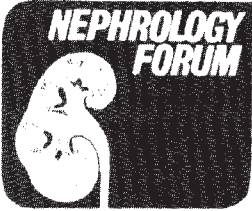


Pheochromocytoma: New concepts and future trends

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Case presentation

A 37-year-old white woman was referred to the Cleveland Clinic Foundation for evaluation of a right suprarenal mass. Beginning 5 years before, she had experienced episodes of severe headache, pounding heart, and flushing, followed by facial pallor and tremulousness. Neither blood pressure nor heart rate was checked during these spells. The attacks occurred about twice monthly and lasted for 5 to 20 minutes. She noted that "bearing down" during defecation or "curling up" on her left side often precipitated these episodes.

She consulted 6 physicians over the subsequent 4 years; no diagnosis was made to explain her symptoms. One year ago, she consulted a neurologist, who performed a thorough examination and obtained a magnetic resonance image of the head; no abnormalities were detected. One month before she came to the Cleveland Clinic, her private physician obtained an abdominal sonogram because he suspected an abdominal aneurysm. The study revealed a "5.2 × 5.1 cm solid, hyperechoic suprarenal mass" on the right side. Neither she or her family had a significant medical history.

Physical examination revealed a blood pressure of 122/76 mm Hg; pulse, 80 beats/min and regular; and respiratory rate, 16/min. The rest of the examination was unremarkable.

Laboratory studies revealed: normal SMA-16 values except for a blood glucose of 133 mg/dl; normal thyroid function; serum calcium, 8.8 mg/dl; plasma norepinephrine, 1456 pg/ml; epinephrine, 259 pg/ml; 24-hr urinary metanephrine, 5728 μg/24 hr; normetanephrine, 10,465 μg/24 hr; and serum chromogranin A, 162 ng/ml (normal, ≤ 50 ng/ml).

An abdominal CT scan revealed a right suprarenal mass measuring about 6.0 cm diameter, which demonstrated a high signal intensity on the T₂-weighted image by MRI (Fig. 1). The mass concentrated high

amounts of radioiodinated metaiodobenzylguanidine (¹³¹I-MIBG) 72 hours after intravenous administration of the radioisotope (Fig. 2).

A right adrenal mass was excised without incident. The mass weighed 95 g and measured 6.0 × 5.3 × 4.4 cm. The cut surface was variegated, and focal hemorrhagic areas were scattered throughout. A large cystic area measured 1.6 cm in diameter. Histologic examination was compatible with pheochromocytoma.

Discussion

DR. EMMANUEL L. BRAVO (*Head, Endocrine/Hypertension Research Laboratory, Department of Heart and Hypertension, Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio*): This case exemplifies the patient with a pheochromocytoma who remained undiagnosed for years. Diagnosing this condition early is very important because removal of the tumor results in cure in approximately 90% of patients but, if left untreated, pheochromocytoma can be lethal. The principal focus of my discussion will be on non-malignant pheochromocytomas, which account for more than 90% of all such tumors. I will discuss malignant pheochromocytomas briefly near the end of this Forum.

The diagnosis of pheochromocytoma is not difficult to make when the patient presents with classic manifestations of the disease, or when an increase in catecholamine production is clear-cut. When the patient presents with uncommon symptoms and equivocal biochemical tests, however, the disease provides a diagnostic challenge. In this setting, a carefully planned sequence of studies including appropriate biochemical testing and localizing techniques is required to substantiate the diagnosis of pheochromocytoma.

Clinical manifestations

Pheochromocytomas can cause a wide variety of symptoms. The most common set of findings comprises attacks of headache, sweating, and tachycardia [1]. In one study, the symptomatic triad of headache, sweating attacks, and tachycardia in a hypertensive patient was found to have a specificity of 93.8% and a sensitivity of 90.9% in the diagnosis of pheochromocytoma [2]. Palpitations, anxiety, and tremulousness are common when the tumor produces a large amount of epinephrine; these symptoms are present only in approximately 50% of patients, however. Hypertension, the most common feature, occurs in more than 90% of patients and is paroxysmal in 25% to 50% of patients [3].

In a patient with a pheochromocytoma, endocrine abnormalities can dominate the clinical picture. Hypercalcemia can be related to excessive production by the pheochromocytoma of parathyroid hormone [4]; diarrhea can result from increased

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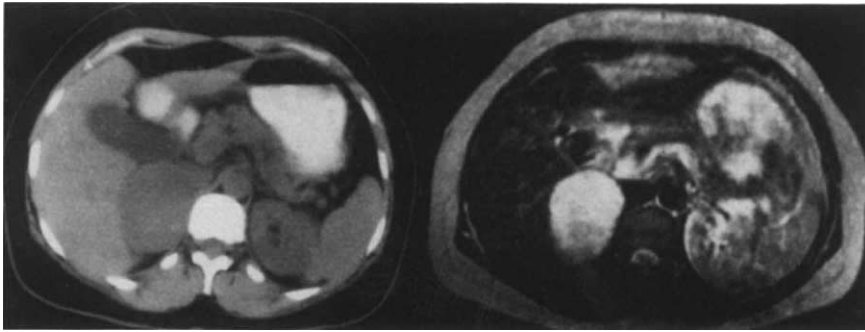


Fig. 1. Localization of pheochromocytoma by abdominal CT scan (left) and by MRI (right, T₂ weighted image.) (From case presentation.)

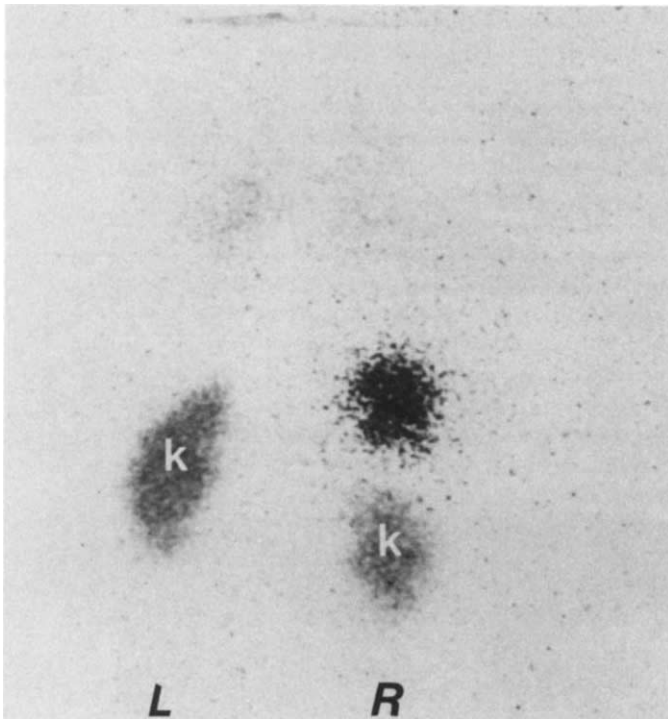


Fig. 2. Localization of pheochromocytoma employing ¹³¹I-MIBG. Uptake of ¹³¹I-MIBG by the same tumor shown in Fig. 1, 72 hours after radioisotope injection. (From case presentation.)

with decreases in oxygen delivery and increases in oxygen utilization.

