Pheochromocytoma – An Institutional Experience

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Objective: The present study envisages evaluating the clinical presentation, diagnosis, management, with particular reference to pharmacological and anesthetic considerations, and outcome in patients with pheochromocytoma. **Design:** A retrospective study. **Place and Duration of Study:** The study was conducted at the Department of Surgery, Kasturba Medical College Hospital, Manipal, India from January 1, 1996 to December 31, 2003. **Patients and Methods:** Seventeen patients diagnosed to have pheochromocytoma were included for this study. Our assessment of age at presentation, sex, presenting complaints with details of hypertension (HT), diagnostic tests, surgical procedure and follow-up was based on patient records. **Results:** Peak incidence was observed in 40-50 years age group, with male preponderance. All the patients had diastolic HT of more than 100 mm of Hg at presentation. Systolic blood pressures (SBP) were between 150 mm Hg to 230 mm Hg, with mean of 170 mm Hg; nine patients presented with persistent HT and seven had paroxysmal HT. One patient infact presented with hypotension due to septic shock and was incidentally detected to have an adrenal tumor. Computed tomography (CT) scan and urinary levels of vanillylmandelic acid (VMA) were mainstay of diagnosis. These patients had adequate preoperative control of HT. All patients underwent exploration of the tumor by an extraperitoneal approach. 70% tumors were on the right and 30% were on the left side. Histopathologically, all the tumors were benign except for one, which was malignant. An average of three to five units of blood transfusion was required and mean operating time was 4.5 hours. Six patients had extensive intra-operative blood pressure (BP) fluctuation, but were adequately managed by the anesthetic team. One patient with post-operative pulmonary edema died in our series; rest all the patients are on regular follow-up, till date and doing well. **Conclusion:** Pheochromocytoma is an important cause of endocrine HT. Elevated urinary VMA is diagnostic of this tumor with imaging studies used to localize the tumor. Adrenalectomy results in complete cure of HT with an excellent long-term outcome.

Key words: Pheochromocytoma, proxysmal hypertension, urinary vanillylmandelic acid, catecholamines, adrenalectomy.

Pheochromocytomas are rare tumors that occur in young and middle aged patients, with equal frequency in males and females.[1] Most of these arise in the adrenal gland and only 10% are extra-adrenal in origin. This tumor is a causative factor of HT in less than 1% of hypertensive population, however detection is mandatory, not only for potential of cure of the HT, but also to avoid the potentially lethal effects of the unrecognized tumor, due to the paroxysmal HT it produces.[2] Literature is replete with case reports of pheochromocytoma diagnosed at postmortem in patients who have died during or after a surgical procedure.[3,4] Due to the widespread use of ultrasonography (USG) and CT scan[5] diagnosis of pheochromocytoma has become easy in suspected cases. With adequate pre-operative preparation[6], good surgical technique, careful and judicious anesthesia with intra-operative monitoring and post-operative care[7] mortality rates have come down to less than 1%. We present our experience of 17 cases of pheochromocytoma.

Patients and methods:

This is a retrospective study where in medical records of nineteen patients with histopathologically verified diagnosis of pheochromocytoma between January 1, 1996 and December 31, 2003, admitted in Kasturba Medical College Hospital, Manipal, India were analyzed. Two patients with incomplete records were excluded from the study. Hospital records of these patients were reviewed for demographic data, modes of presentation with details of HT, diagnostic modalities and surgical procedure including peri-operative drug therapy and anesthetic management, were analyzed. These patients are being followed up actively thereafter, till date.

Results:

Among these 17 patients, 11 were male. The age at presentation varied between 17 - 53 years, with peak incidence in the 40-50 age group (12 patients) and the remaining three patients were in the age group of 30-40 years (Table 1). Thirteen patients were symptomatic for less than 6 months, three had symptoms for almost a year and one patient had relatively recent onset of symptoms, of less than one-month duration.

