RESEARCH BRIEF

Pediatric and Adolescent Pheochromocytoma: Clinical Presentation and Outcome of Surgery

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Objectives: To describe the clinical presentation and outcome of surgery in children with pheochromocytoma in a tertiary care hospital in India.

Methods: Clinical records of 24 children who were operated between January 1990 and January 2011 were reviewed. The diagnosis of familial disease was established based on clinical examination and follow-up events.

Results: Familial, bilateral, extra-adrenal and malignant pheochromocytoma were observed in 20.8%, 20.8%, 12.5% and 4.2% children, respectively. Median follow-up duration was 36 months. Persistent hypertension was noted in 12.5% patients and similar proportion died in follow-up.

Conclusions: In the absence of routine genetic screening, good history and long- term follow up are essential to rule out familial pheochromocytoma.

Keywords: *Adrenal medullary tumor, Secondary hypertension*.

Pheochromocytoma (PCC) is an exceptionally rare neoplasm in children, accounting for 1% of pediatric hypertensive patients [1]. Approximately 20% of PCC are found in the pediatric population [2,3]. PCC can arise either from adrenal or extra-adrenal ganglion. Tumors arising from the adrenal gland are known as PCC and those from the extra-adrenal locations are called PGL or paraganglioma [4]. Alhough there is some consistent literature about their clinical presentation, long term follow-up studies on pediatric PCC are not available [2,5-10]. The recently delineated genetic screening strategies are often not within reach of the general population in developing countries [11,12]. The aim of this study was to investigate the clinical presentation and outcome of surgery in children with PCC presenting at a tertiary care center in a developing country.

METHODS

Clinical records of 24 children (aged ≤18 years) with PCC, who were operated between January 1990 and January 2011 were reviewed. Follow-up status of those who had dropped out from follow-up was obtained by sending letters or telephoning the family and the referring physician.

The biochemical diagnosis of PCC was established by 24-hour urinary metanephrine levels. Urinary metanephrines were measured by Column chromatography method (Bio-rad USA) before the year 2005 and later by ELISA technique (Labor Diagnostika Nord GmbH & Co. Nordhorn,). The upper reference values for metanephrine and nor-metanephrine < 350 and < 600 µg /d, respectively. After confirming biochemical diagnosis tumor localization is done and unless contraindicated, contrast enhanced computerized tomography (CECT) is the preferred modality in our institute. Pre-operative I^{131}-Meta-Iodo-Benzyle-Guanidine (MIBG) study is not performed routinely. Screening for familial disease was done by family history-taking, and investigating for other components of Multiple Endocrine Neoplasia Syndrome-2A and 2B (MEN-2A and MEN-2B), Neurofibromatosis and Von Hippel Lindau (VHL) syndrome. Serum calcitonin estimation (Ct), thyroid ultrasonography, serum calcium (Ca) and parathormone (PTH) estimation is done in all cases. All children were pre-operatively prepared with alpha-blockers (prazocin/phenoxybenzamine) with adequate fluid and salt replacement. Beta-blockers were added three days prior to surgery or earlier in case tachycardia or arrhythmias were observed. Additional anti-hypertensive medications were added, if required. Intra-operative hemodynamic fluctuations were taken care of with intravenous sodium nitoprusside, esmolol, noradrenaline, dopamine, and crytalloid/ colloid infusion. Metanephrines estimation was repeated on 7^{th} to 10^{th} postoperative day. In case the post-operative values were abnormal or equivocal, a repeat measurement was done after six weeks;

otherwise annual urinary metanephrines estimation was done to detect the recurrent disease. On follow-up, a detailed clinical examination was performed, particularly to look for familial syndromes and in known cases of MEN 2 syndrome, annual serum Ct, Ca and PTH estimations were done. If metanephrines were found raised I^{131}-MIBG scanning and/or was performed to localize the disease.

Statistical analysis was done using SPSS software version 13.0. Mann-Whitney and Chi-squared tests were used where applicable and 2-tailed *P* values of less than 0.05 were considered significant.

RESULTS

The proportion of pediatric PCC in our center was 16% (24/150). Among familial group, two had MEN-2A and one had MEN-2B syndromes with co-existent medullary thyroid carcinoma (MTC). Child with MEN-2B was normotensive and PCC was diagnosed by routine biochemical screening. Two other children with bilateral adrenal PCC on follow-up were found to have a sibling each who also had adrenal PCC. One of these children had presented with synchronous bilateral PCC and other with metachronous bilateral PCC after 9 years of follow-up. All the extra-adrenal PCC were located in the abdomen. The lone malignant tumor was located in the organ of Zukerkandl and was metastatic (liver) at presentation.