Cardiovascular abnormalities occur commonly in patients with pheochromocytomas, the commonest probably being myocarditis [17]. Patients often present with signs and symptoms like those observed in acute myocardial infarction [18]. Cardiac arrhythmias, including atrial and ventricular fibrillation, can be precipitated by anesthetic agents or surgery for unrelated conditions. These arrhythmias probably are due to the sudden release of catecholamines. Dilated congestive cardiomyopathy, believed to be related to myocarditis, has been described in some patients [17]. Pulmonary edema, which can be either cardiogenic or noncardiogenic in origin, can be the first manifestation of a pheochromocytoma. Noncardiogenic pulmonary edema is believed to result from transient increases in pulmonary capillary pressure due to pulmonary venoconstriction and increased pulmonary capillary permeability [19, 20].

Altered mental status, focal neurologic signs and symptoms, and/or seizures occasionally are observed during a hypertensive crisis [1]. Stroke due to cerebral infarction, intracerebral hemorrhage resulting from severe arterial hypertension, and/or emboli secondary to mural thrombus from a dilated cardiomyopathy also can complicate pheochromocytoma. Finally, certain drugs sometimes precipitate a hypertensive crisis in patients harboring a pheochromocytoma. Such drugs include tricyclic antidepressants [21], antidopaminergic agents (for example, sulpiride) and metoclopramide [22], and naloxone [23].

Unrelated disorders are likely to be confused with pheochromocytoma on the basis of catecholamine levels (Table 1). Angina pectoris, acute clonidine withdrawal, hypoglycemia, and vasodilator therapy (with either minoxidil or hydralazine) can produce plasma catecholamine values as high as those observed in pheochromocytoma [24].

The fact that pheochromocytomas can present in many ways explains why so many of these tumors are missed. In a series from the Mayo Clinic, 41 of the 54 autopsy-proven cases were unsuspected clinically during life [25]. Of the 13 (of the 54 cases) correctly diagnosed before death, 4 cases were discovered incidentally at laparotomy for unrelated conditions. Of those diagnosed after death, only 54% had had hypertension. Headaches (27%), diaphoresis (17%), and palpitations (17%) were much less common than in patients whose tumor was diagnosed before death. Twelve patients were older than 68 years; in 9 of these elderly patients, the diagnosis was unsuspected. In a retrospective study from Australia, 29 of 46 proven cases were diagnosed and treated during life, whereas 17 were diagnosed at

production of vasoactive intestinal peptide [5, 6]; and cushingoid features, accompanied by severe hypokalemic alkalosis, can arise from overproduction of ACTH [7-9].

Some patients present with an acute surgical abdomen due to bowel ischemia and/or hemorrhagic necrosis of the tumor [10-14]. Others present with constant abdominal pain associated with marked hypertension followed by hypotension and even shock and sudden death [13, 14]. Sudden death probably results from marked arterial and venous dilation due to sudden withdrawal of catecholamines, the hypotension being compounded by the presence of intravascular hypovolemia.

Overt diabetes can occur in patients with pheochromocytoma because catecholamines antagonize insulin release [15]. Lactic acidosis in the absence of shock should arouse suspicion of pheochromocytoma [16]. The increase in lactate production is thought to reflect a direct stimulation by epinephrine associated

Table 1. Clinical syndromes likely to be confused with pheochromocytoma^a

| |
|--|
| β -Adrenergic hyperresponsiveness |
| Angina pectoris |
| Acute infection |
| Autonomic epilepsy |
| Hyperthyroidism |
| Idiopathic orthostatic hypotension |
| Cerebellopontine angle tumors |
| Acute hypoglycemia |
| Tyramine ingestion in patients receiving MAO inhibitors ^b |
| Menopausal syndrome with migraine headaches |
| Acute drug withdrawal |
| Clonidine |
| β -Adrenergic blockade |
| α -Methyldopa |
| Vasodilator therapy |
| Hydralazine |
| Minoxidil |
| Factitious administration of sympathomimetic agents |

^a From Ref. 24.^b MAO = monoamine oxidase.

autopsy [26]. Of the latter, 14 died of cardiovascular complications that were attributed to their disease. Most of the tumors discovered at autopsy were found in patients 60 years or older. Stenstrom and Svardsudd reviewed their experience in 439 patients with pheochromocytoma registered in Sweden from 1958 to 1981 [27]. The incidence of pheochromocytoma increased continuously with advancing age both for men and women. In 184 cases (40%) the diagnosis was made at autopsy. Pheochromocytoma was an incidental finding in 60 (14% of all cases). The average age at diagnosis in those whose disease was discovered before death was 48.5 years, significantly lower than the average age at death in those diagnosed only at autopsy, which was 65.8 years. Similarly, Krane found that of 32 patients with pathologically confirmed tumors, 11 patients had tumors that were clinically unsuspected [28]. Of these 11, 9 patients were considered asymptomatic during their lifetimes.

These observations indicate that a high percentage of patients with pheochromocytoma present with minor or no signs and symptoms. Further, elderly patients appear to present a special diagnostic challenge. A contributory factor to the rarity of the antemortem diagnosis of pheochromocytoma in the elderly may be a decrease in sensitivity to catecholamines with age. Additionally, most elderly patients have concomitant disease, the signs and symptoms of which can confound the diagnosis. Cardiac and neurologic symptoms often are attributed to coronary artery and cerebrovascular disease from atherosclerosis.

