dilatation Uterine contraction Intestinal relaxation	Agonist: Phenlepherine Antagonist: Prasozin	
Alpha 2	Presynaptic location Inhibition of NE release Vasoconstiction	Agonist: Methyl dopa; Clonidine Antogonist: Yohimbine	
Beta 1	Positive ionotrophic and chronotrophic effect Lipolysis	Agonist: Dopamine Antagonist: Metoprolol Atenolol	
Beta 2	Bronchodilatation Vasodilatation Increased release of NE from synapses	Agonist: Terbutaline	Beta1 and 2 antagonist: Propranolol Nadolol

Figure 2: Actions of catecholamines on the various receptors and drugs modifying these actions

Clinical signs

The important clinical feature is hypertension. However, paroxysmal hypertension is reported only in 50% cases. 13% of patients may have normal blood pressure (Normotensive pheochromocytoma). Headache, sweating and palpitations may be presenting feature in some. Weight loss, pallor and tremor are other associated findings. Complications of hypertension like hypertensive retinopathy may be presenting feature in some cases. Precipitation of hypertensive crisis during induction of anaesthesia, use of cold medications or use of radiographic contrast agents may be suggestive of unrecognized pheochromocytoma. Presence of neurofibromas and Cafe au lait spots suggests association of pheochromocytoma with neurofibromatosis.

Differential diagnosis

The symptoms of headache, sweating, palpitations may mimic many conditions like anxiety disorders, factitious disorders, angina pectoris, hypoglycemia, hyperthyroidism, acute intermittent porphyria, paroxysmal supraventricular tachycardia and alcohol withdrawal. One has to exclude these during the making of a diagnosis.

Investigations

24 hr urinary Metanephrines (metanephrine and normetanephrine)

Proper collection of urine sample has to be ensured. The collected sample should be acidified; 20ml of 6N hydrochloric acid or 25 ml of 50% acetic acid is used. Sample need not be refrigerated. Certain precautions are necessary during the sample collection. Use amine free diet. Avoid coffee, cold beverages and bananas. Certain antihypertensive like alpha blockers are to be avoided prior to confirmation of the diagnosis of pheochromocytoma. Since ACE inhibitors, diuretics, calcium channel blockers do not affect the urinary catecholamine estimation they are preferred as antihypertensives in these patients before the definite diagnosis is made. In MEN 2 only epinephrine may be produced and hence such tumors release only metanephrines so always measure fractionated metanephrines. Tumors < 50gms have high turnover rate and hence release more of free catecholamines than the metbolised fraction. Results are expressed as micrograms of catecholamines per mg of urinary creatinine.

Important considerations while ordering investigations for diagnosing Pheochromocytoma

NE (Nor epinephrine (NE) is metabolized in the peripheral nerves to DHPG (3,4 di hydroxyl phenyl glycol) by MAO (Mono amine oxidase). DHPG is then acted by COMT (Catechol-O-Methyl transferase) in circulation to produce MHPG (3 Methoxy 4 hydroxyl phenyl glycol) both of which are eventually converted to VMA (Vanillylmandelic acid) (**Figure 1**). VMA thus, is derived from peripheral neuronal sources and hence not specific for screening tests. VMA is produced in the liver by alcohol dehydrogenase from DHPG and MHPG [4].

NE produced in pheochromocytoma is converted in the tumor (90%) to metanephrine and normetanephrine by COMT. NE/DHPG ratio >2 is suggestive of pheochromocytoma and < 0.5 rules out pheochromocytoma. In pheochromocytoma NE levels rises but very little rise is seen in DHPG levels.

94% of metanephrine and normetanephrine excreted in urine are produced in the adrenal medulla so measurement of these in urine after an attack of hypertensive crisis is not necessary. Pheochromocytoma may not secrete large amounts of free catecholamines into circulation and hence measurement of urinary and plasma free catecholamines cannot be reliably used for screening. But

metanephrines are constantly produced and hence they are better for screening purposes.

