ORIGINAL ARTICLE

Phaeochromocytoma in the Hong Kong Chinese population

CME

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Objective To review the clinical manifestations of phaeochromocytoma in a Hong Kong Chinese population.

Design Retrospective review.

Setting Five public hospitals in Hong Kong.

Patients Seventeen patients with operated phaeochromocytoma between 1994 and 2003 were reviewed retrospectively.

Results Six patients (35%) were men, 11 (65%) were women. The mean age at presentation was 47 (range, 17-72) years. The diagnosis post-presentation was delayed by 1 to 132 months. Over 70% of the patients had hypertension. The most frequent symptoms were headache (53%), palpitations (53%), and sweating (41%); all these symptoms were present in 24% of the patients. Four (24%) had hereditary phaeochromocytoma/paraganglioma syndrome. The sensitivity of 24-hour urinary catecholamine measurements was 82%. Mean urinary adrenaline and noradrenaline concentrations were respectively 7- and 8-fold greater than the upper reference limits. Computed tomography and metaiodobenzylguanidine scintigraphy were the most widely used means for tumour localisation (sensitivity, 100% and 87% respectively). Approximately 65% of the patients had intra-adrenal tumours; 53% were on right side, 18% were bilateral. All the patients were prescribed phenoxybenzamine (dosage range, 20-120 mg/day) preoperatively. Two thirds of the patients had improved blood pressure 1 year after the operation. No malignancy was reported after a mean follow-up period of 7 years.

Conclusion Our series of patients with phaeochromocytomas commonly had a high frequency of normotension and extra-adrenal tumours. A high index of clinical suspicion and appropriate biochemical investigations are necessary to make the diagnosis, especially for patients manifesting adrenal incidentaloma and extra-adrenal lesion.

Key words
Adrenal gland neoplasms; adrenal medulla; Catecholamines; Paraganglioma; Pheochromocytoma

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Introduction

Phaeochromocytomas arise from chromaffin cells and are sometimes referred to as adrenal tumours. Paragangliomas are referred to as tumours that arise from extra-adrenal chromaffin cells and originate in either the parasympathetic or sympathetic ganglia.[1] Phaeochromocytomas account for 0.1% of all patients with hypertension and can present with a highly variable clinical picture.[2,3] Studies evaluating the clinical presentations of phaeochromocytoma in Chinese populations are scarce. This study describes our 10-year experience with respect to the diagnosis and management of phaeochromocytoma, and reviews its clinical manifestations in our locality.

Methods

All our patients with phaeochromocytoma operated in the year of 1994 to 2003 and being followed up in the endocrine clinics of the Kowloon West Cluster hospitals were evaluated. The clinics (five in all) were at the Yan Chai Hospital, the Princess Margaret Hospital, the Caritas Medical Centre, the Kwong Wah Hospital, and Our Lady of Maryknoll Hospital. The medical records of these patients were retrospectively reviewed. Demographic data, clinical symptoms, familial disease, pre- or post-operative urinary concentrations of catecholamines or its metabolites, localisation procedures, preoperative pharmacological treatment, surgical findings, and follow-up status were recorded.

Familial disease was diagnosed by the presence of germline mutations in the *RET,*

VHL, *NF1*, or *SDH* genes, which are responsible for multiple endocrine neoplasia type 2 (MEN IIA), von Hippel–Lindau disease (VHL), neurofibromatosis, and hereditary paraganglioma, respectively.

Measurements of urinary adrenaline, noradrenaline, and metanephrines concentrations were performed using high-performance liquid chromatography (HPLC). Urinary vanillylmandelic acid was measured either by HPLC or a colorimetric reaction.

The size of the tumour was taken as its largest dimension as determined in pathological reports. The follow-up period was defined as the time from surgery to the last follow-up if the patient was alive or to the date of death. Patients lost to follow-up within the first postoperative year were excluded from the assessment. As appropriate, data were expressed as means with standard deviations (SDs), or a mean with a range.

Results

Demographic data

In our hospitals, 19 patients underwent resection of phaeochromocytoma/paraganglioma over the 10-year period from 1994 to 2003. Among them, two patients were lost to follow-up within the first year of their operation. The clinical features of the remaining 17 patients (6 men, 11 women) are shown in Table 1. At presentation, their ages ranged from 17 to 72 (mean, 47; SD, 14) years and the time interval between presentation and diagnosis ranged from 1 to 132 months. The familial form of phaeochromocytoma was confirmed in four (24%) of the patients—three had MEN IIA, and one had VHL.