New concepts in pathophysiology

At first blush, the mechanism of elevated blood pressure in patients with pheochromocytoma might seem to be the most straightforward of all the secondary forms of hypertension. Surprisingly, however, approximately 15% of patients are normotensive [29]. In addition, no relationship exists between the prevailing levels of plasma catecholamines and the height of arterial blood pressure (Fig. 3) [30]. Indeed, normotension in the presence of increased circulating catecholamines is not uncommon.

Several factors can alter the response of the vascular smooth muscle to circulating catecholamines. One factor is blood

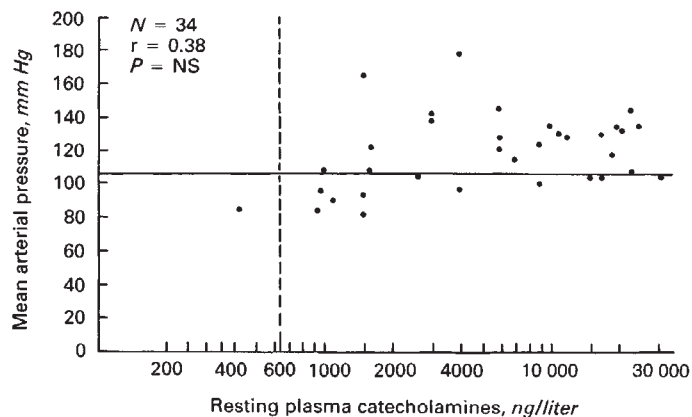


Fig. 3. Relationship between the height of arterial blood pressure and the level of circulating plasma catecholamines in pheochromocytoma. The horizontal line refers to the upper limits of MAP (i.e., 106 mm Hg); the vertical axis refers to the upper limit of 99% confidence intervals of plasma catecholamines (NE + E) in normals. (From Ref. 30.)

volume. Hypovolemia diminishes the blood pressure response to circulating pressor agents. Hypovolemia is not a universal finding in this disorder, however [31], and occurs in only approximately 50% of patients. In addition, blood volume is inversely related to the height of diastolic blood pressure; this relationship would be direct if the height of arterial blood pressure depended solely on the level of intravascular volume.

Prolonged stimulation of a tissue by adrenergic agonists can diminish responsiveness of the tissue to subsequent activation by catecholamines; this phenomenon has been termed desensitization, or tachyphylaxis. Tsujimoto and colleagues examined the in-vivo consequences of prolonged stimulation of vascular alpha-adrenergic receptors in rats harboring norepinephrine-producing tumors [32]. In the early stages of the disease, sensitivity was lost for both α 1- and α 2-adrenergic agonists, whereas responsiveness to arginine vasopressin and angiotension II was intact. Additionally, radioligand binding studies showed that the number of α 1-adrenergic receptors decreased by 36% in mesenteric artery plasma membrane from these rats, whereas the number of α 2-adrenergic receptors was unaltered. These results provide a plausible explanation for the observation that patients can be normotensive or only moderately hypertensive despite high circulating levels of catecholamines.

It has always been assumed that sympathetic nerve activity in patients with pheochromocytoma would be depressed because of the high circulating catecholamines. However, both clinical and experimental evidence suggests that the sympathetic nervous system plays a significant role in the maintenance of hypertension in patients with pheochromocytoma. The clinical evidence for this conclusion comes from our studies of the effects of orally administered clonidine in patients with either essential hypertension or pheochromocytoma [33]. Clonidine, a centrally acting α 2-agonist, inhibits neurally mediated catecholamine release. Clonidine decreases blood pressure to the same degree in patients with pheochromocytoma as it does in those with essential hypertension. These results suggest that the sympathetic nervous system is intact in pheochromocytoma. In essential hypertension, the fall in blood pressure is associated

with decreases in circulating catecholamines, but in pheochromocytoma, plasma catecholamine levels do not change [33]. The discrepancy between the fall in blood pressure in patients with pheochromocytoma after clonidine administration and the persistently high levels of circulating catecholamines suggests that the norepinephrine released from axon terminals of sympathetic postganglionic neurons is biologically more significant than circulating catecholamines. This discrepancy could be related to the easier access of norepinephrine released from postganglionic neurons to its site of action at effector cells.

Neural control of blood pressure also exists in rats implanted with a pheochromocytoma. Eliminating sympathetic nerve activity by pithing caused a greater reduction of blood pressure in pheochromocytoma-bearing rats than in age-matched, unimplanted rats [32]. Additionally, Prokocimer and coworkers found that both clonidine and chlorisondamine (a ganglion blocker) markedly decreased blood pressure in intact rats with pheochromocytoma [34]. However, the observation that the blood pressure in pithed rats with pheochromocytoma is further reduced by phentolamine, an alpha-adrenergic antagonist, suggests that high concentrations of circulating catecholamines also are involved in the maintenance of the elevated blood pressure. Thus, the hypertension in pheochromocytoma is a complex process influenced by the sympathetic nervous system, by circulating catecholamines, and by alterations in cardiovascular responses to catecholamines.

Our studies of the hemodynamics of hypertension reveal that despite having tenfold higher levels of circulating catecholamines, patients with pheochromocytoma have hemodynamic characteristics similar to those in patients with essential hypertension [35]. In both groups, increased total peripheral resistance is primarily responsible for maintenance of hypertension. These results further support the concept that the sympathetic nervous system regulates blood pressure in both groups of patients.

Orthostatic hypotension occurs in about 40% of patients with pheochromocytoma and probably is caused by a combination of hypovolemia and impaired venous and arterial constrictor reflex responses. However, blood volume does not differ between patients who exhibit postural hypotension and those who do not. In patients who develop significant blood pressure reductions on standing, the most consistent hemodynamic changes were decreases in systolic arterial pressure (without changes in diastolic blood pressure) and decreases in cardiac output without any compensatory increase in total peripheral resistance [36]. These observations suggest impaired vascular reflexes, but it is unclear why some patients have this hemodynamic abnormality and some do not.

Experimental studies suggest that catecholamines increase protein synthesis and might play a role in cardiac hypertrophy [37]. However, patients with pheochromocytoma had left-ventricular-mass indices similar to those in patients with age- and sex-matched essential hypertension who had tenfold lower plasma catecholamine values [38].