Plasma free metanephrine and nor metanephrine

Plasma free metanephrine and nor metanephrine are the initial screening test of choice (HPLC) because of their higher sensitivity and specificity. If this is not available then 24hr urinary metanephrine and normetanephrine is the next best option [4,5]. **Figure 3** depicts the sensitivity and specificity of the biochemical tets available.

	Sensitivity	Specificity
Plasma free Metanephrines	99%	89%
Plasma Catecholamines	84%	81%
Urinary Catecholamines	86%	88%
Urinary fractionated metanephrines	97%	69%
Urinary total metanephrines	77%	93%
VMA	64%	95%

Figure 3: Sensitivity and specificity of biochemical tests

Imaging

CECT scan

Adrenal pheochromocytoma of 0.5-1cm and extraadrenal pheochromocytoma of 1-2cm can be detected by CECT. 2-5mm thick sections are to be done. Homogenous mass with density < 10 HU on noncontrast scan is adenoma. Larger pheochromocytoma may be inhomogenous due to tumor necrosis.

MRI

MRI is the initial choice in children and pregnant women. T1 sequences show signal similar to liver, kidney and muscle. T2 weighted images give a bright signal. Chemical shift MRI differentiates masses based on presence of fat, which is usual in adenomas. No preparation with adrenergic blockade is required for MRI.

Functional imaging

MIBG imaging

Functional imaging picks up extra adrenal pheochromocytoma. MIBG resembles nor adrenaline. It is taken up by sympathomedullary tissues. The amount of free I^{131} in MIBG is 5%. To block I^{131} accumulation in thyroid SSKI (Saturated solution of potassium iodide) is used. It is given one day prior to the scan. 10mCi MIBI is given in adults. Imaging done at 24, 48 hrs if I^{123} is used and at 24,48,72 hrs for I^{131}. Normal adrenal is seen with I^{123} imaging after 24hrs in 32-75%.

I^{131} imaging shows normal adrenal in 16% scans after 48hrs. False positive MIBG scan can occur in adrenal carcinomas. False negative MIBG scans can occur in necrosis and dedifferentiated tumors.

PET scan

^{18}F FDG, C^{11} epinephrine, ^{18}F DOPA are used for PET scan. PET scan is indicated for detecting rapidly growing and dedifferentiated tumors.

The Algorithm for using investigations in cases of suspected Pheochromocytoma is shown in **Figure 4**. The sensitivity and specificity of various imaging modalities are given in **Figure 5**.