Clinical presentation

The frequency of different clinical features is detailed in Table 2. Hypertension was the commonest presentation (71%), followed by headache and palpitation (53% each), and sweating (41%). In all, 29% had postural hypotension, and in 24% the symptoms were paroxysmal. Two patients presented with abdominal pain and one with an incidental abdominal mass.

Biochemical evaluation

All patients had urinary catecholamines measured, of whom 14 (82%) had elevated urinary adrenaline or noradrenaline levels. The mean urinary adrenaline concentration was 7 (SD, 6; range, 1-17) fold that of the upper limit of the normal reference range. The corresponding mean urinary noradrenaline level was 8 (SD, 6; range, 2-17) fold of the upper limit of its range. Fractionated urinary metanephrines were measured in four patients, all but one of whom had abnormal results. Urinary dopamine concentration was elevated in two patients, being 6- and 30-fold that of the upper limit of its range.

香港華籍嗜鉻細胞瘤患者的回顧分析

目的 探討香港華籍嗜鉻細胞瘤患者的臨床表現。

設計 回顧研究。

安排 香港5間公營醫院。

患者 回顧1994年至2003年期間，共17名接受嗜鉻細胞瘤手術的病人。

結果 患者中有6名（35%）男性，11名（65%）女性。他們平均病發年齡47歲（介乎17至72歲之間），正確診斷比發病延遲1至132個月。七成以上的病人有高血壓。最常見的症狀是頭痛（53%），心悸（53%）和出汗（41%）。擁有以上3種症狀的病人比率為24%。4名病人（24%）有遺傳症候群。測定24小時尿液中catecholamine的敏感性是82%，尿液中adrenaline和noradrenaline的濃度比最高正常值分別大7和8倍。電腦掃描和MIBG是最常用作腫瘤定位的檢查，其敏感度分別為100%及87%。約65%出現在腎上腺：53%位於右邊，18%在雙側。所有病人在手術前均服用phenoxybenzamine（劑量每日20至120 mg）。術後1年，三分之二的病人血壓有所改善。在平均7年的覆診期間沒有發現惡性腫瘤。

結論 研究顯示正常血壓和位於腎上腺外的嗜鉻細胞瘤發病率高。要診斷此病，必須有臨床高度警覺性，並配合適當的生物學測定，尤其在偶然發現的腎上腺病變和腎上腺外的腫瘤病人身上。

Localisation procedure

Computed tomographic scans were used to localise the tumours in 15 patients and yielded 100% sensitivity. Magnetic resonance imaging was performed in three patients. Metaiodobenzylguanidine showed positive uptake in 13 patients, with a sensitivity of 87% (13/15).

Preoperative preparation

All patients received phenoxybenzamine before the operation; the mean dose being 69 (range, 20-120) mg per day. Twelve patients received propranolol and two received metoprolol.

Surgical findings

In all, 20 tumours were resected (65% intra-adrenal, 35% extra-adrenal). Most (53%) were located on right side and 18% were bilateral. The mean tumour size was 5 (SD, 2) cm. None showed evidence of malignancy as judged by local infiltration or presence of metastasis.

Blood pressure changes after surgery

Ten (59%) patients were taking antihypertensive drugs before the diagnosis, and after surgery only

TABLE 1. Clinical features of the patients with phaeochromocytoma/paraganglioma

Patient No.	Age (years) at presentation/sex	Hypertension	Familial sign*	Raised urinary Cats/MN/VMA/dopa (x fold ULN)†	Location‡	Size (cm), largest dimension	Last follow-up (years)
1	72/F	Y	MEN IIA	A 13x, NA 4.5x	Lt + Rt adrenal	3, 4	1
2	37/M	Y	-	A 1.7x, NA 1.1x	Pgl (near Lt adrenal)	5	6.5
3	70/F	N	-	Dopa 30.0x	Pgl (Lt superior para-aortic)	11.5	2
4	46/M	N	-	-	Pgl (Lt renal hilim)	3	6.4
5	63/F	Y	-	-	Pgl (near Rt adrenal)	5	14
6	58/F	Y	MEN IIA	A 16.6x, VMA 2.2x	Lt + Rt adrenal	2.5, 4.3	16.8
7	40/F	N	MEN IIA	A 1.4x, MN 1.6x	Lt adrenal	1.8	6
8	34/F	Y	-	A 2.9x, MN 2.4x, NM 1.1x	Lt adrenal	5	9.7
9	45/F	Y	-	A 4.1x, NA 11.6x, VMA 3.8x, NM 5.7x, NM 37.3x	Rt adrenal	2	6.3
10	51/F	N	-	A 12x, NA 1.7x	Pgl (near Lt adrenal)	6	6.2
11	49/M	Y	-	NA 12.3x	Lt adrenal	4	2.7
12	52/M	Y	-	A 3.5x	Lt adrenal	4	12.8
13	36/F	Y	-	A 1.3x, NA 3x, dopa 5.6x	Pgl (Lt renal hilim)	3.2	15.2
14§	47/F	Y	-	NA 3.2x	Rt adrenal	4	8.2
15	17/M	Y	VHL IIC	NA 17.2x	Lt + Rt adrenal	8, 8	6
16	48/F	N	-	A 4.8x, VMA 1.4x	Rt adrenal	2.5	8.2
17	37/M	Y	-	NA 13.6x	Lt adrenal	4.5	4.8

