Phaeochromocytoma in Nepal – A Single Centre Experience

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ABSTRACT

Background

Phaeochromocytomas are rare tumors of chromaffin cells of neural crest that classically present with symptoms of catecholamine excess such as palpitations, headache and sweating. They are diagnosed by measuring plasma or urinary levels of catecholamines or their metabolites. Anatomic localization is done by computed tomographic scan or magnetic resonance imaging, or meta-iodobenzyl guanidine scan in certain cases. Adequate preoperative catecholamine blockade prevents perioperative hemodynamic instability.

Objectives

To study the clinical spectrum and management of phaeochromocytomas in a tertiary care centre, Tribhuvan University Teaching Hospital, in Nepal.

Methods

Retrospective review of case records of histologically proven cases of phaeochromocytomas from 2008 -2011 was done, and data collected on clinical spectrum, diagnostic modalities, perioperative management and follow-up.

Results

Tweleve cases of phaeochromocytomas were operated. The mean age was 36.41±14.07 years. There were 2 bilateral phaeochromocytomas and 1 extra-adrenal paraganglioma. Apart from the common symptoms of catecholamine excess, patients had atypical presentations like psychiatric manifestations and blurred vision. A combination of urinary Vanillyl Mandelic Acid and computed tomographic scan was used for diagnosis, and open surgery was done in all cases. Pre-operative blood pressure control was achieved by prazocin or calcium channel blockers. Ten patients had intraoperative surge in blood pressure. There were no major morbidity or mortality. Three patients had high blood pressure post-operatively, but were effectively managed with antihypertensives.

Conclusion

Phaeochromocytomas can have variable presentation. Good preoperative preparation and perioperative management can result in an excellent outcome.

KEY WORDS

Hypertension, Paraganglioma, Phaeochromocytoma, Prazocin, Vanillyl Mandelic Acid

INTRODUCTION

Phaeochromocytomas are rare tumors arising from the chromaffin cells of the neural crest, commonly from the adrenal medulla. They classically present with symptoms of catecholamine excess such as headache, palpitation and sweating (the classical triad), and hypertension. However, the classical triad is present in only 30 - 40% of cases, and many patients can present with a wide range of atypical symptoms.[1] They are diagnosed biochemically with urinary or plasma measurements of catecholamines or their metabolites, viz metanephrines, normetanephrines or Vanillyl Mandelic Acid (VMA). Anatomic localization of tumor is commonly done by computed tomographic (CT) or magnetic resonance imaging (MRI) scan, and meta-iodobenzyl guanidine (MIBG) scintigraphy in certain

cases. The tumor can elaborate life-threatening levels of catecholamines, hence a good preoperative preparation is necessary for safe surgery. Most of these tumors can be resected laparoscopically.[2] However, these diagnostic and treatment modalities are still lacking in Nepal. Here, we would like to outline the pattern of presentation of phaeochromocytoma and the current scenario of their management in Tribhuvan University Teaching Hospital (TUTH), a tertiary-care centre in Nepal.

METHODS

This was a retrospective review of case records. All patients with histologically proven phaeochromocytoma from May 2008 until May 2011 managed in the Department of Surgery, TUTH, Nepal, were included in this study. Data were analyzed on demographics, presenting features, clinical examination findings, investigations, perioperative events and follow-up events. Statistical analysis was done by SPSS 17. Numerical data were presented as mean ± standard deviation.

RESULTS

A total number of 12 cases were operated. There was a predominance of female patients with male: female ration of 1:4. The mean age of the patients was 36.41 ± 14.07 years (12-65), and the most common age group was 40 – 50 years. There were seven females and four males. The most common presenting symptom was palpitation (n=10, 83.33%), followed by headache and sweating (n=7, 58.33%). Six cases also had hypertension as their presenting feature. The classical triad was seen in only 4(33.33%) cases. Four cases had abdominal pain, three had syncopal attack and two had flushing as their presenting symptoms. There were other patients who presented with atypical symptoms such as depression, blurred vision, hemiparesis, haemoptysis and tingling sensation. Duration of symptoms ranged from 1 month to two years.

During examination, 2 (16.6%) cases were found to be normotensive, and the remaining patients had systolic blood pressure ranging from 140-220mm Hg, and diastolic pressure ranging from 100-140mm Hg.