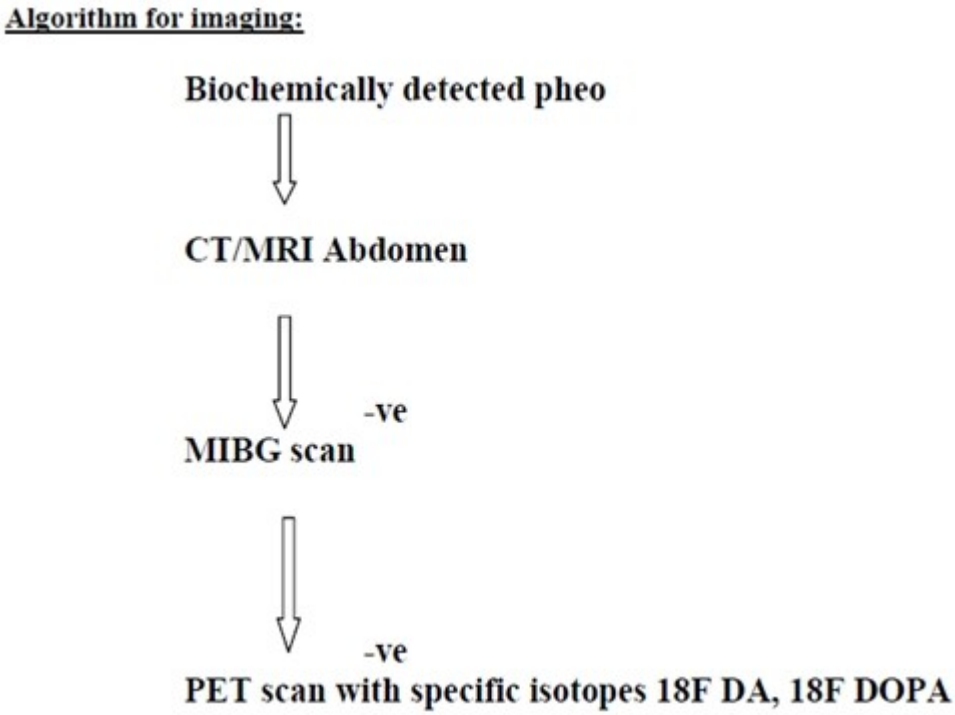

Figure 4: Algorithm for imaging

Investigative modality	Sensitivity	Specificity
CT scan	85-98%	70%
MRI scan	85-100%	67%
I131 MIBG scan	75-83%	100%

Figure 5: Sensitivity and specificity of various imaging modalities

Pre operative preparation

Alpha blockade is initiated with either phenoxybenzamine or Prazocin [6].

Phenoxybenzamine

Phenoxybenzamine results in nonspecific, prolonged, complete blockade of the alpha receptors. 10 mg twice daily is started and dose gradually increased. It produces reflex tachycardia, postural hypotension and severe post operative hypotension. Stop Phenoxybenzamine 48 hrs prior to surgery because of its long duration of action.

Prazosin

Dose used is 2 to 5 mg in two to three divided doses. Gradually increased to 15 to 20 mg. Since there is no reflex tachycardia, shorter duration of action it permits rapid adjustment of dosage and decrease the duration of post operative hypotension. Stop Prazosin 12hrs in advance before the surgery.

Terazosin and Doxazosin are used once daily. (2-5 mg)

Other Agents

Calcium channel blockers do not cause orthostatic hypotension. Even though used by some centers, when used alone it cannot prevent haemodynamic instability. They inhibit the norepinephrine mediated transmembrane influx of calcium in the vascular smooth muscles. They also prevent coronary artery spasm and myocarditis. They can also be used intra operatively as continuous infusion to control hypertension during tumor manipulation. It has been suggested as useful in normotensive pheochromocytoma with occasional paroxysms. Alpha methyl paratyrosine can bring down the dose of antihypertensives required to control the blood pressure.

Beta blockers are added to control tachycardia if required. Propranolol and Metoprolol are the preferred drugs.

Adequate pre operative blockade should achieve Roizens criteria. The criteria includes supine arterial blood pressure not > 160/90 mm of Hg, orthostatic hypotension not exceeding 80/45, ECG free of ST segment and T wave changes for last 2 weeks and not > 1 ventricular premature beat/ 5 minutes.

Intraoperative management

Intra-operatively the catecholamine release and its consequences are managed with:

- Phentolamine by its alpha blockade action controls BP used as bolus (2mg) / infusion. Phentolamine leads to tachycardia necessitating esmolol
- Sodium nitropruside to control the BP (minute by minute titration is provided)
- IV Labetolol/ Esmolol for the control of arrhythmias
- IV calcium channel blockers as infusion as well as bolus
- IV Magnesium sulphate: It inhibits the release of NA from the adrenal medulla and sympathetic nerve endings. 40-60 mg/kg bolus followed by infusion of 1-2 gm/hr

Management of post operative hypotension

Use colloids, intravenous (IV) noradrenaline, IV dopamine and blood transfusions

Surgical Management

Various operative approaches to adrenal glands are available. Thornton (1889) did first adrenalectomy. Charles Mayo (1927) did first adrenalectomy for pheochromocytoma using a flank incision. Young (1936) advocated the posterior approach to the adrenal gland. There are certain factors to be considered when deciding the surgical approach to the adrenal glands. These are:

- Presence or likelihood of malignancy
- Unilateral versus bilateral disease
- The type of adrenal disease
- Size of the adrenal tumor
- Presence of other abdominal disease
- The type and risk of complication with each approach
- Familiarity of the surgeon with these procedures

The different approaches are either Open or Laparoscopic.