* MEN IIA denotes multiple endocrine neoplasia type 2, and VHL IIC von Hippel–Lindau disease type IIC
† Cats denotes catecholamines, ULN upper limit of normal, A adrenaline, NA noradrenaline, dopa dopamine, VMA vanillylmandelic acid, MN metanephrine, and NM normetanephrine
‡ Lt denotes left, Rt right, and Pgl paraganglioma
§ Residual

TABLE 2. Percentage distribution of symptoms in the 17 patients with phaeochromocytoma

Symptoms	Distribution (%)
Hypertension	71
Palpitations	53
Headache	53
Sweating	41
Anxiety	29
Chest pain	29
Postural hypotension	29
Nausea	24
Flushing	24
Paroxysmal symptoms	24
Tremors	18
Weight loss	18
Abdominal pain	12
Malignant hypertension	12
Heart failure	12
Reflex bradycardia	12
Pallor	12
Abdominal mass	6

three (18%) resumed antihypertensive medication within the first year. On subsequent follow-up, eight (47%) of the patients were hypertensive and received medication for blood pressure control. However, improved blood pressure control after surgery was likely as judged by recourse to fewer antihypertensive agents after surgery and during follow-up; six (75%) out of eight patients received only one antihypertensive medication on follow-up, whereas five (50%) out of the initial 10 patients received more than one antihypertensive agent before the operation.

Follow-up

Patients were followed up for 1 to 15 (mean, 7; SD, 4) years. Two patients died during the follow-up period due to intracranial haemorrhage and carcinoma of lung. One patient defaulted follow-up 8 years post-surgery. One patient had residual tumour.

Discussion

Phaeochromocytoma is a rare tumour with an incidence of 2 to 8 cases per million inhabitants per year.[4] If left undiagnosed, it is associated with long-term morbidity, if not mortality.[5,6] The wide spectrum of its clinical manifestations renders the diagnosis difficult. Hypertension or paroxysmal symptoms are only present in about 50% of patients.[7] The frequency is even lower (37%) for phaeochromocytoma patients who present with the classical triad of headaches, palpitations, and sweating.[8]

In our cohort, hypertension was present in 12 (71%) of the 17 patients, but only four (23%) had hypertension together with paroxysmal symptoms. Consistent with most other studies, headaches, palpitations, and sweating were the most frequent presenting symptoms, each being present in about half of our patients (53%, 53%, and 41%, respectively); only five (29%) of the 17 patients had all three symptoms. Five patients were normotensive. Among the normotensive patients, two presented with abdominal pain and an abdominal mass. One patient was diagnosed through family screening of first-degree relatives of another MEN IIA patient. In one study, the primary complaint of normotensive phaeochromocytoma was reported as flank/abdominal pain.[9] In other reports, phaeochromocytomas were found as an incidental adrenal masses (11-15%) or at autopsy.[8,10]

In our study, six (35%) of the 20 tumours were extra-adrenal, which is in line with most recent studies in which ectopic tumours comprise 10 to 29% of the adult phaeochromocytomas.[11-13] The 10% rule is no longer applied; the higher rate may well reflect increased disease awareness and improved tumour localising facility since the last century. A large review of 236 extra-adrenal paragangliomas found that the majority were located in the head and neck area (69%), followed by intra-abdominal (22%) and intrathoracic locations (10%). The periaortic and pericaval regions, followed by Zuckerkandl's were the commonest sites of abdominal paragangliomas.[14] In our cohort, all paragangliomas were intra-abdominal. Three were located in the superior para-aortic region and three were adjacent to the adrenals. Our findings emphasise the need to search for extra-adrenal lesions in confirmed cases.