Evaluation for suspected pheochromocytoma

Priority for evaluation for the presence of pheochromocytoma should be given to patients with any of the following: (1) the triad of episodic headaches, tachycardia, and diaphoresis (with or without associated hypertension); (2) family history of

pheochromocytoma; (3) signs or symptoms indicating a multiple endocrine adenoma (MEA) syndrome; (4) "incidental" suprarenal masses; (5) hypertension associated with equivocal increases in catecholamine production; and (6) adverse cardiovascular manifestations in response to anesthesia, to any surgical procedure, or to certain medications known to precipitate symptoms in patients with pheochromocytoma.

Biochemical tests. The most useful urine tests measure concentrations of metanephrine, vanillylmandelic acid (VMA), and free (unconjugated) catecholamines. These tests have been compared in patients with confirmed pheochromocytoma and in hypertensive patients without the tumor. In 43 patients with tumors, the false-negative rates were 30% for urinary VMA and 10% for urinary metanephrines [39]. In another study, none of 25 patients with pheochromocytoma had a false-negative rate for urinary free norepinephrine [40]. Thus, assays of 24-hour urinary catecholamines and metanephrines are adequate for diagnosing pheochromocytoma in most patients.

Sole reliance on determination of urinary catecholamine metabolites as indices of catecholamine production can be misleading, however. The amounts and types of metabolites excreted in urine depend on a number of factors. *First*, the handling of catecholamines by the kidney depends on both degradation and excretion [41]. *Second*, in patients with pheochromocytoma, the activities of the enzymes involved in catecholamine synthesis (tyrosine hydroxylase, aromatic amino acid decarboxylase, and dopamine β -hydroxylase) are markedly increased, whereas the activities of the enzymes involved in catecholamine catabolism (monoamine oxidase and catechol-O-methyltransferase) are reduced [42]. Thus, excess amounts of newly synthesized norepinephrine that cannot be stored in the filled catecholamine storage vesicles are not always degraded, and the norepinephrine diffuses from the pheochromocytoma into the circulation. This efflux could result in large amounts of circulating norepinephrine with relatively small increases in urinary catecholamine metabolites. *Third*, the size of the tumor is an important determinant of the relative amounts of catecholamine excretory products. Crout and Sjoerdsma demonstrated that tumors weighing less than 50 g have rapid turnover rates and release mainly unmetabolized catecholamines into the circulation, producing low concentrations of metabolites relative to free catecholamines in the urine [43]. On the other hand, tumors weighing more than 50 g have slow turnover rates and release mainly metabolized catecholamines into the circulation, resulting in high concentrations of metabolites relative to free catecholamines in the urine. These observations have important clinical implications. Because small tumors release free unmetabolized catecholamines into the circulation, they tend to produce more symptoms and are best diagnosed by the measurement of plasma catecholamines. In contrast, patients who have large tumors that metabolize most of the secreted catecholamines exhibit few symptoms and have relatively lower circulating free catecholamines but high urinary excretions of catecholamine metabolites.

Figures 4 and 5 depict plasma catecholamine levels in a group of patients with pheochromocytoma; these values are compared with those from patients with essential hypertension [44]. It is clear that the majority of patients with pheochromocytoma

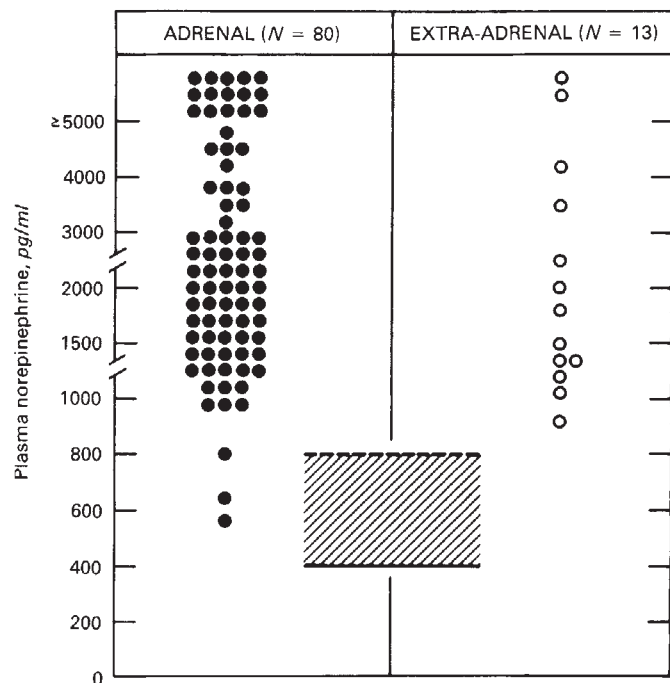


Fig. 4. Plasma norepinephrine values in adrenal and extra-adrenal pheochromocytoma. The cross-hatched area represents the mean (425 pg/ml) and the 95% confidence limits (upper limit, 811 pg/ml) of values obtained from 104 patients with essential hypertension. (From Bravo EL: Adrenal medullary function, in *Diagnostic Endocrinology*, edited by MOORE WT, EASTMAN RC, Philadelphia, BC Decker, 1990, p 220.)

have elevated plasma catecholamine levels that markedly exceed those in patients with essential hypertension. Three patients had plasma norepinephrine values that fell within the 95% confidence limits for values obtained in patients with essential hypertension (that is, below 811 pg/ml). None had values that fell within the range for sex- and age-matched normotensive subjects (that is, below 402 pg/ml). It is evident that the plasma epinephrine concentration has little value in predicting the location of a tumor. Although some patients with adrenal pheochromocytomas have plasma epinephrine values within the normal range, some patients with extra-adrenal tumors have values distinctly above the normal range. In practice, plasma catecholamine values (the sum of norepinephrine and epinephrine) that exceed 2000 pg/ml are considered abnormal, and values less than 500 pg/ml are normal; values between 500 and 2000 pg/ml are equivocal, should be repeated, and require confirmation by measurement of 24-hour urinary catecholamine metabolites and/or pharmacologic testing.