Open surgical approaches

The approaches are either Anterior approach, Posterior approach, or Thoraco abdominal approach

Anterior Approach [5]

In this approach both adrenals can be exposed simultaneously, tumors of any size can be removed, entire peritoneal cavity can be exposed and inspected, intra venous extension of adrenal tumors can be removed and extensive resections in cases of local infiltration can be performed.

Disadvantage: Patient is subjected to a major laparotomy and thus the disadvantages of major abdominal procedure. Operative time, blood loss, hospital stay are longer for this approach. This is performed via midline or bilateral subcostal approach.

Right Adrenalectomy: Here hepatic flexure is mobilized, wide kocherization is done. Full visualization of IVC has to be obtained which partially overlies the adrenals. Right lobe of the liver is mobilized if visualization is difficult for which right triangular ligament is incised. Right adrenal vein is located at the superomedial aspect of the gland and is carefully dissected and ligated. Right hepatic vein injury has to be avoided during right lobe mobilization. Care is to be taken to meticulously ligate all small veins which may directly drain to IVC.

Left Adrenalectomy: The gland may be located behind, inferior to or above the pancreas. The peritoneum along the lower border of pancreas to be incised if required. The kidney is retracted inferiorly and pancreas superiorly to expose the gland. The left adrenal vein leaves the gland at its inferomedial aspect.

Posterior Approach

It is the most direct approach to the adrenals. Glands upto 5cm can be removed. Takes lesser operative time, less blood loss hospital stay is shorter. Limited access to major vascular structures is the major draw back.

Thoraco abdominal/ Lateral transthoracic approach

Gives the widest exposure of the adrenal gland for very large tumors and cases which needs extensive vascular control. Both the thoracic and peritoneal cavity are violated and hence all complications of major surgeries like respiratory complications, venous thromboembolism are associated with this approach.

Laparoscopic Adrenalectomy

Laparoscopic Adrenalectomy is the gold standard for the management for adrenal pheochromocytomas [5,6]. Can be safely used even upto tumors of 8-10 cm in size. The commonly employed approach is the transperitoneal approach. However retroperitoneoscopic approach can be used for tumors less than 5 cm. Usually on the right side four ports and on the left 3 ports are employed. Laparoscopic adrenalectomy results is less post operative pain, early recovery and discharge from the hospital. However the reports on blood loss and blood pressure fluctuations in open versus laparoscopic approaches has been controversial.

Contraindications to laparoscopic adrenalectomy: Adrenal Carcinoma, malignant pheochromocytoma, previous surgery like nephrectomy/spleenectomy, diaphragmatic hernia and masses more than 8-10cm.

Successful adrenalectomy results in the fall of blood pressure after the adrenal vein ligation. Normalization of blood pressure depends on several factors like duration of the hypertension and associated idiopathic hypertension. Biochemical cure is assessed by plasma metanephrine/24 hour urinary metanephrine assessment which is usually performed 10 days after the surgery [7]. Persistent elevation necessitates further evaluation with MIBG to look for thoracic/ abdominal extra adrenal pheochromocytoms.

Conclusion

Pheochromocytoma though rare is an important cause of secondary hypertension. Detection of such a tumor should lead the clinician to look associated familial syndromes like MEN, PGL, NF, VHL etc. Appropriate biochemical evaluation taking necessary precautions to avoid the false positive and negative results associated with improper sample collection has to be avoided. Once biochemically localized, radiological imaging like CECT is used to localize the tumor. Surgical removal should be attempted only after adequate pre operative preparation. Experienced anesthesiologist is critical to the outcome in the operating room. Aggressive post operative management of the hypotension is critical to patient recovery.

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