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Diagnostic Difficulties Associated with Phaeochromocytoma - 4 Case Illustrations

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ABSTRACT

The diagnosis of phaeochromocytoma can be extremely difficult with 40% - 76%[1,2] of cases escaping diagnosis during life. Until recently, the only available biochemical test for the detection of phaeochromocytoma in Singapore has been the 24-hour urinary vanillyl mandelic acid (VMA). Urinary VMA has been reported to have a high specificity (85% - 100%)[3,4] but variable sensitivity (28% - 90%)[3,5] in the diagnosis of this disease.

In 1993, high performance liquid chromatography (HPLC) assays for the measurement of urinary catecholamines and metanephrines were introduced at the Singapore General Hospital. Since 1993, 4 cases of phaeochromocytoma have been detected at our institution. We report here, the diverse clinical presentations of these patients. The urinary-free catecholamine and catecholamine metabolite levels of these patients were compared with corresponding levels from 12 non-phaeochromocytoma patients. Using the reference value of 65.6 μmol/day, we found the urinary VMA to be a highly sensitive (100%) test with a specificity of only 31%. In contrast, a urinary total metanephrine level of ≥ 9,000 nmol/day was both sensitive (100%) as well as specific (100%).

Keywords: phaeochromocytoma, metanephrines, catecholamines, vanillyl mandelic acid, hypertension

INTRODUCTION

Phaeochromocytoma has been variously described as the great mimic[6] and the great simulator[7]. It is an uncommon cause of hypertension, accounting for between 0.05% to 0.1%[8] of patients with hypertension, but is eminently correctable by surgery, with a success rate of 90%[9].

The first case of phaeochromocytoma was reported in Singapore in 1967 in a patient presenting with paroxysms of headache and palpitations[10]. Monitoring revealed episodic elevations of blood pressure. The classic triad of palpitations, perspiration and pain (headache) is well-known, but the diagnosis is often missed with 40% - 76%[1,2] of cases being diagnosed only at autopsy.

We report here the diverse presentations of 4 patients with phaeochromocytoma. We also compared their urinary-free catecholamine and catecholamine metabolite levels with those of 12 patients who presented with symptoms associated with phaeochromocytoma but who were subsequently found not to have the disease.

Case 1

A 46-year-old woman with a 6-year history of hypertension was referred to our department because her blood pressure was difficult to control. She also gave a history of hot flushes, anxiety attacks, episodes of breathlessness and palpitations of 4 months duration. Twenty-four hour urinary VMA, catecholamines and metanephrines were elevated (Table I). The CAT scan showed a large tumour arising from the left adrenal gland. At surgery, a 7.2 cm phaeochromocytoma was removed.

Case 2

A 37-year-old housewife presented with acute pulmonary oedema, to the coronary care unit. She had no previous history of hypertension. Blood pressure was 97/46 mmHg. A 2-D echocardiogram showed normal contractility. She gave a history of daily episodes of palpitations and breathlessness associated with numbness of the hands and feet for 2 years. These attacks lasted approximately 30 minutes each time. Blood pressure monitoring revealed marked lability ranging from 84-270 mmHg systolic and 60 - 150 mmHg diastolic. Twenty-four hour urinary VMA and metanephrines were elevated (Table I). A CAT scan showed a 4.4 cm right adrenal tumour which was subsequently resected.

Case 3

A 71-year old woman complained of attacks of giddiness and paraesthesia of her arms for 2 months. She had a long-standing history of palpitations. A left hypochondrial mass was found on examination. Blood pressure was 110/70 mmHg. A CAT scan and an angiogram revealed an adrenal mass. Her 24-hour urinary VMA, catecholamines and metanephrines were elevated (Table I).

Case 4

A 56-year-old man presented with substantial weight loss and was found to have a left hypochondrial mass. His blood pressure was 140/60 mmHg. His CAT scan and magnetic resonance imaging (MRI) results showed a 15 cm mass arising from the left adrenal as well as a mass in the right adrenal. The liver was studded with metastatic deposits. I-131

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Table I - Patients with phaeochromocytoma

Case	Age	Sex	Hypt	VMA (15.1-65.6)	EPI (0-109)	NEPI (89-473)	DOP (424-2,612)	MET (400-1,600)	NMET (600-1,900)	CAT Scan
1	46	F	+	87.5 107.6	70	2,321	2,953	1,620	68,224	7cm L adrenal
2	37	F	-	104.6	-	-	-	112,617	12,657	4cm R adrenal
3	71	F	-	184	189	422	4,237	15,047	4,077	18cm L adrenal
4	56	M	-	1,705	363	2,222	7,882	24,430	871,560	15cm bilat adrenal

VMA – vanillylmandelic acid, EPI - epinephrine, NEPI - norepinephrine, DOP - dopamine, MET - metanephrine, NMET - normetanephrine
24 hour urinary VMA in μmol/day; EPI/NEPI/DOP/MET/NMET in nmol/day. Values in brackets denote normal laboratory range
Hypt +/- – presence or absence of hypertension on presentation
bilat/R/L adrenal – bilateral/right/left adrenal gland involvement

metaiodobenzylguanidine (MIBG) scanning showed increased uptake by the adrenal masses and the liver secondaries. His 24-hour urinary VMA, catecholamines and metanephrines were markedly elevated (Table I). He was diagnosed to have bilateral malignant phaeochromocytomas with metastatic spread to the liver and was started on chemotherapy.