Table I: Age at presentation

Age group (years)	No. of patients
<30	1
30-40	3
40-50	12
>50	1

All patients had diastolic HT of more than 100mm of Hg at the time of admission, except for one with hypotension and septic shock, with a mean of 105mm of Hg. Two patients had diastolic blood pressure of 150mm of Hg, associated with blackout. SBP varied between 150 and 230mm of Hg (mean =170mm of Hg). Persistent HT was observed in nine patients, of which 3 had superimposed paroxysms. "Dramatic attacks" (paroxysms) alone were seen in 7

patients. All female patients experienced paroxysms at some point of time during the course of their illness, four experienced paroxysms alone and two paroxysms superimposed on persistent HT (Table II).

Table II: Patterns of hypertension

Pattern	Males	Females
Persistent HT only	6	None
Persistent HT with superimposed paroxysms	1	2
Paroxysmal HT alone	3	4

Paroxysmal attack was associated with palpitations in 5 patients [50%], sweating in 5 patients (50%), chest pain in 2 patients (20%), and black out in 2 (20%) patients. Interestingly, one patient had paroxysms on brushing the teeth. Five patients presented to the hospital due to the severe headache more in the occipital region and were diagnosed to have HT due to pheochromocytoma. One patient had severe itching all over the body and was found to have HT, which on further investigations proved to be due to pheochromocytoma. Four patients presented with abdominal pain in the right hypochondrium with vomiting and later they were diagnosed to have pheochromocytoma. One patient presented to the hospital with hypotension and septic shock due to pneumonia. Incidental abdominal ultrasound scan in this patient detected an adrenal tumor and further enquiry, he admitted revealed having palpitation and anxiety disorder for the last 6 months and was on treatment. Four patients (24%) were diagnosed to have diabetes of more than 6 months duration when they were referred to us. None of the patients had cerebro-vascular accident but one had convulsions (Table III).

Table III: Associated symptoms

Symptoms	No. of patients
Palpitations	5
Headache	5
Sweating	5
Abdominal pain	4
Chest pain	2
Black outs	2
Itching	1
Convulsions	1

Fifteen patients were referred to us with diagnosed HT and USG evidence of an adrenal tumor. These were reconfirmed by CT scan, which showed calcification in 3 and central necrosis in 4 patients. In one patient, the diagnosis of pheochromocytoma was made by VMA levels, but localization could not be done by USG and CT scan. Hence she was subjected to a metaiodobenzyl-guanidine (MIBG) scan that revealed a right adrenal tumor. VMA levels in 24-hour urine sample were elevated in all these patients ranging from 7.9 to 39.5mg% with an average of 15.5mg%. The levels of the VMA did not correspond to the severity of the symptoms.

All these patients were hospitalized for the definitive treatment. Adequate control of the HT was achieved by alpha-adrenergic blocking agent, Phenoxybenzamine 10mg thrice a day. Atenolol 25mg OD along with phenoxybenzamine was administered to 5 patients for adequate control of hypertension. In three patients Propranolol 20mg BD was added to control tachycardia. These drugs were given for 15 days prior to the surgical procedure.

All patients underwent exploration and adrenalectomy by an extraperitoneal, thoracoabdominal route, incision being placed at the bed of the 10th rib. Twelve (70%) tumors were on the right side and five (30%) were on the left side. In one case, the tumor was found to be adherent to the diaphragm on the right side. As it clinically seemed to be malignant, a cuff of the diaphragm was excised along with the tumor. Histopathology later confirmed this to be malignant. An average of 3.5 units of blood transfusion was required with minimum of 2 and maximum of 8 units. Operating time, which included anesthesia time, ranged from 3 hours 45 minutes to 8 hours with the mean of 4.5 hours.

Intra-operative monitoring included electro-cardiography (ECG) in V5 and lead II, BP both invasive and right atrial, central venous pressure (CVP) by right internal jugular vein, nasopharyngeal temperature, finger-probe pulse oximetry, capnography and urine output. In 6 patients, large fluctuations of BP were recorded intra-operatively which was controlled with phentolamine (4 patients) and sodium nitroprusside (2 patients). Post-operatively, all patients were managed in ICU. Fifteen patients were shifted to the ward within 34 hours of the surgery. One patient with malignant pheochromocytoma required 5 days of ICU admission. One patient developed pulmonary edema and significant edema of the head and neck. This patient required dopamine and adrenaline to maintain BP in the post-operative period. She also developed hypocalcemia resulting in carpopedal spasm, which did responded to intravenous calcium gluconate initially, but succumbed. This was the only death in our series.