Figure 6 compares simultaneously measured plasma catecholamines, urinary metanephrine, and VMA in patients with pheochromocytoma [39]. Using measurements in patients with essential hypertension as reference values, we found false-negative results for urinary VMA in 25 of the 43 patients. On the other hand, only 9 had false-negative results for urinary metanephrine. In one patient, all three biochemical measurements were within the ranges seen in essential hypertension. In another patient, an elevated level of urinary metanephrine was the only biochemical abnormality, and in 3 patients, the only

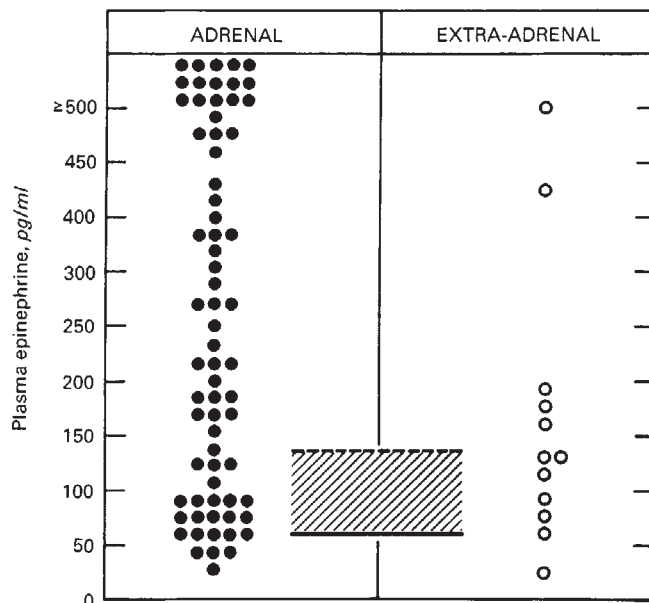


Fig. 5. Plasma epinephrine values in adrenal and extra-adrenal pheochromocytoma. The cross-hatched area represents the mean (59 pg/ml) and the 95% confidence limits (upper limit, 145 pg/ml) of values obtained from 104 patients with essential hypertension. (From Bravo EL: Adrenal medullary function, in *Diagnostic Endocrinology*, edited by MOORE WT, EASTMAN RC, Philadelphia, BC Decker, 1990, p 221.)

abnormal result was an elevated plasma catecholamine level. These findings are in accord with the demonstration of variable metabolism and degradation of catecholamines in pheochromocytomas. Further, these results suggest that of the urinary catecholamine metabolites, urinary metanephrine provides a more reliable clue to the presence of pheochromocytoma than does urinary VMA, and that plasma catecholamine measurements are at least as reliable as is measurement of urinary metanephrine in predicting the presence of pheochromocytoma.

Catecholamine values in normotensive and hypertensive subjects are shown in Table 2. The sensitivity and specificity of the various biochemical tests appear in Table 3. Measurement of plasma catecholamines seems to have the highest sensitivity and specificity; the measurement of urinary VMA has the lowest. All three tests provide excellent positive predictive value when values are elevated, however.

The availability of tests in any given center necessarily determines the nature of the investigation in an individual patient, and debate over the relative merits of various tests will continue. However, it seems likely that for 100% diagnostic accuracy, multiple tests may have to be performed taking into account the limitations and pitfalls of some analytical methods. Because the metabolism of catecholamines in patients with pheochromocytoma may be modified by either a lack or an excess of metabolizing enzymes, plasma catecholamines as well as catecholamine metabolites in urine (preferably metanephrine) should be measured in equivocal cases.

Plasma chromogranin A concentration has been proposed as a diagnostic test for pheochromocytoma; plasma levels are about tenfold higher than those in other hypertensive patients

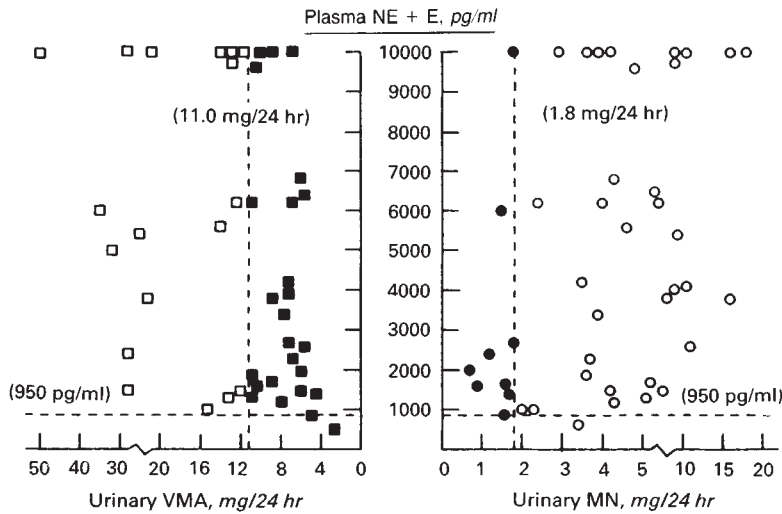


Fig. 6. Comparison of simultaneously measured indices of catecholamine production in 43 patients with surgically confirmed pheochromocytoma. The vertical broken lines represent the 95% upper confidence limits of values for urinary vanillylmandelic acid (VMA) (i.e., 11 mg/24 hr) and urinary metanephrines (MN) (i.e., 1.8 mg/24 hr) in 30 subjects with essential hypertension. NE + E denotes norepinephrine plus epinephrine. Solid symbols denote false-negative tests. (From Ref. 39.)

Table 2. Catecholamine values in normotensive and hypertensive patients with proven pheochromocytoma^a

| Biochemical measurements | Normotensive subjects (n = 40) | Hypertensive subjects (n = 70) |
|-------------------------------|--------------------------------|--------------------------------|
| Plasma norepinephrine | 218 ± 92 pg/ml ^b | 425 ± 193 pg/ml ^b |
| Plasma epinephrine | 42 ± 18 pg/ml ^b | 59 ± 38 pg/ml ^b |
| Urinary VMA ^c | <6.8 mg/24 hr | <11.0 mg/24 hr |
| Urinary NMN + MN ^c | <1.3 mg/24 hr | <1.8 mg/24 hr |
| Urinary norepinephrine | <100 µg/24 hr | <156 µg/24 hr |

^a From Ref. 24.

^b Values are mean ± 1 sd.

^c VMA = Vanillylmandelic acid; NMN = normetanephrine; MN = metanephrine.