NON-PHAEOCHROMOCYTOMA

A retrospective analysis of 50 patients referred to our department for the exclusion of the diagnosis of phaeochromocytoma was carried out. Of these cases, only 12 patients had CAT scans of the adrenals and abdomen performed. Their 24-hour urinary VMA, catecholamine and metanephrine levels served as a basis for comparison. All patients were less than 65 years old. Eight were male and 4, female. Seven were hypertensives but were otherwise asymptomatic. The remaining 5 had one or more of the symptoms associated with phaeochromocytoma such as flushing, sweating and palpitations. Of this group, 3 were hypertensive. Nine out of 12 had their 24-hour urinary VMA level elevated, while 10 had elevated urinary free catecholamine or catecholamine metabolite levels.

Urinary-free catecholamine and catecholamine metabolite levels

Urinary VMA ranged from 87.5 - 1,705 nmol/day (normal 15.1 - 65.6) in the phaeochromocytoma patients and 27.3 - 87.7 nmol/day in those without the disease (Fig 1). Urinary total metanephrines ranged from 19,124 - 895,990 nmol/day (normal 1,000 - 3,600) in phaeochromocytoma patients and from 1,987 - 5,501 in non-phaeochromocytoma patients (Fig 2). Urinary-free catecholamines ranged from 431 - 2,585 nmol/day (normal 89 - 582) and 111 - 786 nmol/day in phaeochromocytoma and non-phaeochromocytoma patients respectively. A urinary epinephrine level of greater than 920 nmol/day was 100% predictive but had low sensitivity (50%).

DISCUSSION

The symptomatology of phaeochromocytoma is protean. To consider this diagnosis only in hypertensives would be misleading, as hypertension is absent in approximately one-fifth and paroxysmal in a-third of patients[9]. The classical triad of headaches, palpitations and sweatiness in a hypertensive patient is said to be 90% sensitive[11], and each symptom in isolation, is said to be present in 60%[12] of patients with phaeochromocytoma. But these are common complaints by the general population and specificity is only 67%[11]. Other symptoms[12] associated with phaeochromocytoma include pallor (42.9%), nausea (34.5%), tremor (33.5%), anxiety (28.9%), abdominal pain (25.8%), dyspnoea (17%) and weight loss (16.5%). Although flushing often brings to mind the diagnosis of phaeochromocytoma, only 14.8% of patients have this symptom. In addition, phaeochromocytoma may present catastrophically as myocardial infarction[13], cerebrovascular accident[14], acute pulmonary oedema[15], cardiovascular collapse mimicking septicaemic shock[16] or even sudden death. Symptoms may occur episodically in paroxysms, which although vary between individuals, are stereotypic for each person. It has been noted that numbness of the extremities especially of the upper limbs[11] may precede one of the more classical symptoms, and this has been the case in two of our patients.

Various combinations of symptoms can occur as in other medical conditions (eg. thyrotoxicosis), during menopause, and non-specifically, in the elderly; so that by the time the diagnosis is made, there may be a palpable abdominal mass.

Our series, though small, illustrates four points: Firstly, alertness to the possibility of phaeochromocytoma should not be restricted to any particular age group. The 4 patients described here depict that phaeochromocytomas can present in the age spectrum of the middle aged to the elderly.

Secondly, the inclusion of additional symptoms of flushing, breathlessness, anxiety and numbness of the upper extremities would add diagnostic value to