All patients are being actively followed up till date. Cure of HT has been achieved in all patients. Repeat USG done after a gap of one year does not show evidence of any recurrence or other pheochromocytoma. Three of the four diabetics were cured of the disease as blood sugar reports were within normal limits, however one patient is on oral hypoglycemic agents with reasonably good control of diabetes.

Discussion:

Pheochromocytoma is an uncommon endocrine neoplasm and is an important cause of surgically correctable/curable HT[8]. The present study is a small study of this uncommon neoplasm involving 17 patients. Ninety percent of these tumors are solitary[8], as in our series. Less than 10% of

pheochromocytomas are extra-adrenal, multiple and malignant[8,9]. Though our series did not have any extra-adrenal and/or multiple neoplasms, there was one malignant pheochromocytoma.

Pheochromocytoma is known to occur in certain familial syndromes. These include Multiple Endocrine Neoplasia (MEN) 2A and 2B, neurofibromatosis (von Recklinghausen disease) and von Hippel-Lindau (VHL) disease.[10,11] Pheochromocytoma can occur bilaterally in the MEN syndromes in as many as 70% of cases and they tend to be extra-adrenal[11].

Fifteen (88%) patients in our series were in the age group of 30-50 years, which correlates well with available statistics,[8,9] even though pheochromocytomas can be found in all ages. These tumors occur with equal frequency in males and females[8,9], however in the present series male to female ratio is 2:1.

HT is the most common manifestation, which is paroxysmal in 50% of cases.[2,4,12] Sixteen (95%) patients in our series presented with HT, which was paroxysmal in 10 patients. One patient had hypotension; secretion of the hypotensive adrenomedullin may contribute to the hypotension in some patients. One patient had severe itching and found to have HT; this may be explained by the vasodilatation due to the hypermetabolic state of the patient. Four patients were found to have raised blood glucose levels, possibly due to adrenaline excess and in three patients it was completely cured after removal of the tumor.

Elevated level of 24-hour urine VMA confirms the diagnosis, however VMA is not very specific, with a false positive rate of greater than 15%. Metanephrines are considered the most sensitive and specific for pheochromocytoma; two recent studies demonstrated that plasma metanephrine levels are sensitive in detecting pheochromocytomas[13,14]. For now, however, it is not widely available commercially in this country. VMA levels were elevated in all our patients.

Localization of the tumor was a difficult task before the days of USG and CT scan[15,16]. Modlin[16] et al published a series of 72 patients with pheochromocytoma between 1955-1976. They used various methods to localize these tumors like intravenous urography, presacral insufflation, selective arteriography, and selective venous sampling. Today these tests are obsolete due to the availability of USG and CT scan. Abdominal CT scan has an accuracy of 85-95% in detecting adrenal masses with a spatial resolution of 1 cm or greater. However, it is less accurate for lesions smaller than 1cm[15]. Again differentiating an adenoma from a pheochromocytoma is difficult using CT scan. Magnetic resonance imaging (MRI) is preferred over CT scan[1,16,17] in detecting small and extra-adrenal tumors. MRI has a sensitivity of 100% in detecting adrenal pheochromocytomas, does not necessitate contrast, and does not expose the patient to ionizing radiation. We do not advocate routine use of MRI for localization of these tumors unless indicated, due to its wide unavailability and the cost factor.

A MIBG scan is reserved for cases when a pheochromocytoma is confirmed biochemically but CT scan or MRI fail to visualize a tumor[8,17,18]. The molecular structure of iodine - 123 (^{123}I) used for this scan resembles norepinephrine and concentrates within adrenal or extra-adrenal pheochromocytomas. This isotope has a short half-life and is very expensive. It frequently is utilized in cases of familial pheochromocytoma syndromes, recurrent or malignant pheochromocytoma.

Surgical resection of the tumor is the treatment of choice and usually results in cure of the hypertension[18] as in all our patients. Careful treatment with alpha and beta-blockers is required[19] pre-operatively to control BP and prevent intra-operative hypertensive crises. Bravo[20] et al recommend alpha blockade with phenoxybenzamine 7-10 days pre-operatively to allow for expansion of blood volume, volume expansion with isotonic sodium chloride, initiation of a beta blocker only after adequate alpha blockade. If beta blockade is started prematurely, unopposed alpha stimulation can precipitate a hypertensive crisis. All our patients received alpha-blockers till the morning of surgery, but only five patients required beta-blockers.