Table 3. Sensitivity and specificity of various biochemical tests in the diagnosis of pheochromocytoma^a

| Biochemical test | Reference value ^b | Sensitivity (% range) ^c | Specificity (% range) ^c |
|-------------------------------|------------------------------|------------------------------------|------------------------------------|
| Plasma NE + E ^d | >950 pg/ml | 88–100 | 93–101 |
| Urinary NMN + MN ^d | >1.8 mg/24 hr | 67–91 | 83–103 |
| Urinary VMA ^d | >11.0 mg/24 hr | 28–56 | 98–102 |

^a From Ref. 24.

^b Upper 95% confidence limits obtained from essential hypertension subjects under basal conditions.

^c Values are expressed as ± 2 se.

^d NE + E = norepinephrine plus epinephrine; NMN + MN = normetanephrine plus metanephrine; VMA = vanillylmandelic acid.

[45]. Chromogranin A is a soluble protein contained in catecholamine storage vesicles. Because it is released simultaneously with norepinephrine, its level in plasma reflects sympathoadrenal activity [46]. But chromogranin A also is found in blood of patients with other neuroendocrine tumors [47].

Because platelets concentrate catecholamines [48], patients with pheochromocytoma have increased platelet norepinephrine and epinephrine content. Zweifler and Julius have suggested that platelet catecholamine content might discriminate between patients with pheochromocytoma and those with non-pheochromocytoma-associated hypertension [49]. A recent study showed, however, that the usefulness of platelet catecholamines in diagnosing pheochromocytoma is limited because of the high false-positive rates—36% for platelet norepinephrine and 19% for platelet epinephrine [50].

The simultaneous measurement of urinary norepinephrine and 3,4-dihydroxyphenylglycol (DHPG) has been proposed as a means of increasing the specificity of urine testing. Norepinephrine that is released by neurons is again taken up and converted to DHPG [51]. Therefore, DHPG levels reflect the extent of neuronal traffic. In patients with pheochromocytoma, however, norepinephrine is released directly into the circulation and results in higher ratios of norepinephrine/DHPG than observed in other hypertensive patients [52]. Measuring free norepineph-

rine in urine has been shown to be as accurate as the norepinephrine/DHPG ratio, however [40].

Pharmacologic testing. The diagnostic dilemma in the work-up of pheochromocytoma is how to separate patients with pheochromocytoma and relatively low levels of synthetic activity from patients without pheochromocytoma who have secondarily activated sympathetic nervous systems. Pharmacologic tests are designed to either provoke secretion of catecholamines by a pheochromocytoma or to suppress normal or excessive activity of the sympathetic nervous system.

A provocative test usually is employed when the clinical findings are highly suggestive of pheochromocytoma but plasma catecholamine levels are less than 1000 pg/ml and the blood pressure is only slightly increased (less than 160/100 mm Hg). The glucagon stimulation test is widely used because it has few side effects [53]. Glucagon is given as an intravenous bolus dose of 1.0 to 2.0 mg after determination of the patient's blood pressure response to immersion of the hand in water at 4°C (cold pressor test). A positive glucagon test requires a clear increase (at least threefold, or over 2000 pg/ml, in plasma catecholamines) 1 to 3 minutes after drug administration. A simultaneous increase in blood pressure of at least 20/15 mm Hg above the response to the cold pressor test strengthens the test but is not necessary. If a rise in blood pressure is considered

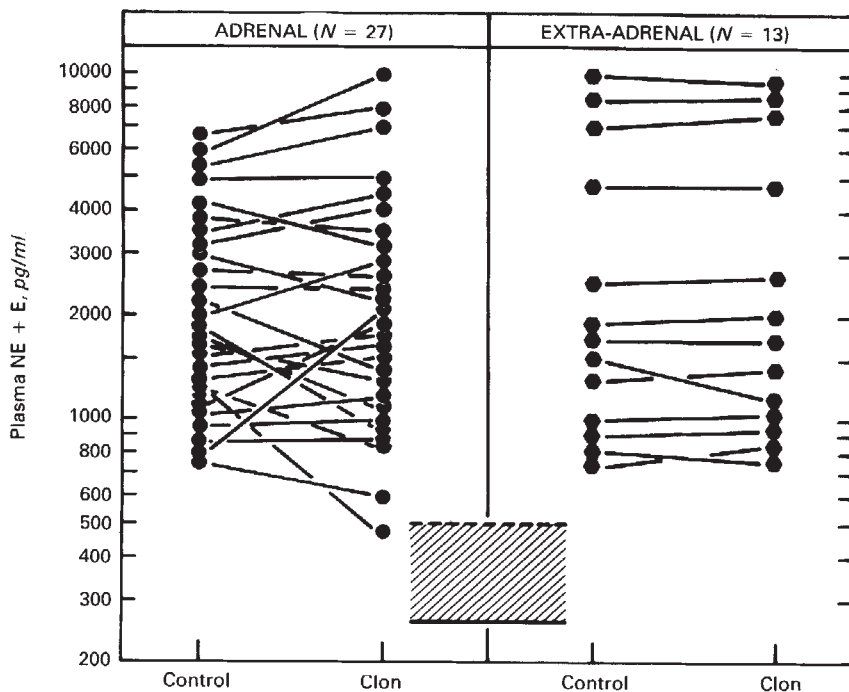


Fig. 7. The clonidine suppression test in pheochromocytoma. The cross-hatched area represents the mean (218 pg/ml) and the 95% upper confidence limits (500 pg/ml) of values obtained from 47 normal subjects. Values shown on the right of each panel represent the lowest values reached (at either 2 or 3 hours) after oral administration of 0.3 mg clonidine. (From Bravo EL: Adrenal medullary function, in *Diagnostic Endocrinology*, edited by MOORE WT, EASTMAN RC, Philadelphia, BC Decker, 1990, p 225.)

risky, the test can be performed with the patient receiving either a calcium antagonist or an alpha-adrenergic blocking drug.

In patients with moderate increases in plasma catecholamines (between 1000 and 2000 pg/ml), a suppression test should be employed. The clonidine suppression test is based on the capacity of clonidine, a centrally acting α_2 -adrenergic agonist, to suppress the release of neurogenically mediated catecholamine release [54]. The test is based on the principle that normal increases in plasma catecholamines are mediated through activation of the sympathetic nervous system. In patients with pheochromocytoma, however, the increases result from the diffusion of excess catecholamines from the tumor into the circulation, bypassing the normal storage and release mechanisms. Clonidine therefore should not suppress the release of catecholamines in patients with pheochromocytoma.