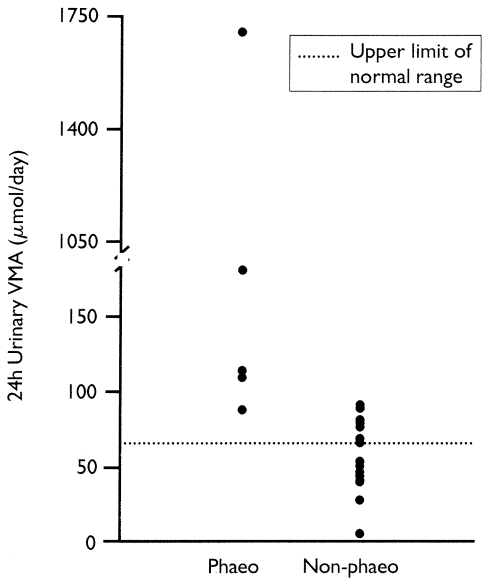

Fig 1 - Urinary VMA in phaeochromocytomas and non-phaeochromocytomas

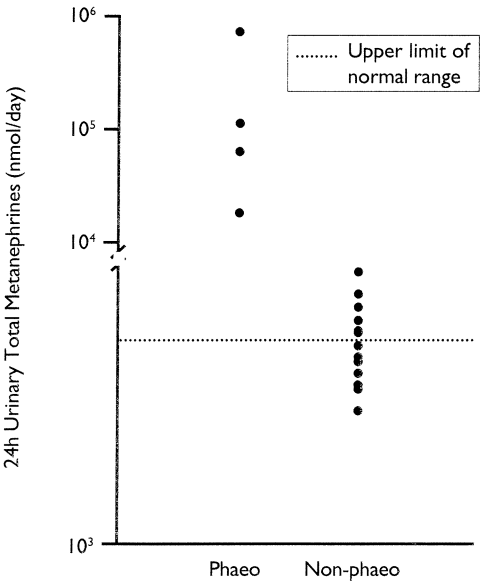

Fig 2 - Urinary metanephrines and normetanephrines in phaeochromocytomas and non-phaeochromocytomas

the classical triad of headaches, sweatiness and palpitations. Isolated symptoms may not be very specific but a combination of symptoms may be both sensitive and specific. Three of our 4 patients (75%) with phaeochromocytoma had three or more such symptoms that occurred paroxysmally.

Thirdly, the absence of hypertension is not unusual. Three of our patients were not known to have hypertension prior to diagnosis and in 2 patients (Cases 3 and 4), monitoring did not reveal any hypertensive episodes.

Fourthly, a high index of suspicion is required. Unusual clinical presentations such as in Case 2, should alert the physician to the possibility of this diagnosis.

Controversy still surrounds the optimal evaluation for phaeochromocytomas. Most authors favour measurement of urinary-free catecholamines and their metabolites as the mainstay of biochemical evaluation. Plasma catecholamines, though useful, are highly labile and collection as well as storage of samples require rigid control. Catecholamines which are more stable in acid urine, are present in higher concentrations and represent an integrated measurement of secretion[17].

HPLC is the current method of choice for the measurement of catecholamines and their metabolites[17]. It is superior to the old spectrophotometric and fluorometric methods, which were more susceptible to interference from drugs and dietary products[18] eg. vanillin in bananas.

We found that elevations of VMA, norepinephrine, dopamine and normetanephrine were a common occurrence among our non-phaeochromocytoma population. The low specificity for VMA is in contrast to most other reports[3,4]. Two reasons could account for this: firstly, VMA levels were measured using a spectrophotometric, instead of the newer HPLC assays. Secondly, some patients may not have been vigilant with their dietary restriction of vanillin, prior to testing. Repeat VMA levels in the non-phaeochromocytoma patients dropped significantly after proper restriction of vanillin in their diet.

The sensitivity of urinary VMA as a screening test for phaeochromocytoma varies in different series from 28% - 90%[3,5]. The high sensitivity of urinary VMA found in our series could be related to the small number of patients. Bravo[9] stated that, with plasma catecholamine levels of $\geq$ 11.7 nmol/L (2000 pg/mL), urinary total metanephrines of $\geq$ 9,000 nmol/day (1.8 mg/24hr), urinary VMA of $\geq$ 64.4 μmol/day (11 mg/24hr) and urinary epinephrine levels of $\geq$ 920 nmol/day (156 μg/24hr), the diagnosis is incontrovertible. Using these values, the sensitivity and specificity of urinary VMA levels was 100% and 31% respectively. Urinary epinephrine levels $\geq$ 920 nmol/day were highly specific (100%) but not sensitive (50%). Urinary total metanephrine levels $\geq$ 9,000 nmol/day were both highly sensitive (100%) and specific (100%).

We agree with other authors that a combination of tests yields the highest detection rate. The urinary VMA, while highly sensitive, overlapped with hypertensives without phaeochromocytoma (Fig 1) and therefore was not specific.

The clear demarcation in urinary total metanephrine levels between phaeochromocytomas and hypertensive non-phaeochromocytomas (Fig 2) makes this investigation a superior one. The urinary metanephrines should replace urinary VMA as the screening test of choice in the diagnosis of phaeochromocytoma.

CONCLUSIONS

The attending physician should familiarise himself with the diverse presentation of phaeochromocytoma. All patients with any of the symptoms classically

associated with this disease should be screened even if normotensive. The urinary VMA, while sensitive, is not specific, and urinary metanephrines should therefore be the screening test of choice.

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