We determined 24-hour urinary catecholamine excretion in patients with suspected phaeochromocytoma. In our cohort, the sensitivity of this test was 82%. Urinary metanephrines were not routinely measured before 2003. From the literature, plasma fractionated–free metanephrines have a high sensitivity (96-100%),[15,16] but low specificity (85-89%).[15-17] The measurement of combined fractionated metanephrines and catecholamines in a 24-hour urine collection has a high sensitivity of 88 to 99% and high specificity of 99%.[17-19] The approach to biochemical confirmation is still regionalised, varying according to institution. Nevertheless, it is suggested that the choice and interpretation of diagnostic tests depends on clinical suspicion. For low probability patients (ie with spells of hypertension, and adrenal incidentaloma), the measurement of 24-hour urinary fractionated metanephrines and catecholamines provide clinically acceptable sensitivity and significantly better specificity than fractionated plasma–free metanephrines. For higher risk scenarios, for example, patients with genetic syndromes with increased risk of phaeochromocytoma (MENII, VHL, neurofibromatosis [NF1], familial paraganglioma), and a family history of phaeochromocytoma, plasma-free metanephrines may be a better basis for a diagnosis, in view of higher sensitivity.[18] In the Mayo clinic, the diagnostic cut-offs for urinary catecholamines and metanephrines are approximately 2-fold higher than the upper limit for the normal population.[18] In our patients with elevated urinary catecholamine levels, all but two had levels 2-fold higher than the upper limit of the reference range. This higher-than-2-fold cut-off achieves a high specificity as it excludes patients with mild or borderline elevations of urinary catecholamine and its metabolites. One of our patients had a large exclusively dopamine-secreting paraganglioma, in whom urinary dopamine showed a 30-fold increase above the upper limit of normal, but the urinary catecholamines and metanephrines were not elevated. Tumours that only produce dopamine are rare, and often they lack the usual clinical features noted in catecholamine-producing tumours. However, they are more likely to be malignant and carry a poor prognosis.[20,21] It is therefore important to include dopamine measurements as part of the routine catecholamine screen, especially if an extra-adrenal paraganglioma is suspected.[20]

We identified four (24%) of the patients as having a hereditary syndrome. Among them, two patients who had MEN IIA were detected through family screening. The other two patients (12%; 1 with MEN IIA and 1 with VHL) presented as sporadic cases. The prevalence of familial form of phaeochromocytoma might have been underestimated, as genetic testing was not performed in every patient. A recent large cohort of 271 patients suggested that 24% of patients with apparently sporadic phaeochromocytomas have unsuspected germline mutations in the *VHL*, *RET*, *SDHB*, or *SDHD* genes. These findings have led to a recommendation for routine screening for hereditary causes in all apparently sporadic cases.[22] However, some groups recommend genetic testing in only certain age-groups, as patients of 50 years old or older have less than 1.3% probability of having a *VHL*, *RET*, *SDHB*, or *SDHD* mutation.[22] Therefore it was not considered cost-effective to perform genetic testing in this age-group.[23] Nevertheless, most studies would agree on systematic sequencing of the five phaeochromocytoma/paraganglioma susceptibility genes (namely *NF1, RET, VHL, SDHB*, and *SDHD*) based on family history and syndromic presentation, or specific features (in those that appear sporadic). In case of bilateral masses, *VHL* gene should first be screened, followed by *RET*, *SDHB*, and *SDHD*. For extra-adrenal tumours, *SDHB* and *SDHD* should be screened for. If patients are found to have malignant tumours, the *SDHB* mutation should be looked for. *VHL* should be screened for in patients aged younger than 20 years.[23,24]

In our cohort, no recurrence or malignancy has been detected hitherto, and only one patient

had residual tumour. The latter had persistent hypertension and elevated urinary catecholamines 1 month after the operation. The frequency of malignant phaeochromocytoma in a Chinese series was 9%.[25] The absence of any malignant lesion in our cohort is rather unusual, and may be explained by the relatively short follow-up period (mean, 6.7 years) to date. In one study, the estimated 10-year probability of recurrence was fairly high (0.16).[10] Recurrence can occur as late as 15 years post-resection.[26] Age, familial disease, tumour site, and size (>5 cm) were independent predictors of recurrence.[10,27] The risk of recurrence was 3.4-fold higher in patients with familial disease than in those with sporadic tumours. Compared with patients with left adrenal tumours, in those with right-sided and extra-adrenal tumours, the recurrence rate was 3.1-fold and 11.2-fold higher, respectively.[10] It is therefore recommended that life-long follow-up (with annual biochemical assessment) should be mandatory for all patients with phaeochromocytomas and paragangliomas.[25,26]

In conclusion, phaeochromocytoma presents variably and can be normotensive. Nowadays, most cases are discovered incidentally and more cases are found to be extra-adrenal. A high index of clinical suspicion is warranted to enable early diagnosis and treatment.

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