Characteristics of children with PCC are summarized in ***Table* I**. The findings in familial and sporadic groups were comparable. A total of 29 tumours were removed

TABLE I COMPARISON OF FAMILIAL AND SPORADIC PEDIATRIC PHEOCHROMOCYTOMA

	All Subjects (n=24)	*Familial (n=5)*	*Sporadic (n=19)*	*P value**
Age	16.0; 14.2 (4.5)	18.0; 13.7 (5.3)	16.0; 14.1 (4.3)	0.47
Male : Female	12:12	2:3	10:9	0.61
Duration of Symptoms, months	6.0; 11.0 (13.5)	5.0; 20.5 (26.5)	9.0; 8.9 (9.0)	0.27
Clinical Presentation, n (%)				
Hypertension	23 (95.8)	04 (80)	19 (100)	0.46
Presence of triad*	13 (54.2)	03 (60)	10 (52.6)	0.76
History of hypertensive crisis	04 (16.7)	02 (40)	02 (10.5)	0.18
Seizures	05 (20.8)	01 (20)	04 (21.0)	0.95
Retinopathy	11 (44)	01 (20)	01 (05.3)	0.42
Hypertension, n (%)				
Sustained	05 (20)	-	05 (26.3)	0.32
Paroxysmal	08 (32)	01 (20)	07 (36.8)	
Sustained with paroxysm	10 (45.8)	03 (60)	07 (36.8)	
Normotensive	01 (04.2)	01 (20)	-	
Metanephrines, µg/day	1210.0; 2626.1 (2212.8)	1130.0; 2432.8 (2292.8)	3475; 3656.7 (1664)	0.21
Tumours, n (%)				
Extra-adrenal	03 (12.5)	-	03 (15.8)	0.8
Bilateral	05 (20.8)	03 (60)	02 (10.5)	0.06
Mailgnant	01 (04.2)	-	01 (05.3)	0.62
Surgical approach, n (%)				
Open	14 (58.3)	02 (40)	12 (63.1)	0.29
Laparoscopic	06 (25.0)	01 (20)	05 (26.3)	
Laparoscopic converted to open	07 (29.2)	02 (40)	02 (10.5)	
Tumour size	5.2; 6.0 (1.8)	5.1; 5.9 (0.9)	6.0; 6.0 (2.0)	0.46
Tumour weight	36.5; 54.4 (52.1)	38.0; 38.4 (28.4)	28.0; 58.6 (56.6)	0.39
Persistent hypertension, *n* (%)	03 (12.5)	01 (20)	02 (10.5)	0.52

*** Classical symptoms triad: headache, sweating and palpitation; All values in median; mean (SD).*

WHAT THIS STUDY ADDS?

- Familial cases of pheochromocytoma are common; family screening and long-term follow up is important.

from 24 children. Only one child received phenoxybenzamine whereas all the others received prazocin for pre-operative preparation. Laparoscopic resection was successful in a quarter of cases. Total adrenalectomy was performed in all but one child with bilateral PCC where cortical sparing adrenalectomy was done. There was no peri-operative mortality.

The mean (SD) follow-up period was 43.2 (50.2) months 36. All except three children had amelioration of hypertension. Among those with persistent hyper-tension, two had raised and one normalized post-operative metanephrines levels. Raised metanephrines levels were observed in cases of malignant PCC and the child who had undergone cortical sparing surgery. The child with malignant PCC was advised ^{131} I- MIBG therapy however, parents couldn't afford it due to the cost. All children but one had amelioration of retinopathy and seizers after surgery. Three children died in follow-up; one each due to metastatic PCC, metastatic MTC and suspected Addisonian crisis 24, 60, and 5 months after surgery, respectively.

DISCUSSION

Clinical presentation of pediatric PCC and incidence of bilateral PCC in the current study was in accordance with the published literature [3,5-10]. However, incidence of familial disease, extra-adrenal PCC and malignancy was low and mean tumor size was more in our study. We could find only two studies published such from India so far [9,10]. Centers, that routinely perform genetic testing report high incidence of familial pediatric PCC that ranges from 30-70% [1,2,8,11,12]. Restricted availability and affordability of genetic testing are the main reasons for low incidence of familial PCC in our study. Low incidence of malignancy and extra-adrenal PCC seem to be inter-related as extra-adrenal PCC are more likely to be malignant than adrenal PCC. However, the reason for diagnosing lesser number of extra-adrenal PCC by Indian centers is difficult to explain [9,10].

Surgery results in cure of hypertension in most of the children and laparoscopic surgery can be offered to a select group of pediatric patients [2,11-13]. Delay in surgical intervention leads to persistent hypertension due to irreversible changes in renal or peripheral vasculature [2]. To circumvent the morbidity of bilateral adrenalectomy, Cortical sparing adrenalectomy is being offered to the patients with bilateral PCC, but long-term results of this procedure are not available [1,11-13]. Majority of our patients presented with large tumor and hence were not candidate for this procedure. PCC in general are radio- and chemo-resistant tumors. ^{131}I-MIBG therapy has also not been found to be very effective. Surgical resection, if feasible, remains the mainstay of treatment of metastatic disease as well [1,14].

The two main limitations of the current study are the possibility of underestimating incidence of genetic disease because routine genetic screening was not performed, and secondly, the short duration of follow-up. Familial PCC may sometimes take a decade to manifest, as was also evident in one of our cases. We had earlier reported clinicopathological profile of 5 pediatric PCC [15]. In the subsequent decade we managed 19 more patients. With dedicated follow-up of these patients we could detect two familial cases. Despite all the limitation and for the fact that mean tumor size was large in our series, the outcome of surgery in our study was comparable to the previous reports.

Early diagnosis and intervention are important for the successful management of this rare pediatric neoplasm. Routine genetic screening of these children is mandatory for the detection and timely management of familial PCC. However, importance of good history taking and long-term follow up cannot be overemphasized. These children should be managed by a multidisciplinary team consisting of pediatricians, endocrinologists, endocrine surgeons, genetic counselors and anaesthetists, who have experience in managing these cases on regular basis.

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