Figure 7 shows the results of the clonidine suppression test in patients with proven pheochromocytoma [44]. The results were compared with those of gender-matched and age-matched subjects with essential hypertension. Of the 40 patients, 27 had adrenal pheochromocytoma and 13 had extra-adrenal pheochromocytoma. After clonidine was administered, plasma catecholamine values fell below 500 pg/ml in all but one patient with essential hypertension. In contrast, in all but one patient with a pheochromocytoma, plasma catecholamine values remained above 500 pg/ml after clonidine administration. According to this experience, a normal clonidine suppression test should consist of a fall in the values of plasma norepinephrine plus epinephrine to a level below 500 pg/ml at 2 or 3 hours after the oral administration of 0.3 mg of clonidine. It is important to record blood pressure and heart rate responses and any effects related to the central nervous system, because certain signs and symptoms (such as drowsiness, thirst, and reductions in blood pressure and heart rate) reflect the completeness of the gastrointestinal absorption of clonidine.

Hypotension is a potential hazard of the clonidine suppression test, but symptomatic hypotension is not a problem in the untreated patient. All reported cases of severe hypotension have occurred in patients who were receiving antihypertensive medications or who had other conditions that would tend to augment the effects of any antihypertensive agents [55, 56]. In particular, the test should not be carried out in a patient with marked volume depletion. In addition, administration of any beta-adrenergic blocking agent should be discontinued approximately 48 hours before the test is performed. Clonidine has a potent vagotonic effect, so concomitant beta-adrenergic blockade could lead to marked bradycardia, further decreases in stroke volume and cardiac output, and severe hypotension. In addition, beta-adrenergic blockers can prevent the plasma-catecholamine-lowering effect of clonidine in a patient without pheochromocytoma because of the ability of such agents to interfere with hepatic clearance of catecholamines [57].

Tumor localization. Tumor localization not only confirms the diagnosis of pheochromocytoma but also assists the surgeon in planning the surgical strategy. Advances in noninvasive imaging techniques now provide a safe and reliable means of localizing pheochromocytomas anywhere in the body. Computed tomographic (CT) scanning is the most widely applied and accepted modality for the anatomic localization of pheochromocytoma [58]; it can accurately detect tumors larger than 1.0 cm. Because of its usual size, the tumor lends itself to visualization in virtually every instance in which the tumor is in the adrenal gland. Magnetic resonance imaging (MRI) is an alternative and has several advantages over CT scanning [59]. First, it requires no radiation exposure. Second, MRI lends itself to in-vivo tissue characterization; pheochromocytomas, unlike other benign tumors that have a low signal intensity, demonstrate a high signal intensity on T₂-weighted image [59,

Table 4. Accuracy of three imaging techniques in the localization and diagnosis of pheochromocytoma^a

| Parameter | CT (%) | MRI (%) | MIBG (%) |
|---------------------|--------|---------|----------|
| Sensitivity | 98 | 100 | 78 |
| Specificity | 70 | 67 | 100 |
| PV (+) ^b | 69 | 83 | 100 |
| PV (-) | 98 | 100 | 87 |

^a From Ref. 62.

^b PV = predictive value; based on a prevalence rate of 41% in this highly selected group of patients.

60]. Third, MRI can differentiate tumor masses from surrounding vascular tissues, eliminating the need for the intravenous administration of contrast material. It is the procedure of choice in pregnant women because it poses no danger to the fetus, and in patients with surgical clips, which interfere with CT. Scintigraphic localization with radioiodinated metaiodobenzylguanidine (MIBG) provides both anatomic and functional characterization of a tumor [61]. However, because this compound is actively concentrated in sympathomedullary tissue through the catecholamine pump, the administration of drugs that block the reuptake mechanism (tricyclic antidepressants, guanethidine, and labetalol) can give false-negative results. Phenoxybenzamine, prazosin, propranolol, and calcium antagonists do not interfere with MIBG uptake.

A comparison of the three imaging techniques is shown in Table 4. The data are from our prospective study involving 109 patients strongly suspected of having a pheochromocytoma [62]. All the patients had CT scanning and MIBG scintigraphy; 40 patients with tumor masses had, in addition, an MRI as a third localizing procedure. Forty-five patients had surgically proven pheochromocytoma, 20 had non-pheochromocytoma adrenal masses, and the remaining 44 were considered free of the disease after repeated biochemical testing and long-term followup. Based on the sensitivity, specificity, and predictive value of each of the three imaging techniques, the following sequence of localization is recommended. One should begin with an abdominal CT (including the pelvic region) with special attention to the adrenal gland. This is appropriate because 97% of pheochromocytomas are located in the abdominal area and 90% are intra-adrenal. In patients with demonstrable tumors, either MRI or MIBG scintigraphy should be performed next. Even if a primary adrenal pheochromocytoma is identified, MIBG can be useful in locating occult secondary or metastatic sites; such sites are present in approximately 10% of cases. Venous catheterization with selective sampling of blood for measurement of plasma catecholamine concentration at various sites along the superior and inferior vena cava is reserved for patients whose clinical and biochemical tests strongly suggest pheochromocytoma but in whom radiologic studies fail to locate the tumor [63].

Treatment

The goals of medical therapy are the treatment or prevention of cardiovascular complications and preparation of the patient for surgical intervention. The most frequently used therapeutic agent is phenoxybenzamine, a long-acting, non-competitive alpha-adrenergic blocker. Typically, treatment is initiated at 20

mg/day and increased stepwise to 80–100 mg/day as tolerated according to the severity of postural signs and symptoms (that is, hypotension, tachycardia, syncope, dizziness). Prazosin hydrochloride, a shorter-acting alpha-blocking agent, also has been used with some success [64]. Calcium antagonists are attractive agents because they are not only effective in controlling blood pressure, but they also are useful in managing cardiovascular complications [65]. They attenuate the pressor response to norepinephrine and can prevent catecholamine-induced coronary spasm and myocarditis. In addition, calcium antagonists have none of the complications associated with chronic use of alpha-adrenergic blockers. Beta-adrenergic blockers are added as needed to control tachycardia and arrhythmias. If beta blockade is absolutely contraindicated, either lidocaine or amiodarone can be used for serious rhythm disturbances [66]. Hypertensive crises can be managed with the parenteral administration of either phentolamine hydrochloride or sodium nitroprusside. Nicardipine, infused continuously at a rate of 2.5 to 7.5 $\mu\text{g}/\text{kg}/\text{min}$, prevents the severe hypertensive crises that usually occur during tumor manipulation at surgery, despite 3- to 85-fold increases in circulating catecholamines [67].