Ultrasonogram of abdomen was unable to identify a mass or confirm its origin in 4 cases. CT scan of abdomen was done in all cases which identified the lesion as heterogeneously enhancing masses. MRI scan of abdomen was done in a 12 years girl who had bilateral phaeochromocytoma. MIBG scan was not done in any of the cases. Six (50%) cases had tumor on the right adrenal gland, three (25%) had tumor on the left gland, and two (16.66%) had bilateral disease, of which one was later diagnosed as multiple endocrine neoplasia (MEN) IIA syndrome because of concomitant medullary thyroid carcinoma. One patient had disease arising from the Organ of Zuckerkandl. The median largest dimension of the tumor was 6 cms (1-12 cms). One patient had a huge adrenal hematoma.

Appendix 1. Presenting symptoms and signs.

Symptoms / Signs	Number	Percentage
Palpitation	10	83.33%
Headache	7	58.33%
Sweating	7	58.33%
Hypertension	6	50.00%
Abdominal pain	4	33.33%
Syncope	3	25.00%
Flushing	2	16.66%
Major depression	1	8.33%
Tingling	1	8.33%
Blurred vision	1	8.33%
Haemoptysis	1	8.33%
Stroke	1	8.33%
Headache + Palpitation + Sweating	4	33.33%

Appendix 2. Age, size of tumor, and urinary VMA levels.

Age (years) / Sex	Size in cms (CT measurement)	Urinary VMA (mg/24hr)
42M	12x8	59.4
35M	6x3.9x1.8	72.7
39F	7x5.5x4, 5x4.5x4	15.0
35F	6x6	28.6
42F	3x3	14.0
49F	6x5.8x5.6	4.3
20F	Large hematoma	6.4
24F	6x5x4	30.0

Twenty four-hour urinary VMA assay was used to establish biochemical diagnosis in all cases (normal < 13.6 mg/24 hr). This was equal to or elevated above the upper limit of reference range in 10(83.33%) cases, and normal in 2. No correlation was seen between the tumor size and level of VMA. Urinary metanephrine level was obtained in two cases, and results were normal.

Nine cases(75%) required 1 or 2 antihypertensive drugs, whereas 3(25%) required 3 or more antihypertensives in the pre-operative period. The antihypertensives used included prazocin, amlodipine, diltiazem, atenolol, metoprolol, enalapril and lasilactone®. Two patients received only amlodipine. All patients were well hydrated preoperatively.

All patients were operated through open transperitoneal approach by either subcostal or chevron or midline incision. Ten (83.33%) patients had marked surge in intraoperative blood pressure necessitating intravenous sodium nitroprusside or nitroglycerine or beta-blockers. These patients also had hypotension in the immediate post-operative period, necessitating fluid boluses and one or more inotropes. Of the two patients who had uneventful intraoperative period, one had adrenal hemorrhage, and the other had extra-adrenal paraganglioma. The two patients who had bilateral disease underwent enucleation

of tumor. All patients except one were kept in intensive care unit for overnight observation. All patients were followed up at one month and at three months. Three patients had persistently elevated blood pressure, but controlled with oral antihypertensives. Post-operative VMA level was normal in all cases.

DISCUSSION

Phaeocheomocytomas are rare tumors, and contrary to the the historical labeling as a 10% tumor, recent studies have shown that 25% can be extradrenal, upto 30% can be familial, and less than 5% of sporadic cases and over one third of extra-adrenal cases are malignant.[3,4,5] Despite the small size of our series, we did have one case of paediatric phaeochromocytoma, one extra-adrenal paraganglioma, and two cases of bilateral disease. The commonest age group of 40-50 years in our series is similar to that reported by Lenders et al.(45±15 years)3 and Noshiro et al.(36±12 years) and Bhageria A et al in the Indian population.[6,7]

One case of bilateral phaeochromcytoma was later found to have medullary thyroid carcinoma, and hence was diagnosed as MEN IIA syndrome. The other bilateral case underwent all available investigations (other than genetic testing) which could not detect possible genetic syndromes at present. At least five types of germline mutations can be detected in patients with familial disease: *RET, VHL, NF1,SDHD and SDHB*.[8,9]

Most of our patients presented with the classical symptoms of phaeochromocytoma. However the classic triad was seen only in 33.3% which is comparable to an Indian series.[10] Hypertension is the most consistent sign, and this could be paroxysmal or sustained. Occasionally, the patients can be normotensive or asymptomatic, and these cases are usually detected incidentally. The prevalence of asymptomatic phaeochromocytomas is 10% to 33%.[11,12] In our series, two patients (16.66%) were normotensive. Of these two patients, one had right loin and upper abdominal pain as the presenting symptom, and the other patient, a 20 years girl presented with adrenal hemorrhage and cerebral infarction. Many of our patients also had atypical presentations, aptly justifying the eponym 'the great mimic'.[1]