Both experienced anesthesiologist and surgeon are crucial to the success of the operation. Surgical mortality rates are less than 2-3% with an experienced anesthesiologist and surgeon[19,20]. Management of anesthesia for patients requiring excision of pheochromocytoma is based on the administration of drugs which do not stimulate the sympathetic nervous system plus the use of invasive monitoring techniques to facilitate early and appropriate intervention when catecholamine induced changes in the cardiovascular system occur.[21,22] These changes are more likely to occur during tracheal intubation, during manipulation of the tumor, and after ligation of the tumors venous drainage[23].

Induction of anesthesia is most often accomplished with intravenous administration of a barbiturate, etomidate or propofol[21,22]. Our anesthesiologist preferred propofol for rapid induction. The depth of anesthesia is increased and maintained by nitrous oxide plus a volatile agent, like isoflurane[22] at most centers' including ours. Nitroprusside or phentolamine must be readily available for administration should gross fluctuation of blood pressure occur intraoperatively[22,24] as had happened in six of our patients. Blood should be available for infusion to replace intraoperative loss as well as to fill the dilated vascular tree after tumor is removed.

Adrenalectomy, by open anterior, posterior or thoracoabdominal approaches or by laparoscopy, completely cures hypertension in majority of cases. Anterior approach to right adrenal requires a long right subcostal incision with patient positioned supine. Left adrenal similarly is exposed through a long left subcostal

incision; both extraperitoneal and intraperitoneal exploration is possible through subcostal incision. In our series all the patients underwent exploration of the tumor by extraperitoneal route. Posterior approach to adrenals requires incision along the twelfth rib with patient placed prone on two chest rolls. Irrespective of the approach used, the important technical points to be taken care of are to avoid disturbing the tumor excessively. The adrenal vein should be identified and ligated as early in the operation as possible to prevent excessive release of catecolamines[25].

Recently, laparoscopic adrenalectomy has become the procedure of choice for well-localized pheochromocytomas. Open surgery is reserved for extra-adrenal tumors, large tumors or cases in which malignancy is suspected[26]. Laparoscopic adrenalectomy, like open procedure, can be done by transperitoneal, retroperitoneal (anterior or lateral) approaches. Most laparoscopic surgeons, however, prefer transperitoneal approach, and retroperitoneal approach is kept reserved for patients who have undergone previous abdominal surgery, or when bilateral adrenalectomy is required as the patient does not require to be repositioned, thereby reducing anesthesia time[17,27].

Invasive monitoring is continued in the immediate post-operative period, as fluctuation in BP is likely. Patient should be best treated in the ICU under the supervision of critical care specialist. Persistent hypotension, which was seen in one of our patient, refractory to intravascular fluid volume replacement is the principal post-operative complication. This hypotension reflects pre-operative down regulation of adrenergic receptors in the presence of excessive catecholamine secretion and requires vasopressor support.

Biochemical cure should be confirmed by assay of 24-hour urinary VMA, 3-4 weeks after surgery. All the patients in the present series had normal urinary VMA levels on follow-up. The role of lifelong, annual urinary VMA, catecholamines measurements, to identify recurrent and or metachronous pheochromocytoma, cannot be underestimated[8,12].

Conclusion:

Pheochromocytoma is a rare catecholamine-secreting tumor derived from chromaffin cells. Because of excessive catecholamine secretion, pheochromocytomas may precipitate life-threatening HT. Biochemical analysis of urine for elevated levels of VMA proves diagnosis in majority. With the advent of CT scan and sonography, the localization of the tumor has become an easy task and nuclear scintigraphy is rarely required for this purpose. Adrenalectomy is a meticulous surgical exercise and requires team effort. With an adequate pharmacologically controlled HT, the results of the surgery are excellent. If the diagnosis of a pheochromocytoma is overlooked, the consequences could be disastrous or fatal; however, if a pheochromocytoma is found, it is potentially curable.

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