Though most of our patients were initially screened by ultrasonography, the sensitivity of this tool to diagnose adrenal lesions is low.[13] Both CT scan and MRI have excellent sensitivity (98-100%) to detect tumors as small as 0.5cm. However, MRI is more sensitive for detecting extra-adrenal lesions (94% versus 90%).[14] Anatomic localization was done by CT scan in all except in one case where a lesion was clearly delineated on right side but not on left side, and MRI scan was helpful to delineate the lesion clearly. Functional imaging in the form of ^{123}I MIBG scan would have been a better option in the latter case, given its high specificity (95%).[14] MIBG scan is also recommended in extra-adrenal paraganglioma, suspected malignancy to detect recurrences and metastases, and in tumors larger than 5 centimeters.[2] The test is expensive and currently not available in Nepal.

The biochemical test used in all of our cases was 24-hour urinary VMA estimation. This test has a low sensitivity (64% -72%) unless it is done after an axial imaging has already revealed a suprarenal mass, like in our series, and has largely been superseded by other tests.[15,16] The current recommendation, as given by the first International Symposium on Phaeochromocytoma, is to measure fractionated metanephrines in urine or plasma, or both, as available, on account of their high sensitivity.[2] The sensitivity of plasma free metanephrines is 99%, and that of urinary fractionated metanephrines 97% - 100%.[15,16] The VMA test nevertheless has high specificity (95%) compared to plasma free metanephrines (89%) or urine fractionated metanephrines (69%).[15] Unfortunately, the metanephrine tests are expensive, and not available in Nepal.

All patients, irrespective of blood pressure and symptoms, should receive catecholamine blockade, 7-14 days prior to surgery because high levels of circulating catecholamines (>1000 times normal) can cause hypertensive crisis and arrhythmias even in normotensive individuals.[2] The most commonly used drug is phenoxybenzamine, which is a long-acting non-competitive blocker of α-adrenoceptors. The blockade is unsurmontable even with surges in catecholamine levels during tumor manipulation. An alternative option is to use calcium channel antagonists, especially in apparently normotensives or those with secondary cardiovascular complications, as this approach avoids the reflex tachycardia and postoperative hypotension associated with α-blockade, and also reduces catecholamine induced coronary spasm.[14] Though there have been reports of successful intraoperative blood pressure control with preoperative use of α1-blockers like prazocin and doxazocin in our series all cases except one, had intraoperative haemodynamic instability with the use of prazocin or calcium channel antagonists.[17] We did not use phenoxybenzamine due to its unavailability in Nepal.

Most tumors upto 10 centimeters in size can be removed laparoscopically.[2] Laparoscopy, apart from the usual benefits of reduced morbidity and hospital stay and improved cosmesis, is associated with reduced intraoperative surge in blood pressure.[12,18] We did open surgery in all cases as we do not have adequate experience with laparoscopic adrenalectomy. In our series two cases with bilateral disease underwent cortex-sparing enucleation. This technique is to be considered in hereditary diseases or patients with bilateral disease to prevent life long steroid dependence, but at the cost of increased risk of disease recurrence.[2]

None of our patients developed significant cardiovascular or neurologic morbidity despite intraoperative haemodynamic lability, and there was no mortality. This highlights the fact that pheochromcytoma management is a team-work of

surgeons, endocrinologists, cardiologists, anesthesiologists and nursing team, and that our good result could be because of good perioperative anesthetic care, including use of arterial line, judicious use of parenteral vasodilators, pressors and antiarrythmics, and our policy of observing all patients overnight in the intensive care unit.

All of our patients were followed up at one month, three months and annually. The follow up consists of blood pressure measurement and urinary VMA estimation. Though the follow-ups have been irregular, we have been able to contact all of our cases by telephone. All of our patients had normal blood pressure during follow-up. The disease can recur in as many as 16% of cases many years after surgery, hence lifelong follow-up is essential.[19] The recommendation is to repeat biochemical testing at 14 days post-operatively, followed by a test at six months, and annual evaluation thereafter.[2,3]

The limitation of the current study is its retrospective nature and the small sample size. However, on account of the rarity of this disease, a multicentre study or a system of referral of cases to a single dedicated centre will be required to better understand the characteristics of this disease in Nepal.

CONCLUSION

Phaeochromocytoma can present with a wide variety of symptoms. Urinary VMA estimation, though highly specific, should be replaced by measurement of plasma or urinary fractionated metanephrines. Though we have been able to achieve good results with our existing armamentarium, we can definitely do better by improving on preoperative catecholamine blockade and acquiring laparoscopic skills. A good follow-up protocol will go a long way in managing patients better.

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