Before surgery, every attempt must be made to minimize the possibility of intraoperative severe hypertension consequent to catecholamine release. The best drug for this purpose is phenoxybenzamine. Its theoretical advantages relate to its ability to permit vascular volume repletion and to block alpha receptors non-competitively, making it difficult for catecholamines released during surgery to overcome the drug's blocking effect [68, 69]. Conventional wisdom dictates that blood pressure should be controlled with phenoxybenzamine for at least 4 weeks before the surgical procedure. The stringent criteria proposed for ensuring adequate preoperative preparation with alpha blockade are: (1) arterial pressure not greater than 160/90 mm Hg for 48 hours; (2) orthostatic hypotension present but not exceeding 80/45 mm Hg; (3) electrocardiogram free of ST-segment or T-wave changes for at least 2 weeks; and (4) no more than one premature ventricular contraction every 5 minutes [70].

However, a recent review of 60 of our patients with pheochromocytoma who underwent 63 surgical procedures disclosed that consistently successful surgical outcomes can be achieved without profound and prolonged alpha-adrenergic blockade preoperatively [71]. Of 29 patients who did not receive alpha-adrenergic blockade, there were no deaths or cerebral or cardiac complications. In addition, 80% of the patients required neither vasopressors nor vasodilators in the immediate postoperative period. Further, there were no differences in the length of stay in the postoperative acute care unit or in the duration of postoperative hospitalization between patients who received alpha blockers and those who did not. These favorable outcomes reflect the recent advances in anesthetic and monitoring techniques and the availability of fast-acting drugs capable of correcting sudden hemodynamic abnormalities.

Some postoperative complications require emphasis. The first is hypotension, which results from marked arterial and venous dilation consequent to the withdrawal of catecholamines and to the presence of diminished receptor sensitivity to endogenous catecholamines. Hypotension can be compounded

by previous postoperative alpha blockade and inadequate volume repletion; volume replacement, rather than vasopressors, is the primary treatment. Second, persistence of hypertension beyond 14 days after tumor excision should raise concern about residual or metastatic pheochromocytoma. If plasma catecholamines are still elevated at this time, the administration of clonidine (0.3 mg orally) will determine whether the hypertension is neurogenically mediated. Third, hypoglycemia can develop postoperatively because of excessive release of insulin previously inhibited by high levels of circulating catecholamines [72]. In some instances, hypoglycemia can manifest as persistent hypotension resistant to pressor agents and volume repletion.

Malignant pheochromocytoma

Malignant pheochromocytomas are, in general, slow-growing tumors. Evidence of malignancy can occur years after successful surgical excision of an apparently benign pheochromocytoma (median 5.6 years) [73]. The 5-year survival for patients with malignant pheochromocytoma is approximately 44%, but some patients have survived for 20 years or longer [73]. These tumors respond poorly to chemotherapy and to radiotherapy. The first goal of treatment is counteracting the effects of increased circulating catecholamines with alpha- or beta-adrenergic blocking drugs and/or calcium antagonists. The second is decreasing catecholamine synthesis by the tumor with alpha-methyltyrosine, a "false" catecholamine precursor that inhibits the rate-limiting enzyme in catecholamine synthesis, tyrosine hydroxylase [74]. Whenever possible, surgical excision or debulking of accessible tumors should be performed. This maneuver often helps decrease the levels of circulating catecholamines and provides easier control of blood pressure and other manifestations. Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine has been used in patients with advanced malignancy and is effective in suppressing the activity of some tumors [75]. However, the effect is only temporary. The administration of ¹³¹I-MIBG to ablate primary and metastatic sites has been used with some success, with remissions and palliation having been reported [76–78]. However, initial therapeutic responses have not produced significant long-lasting benefit even with repeated administration [79].

Questions and answers

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): In the slides you showed on clinically unsuspected pheochromocytoma, it appears that approximately one-third of the pheos showed up only at postmortem; that is, a high percentage were unsuspected during life. Does that mean that they were endocrinologically active but were missed, or were those tumors not endocrinologically active at all?

DR. BRAVO: The patients reported in the five articles were described as dying of cardiovascular complications usually associated with chronic hypertension. This indicates to me that the tumors were functional but that the diagnosis was not suspected before death.

DR. HARRINGTON: You briefly alluded to studies of receptor assays in animals that had been treated with norepinephrine and epinephrine. Have any studies examined receptors in patients? Is there a way of doing such studies after a pheochromocytoma

has been removed? What kind of down-regulation helps account for the 15% of patients who are normotensive?

DR. BRAVO: One study reported that catecholamine resistance in fat cells from pheochromocytomas might be due to (1) the formation of a hormone antagonist, which modulates the cellular response to continuous stimulation by catecholamines or (2) an adaptive increase in phosphodiesterase activity, which modulates cellular sensitivity [80]. In another study, Greenacre and Conolly found marked depression of lymphocytic beta-adrenoreceptor responsiveness in 4 patients with proven pheochromocytoma [81]. The clinical relevance of such findings to the pheochromocytoma patients with normal pressure despite having high circulating catecholamines remains to be established.

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): I was impressed with the high sensitivity and specificity of the symptomatic triad of sweating attacks, tachycardia, and headache in a hypertensive patient in diagnosing pheochromocytoma as reported in a French study you cited [2]. I was wondering how rigorously the diagnosis of pheochromocytoma was pursued in that study that allowed the authors to arrive at those sensitivity and specificity rates?

DR. BRAVO: In that particular study [2], the investigators screened 2585 hypertensive patients for pheochromocytoma by recording the symptoms known to be those most associated with the disease, that is, headaches, palpitations, and sweating attacks. Only 6.5% (168 patients) reported all three symptoms; 72.4% of the entire patient population reported one or another of these complaints. Of the (168) patients who reported all three symptoms, 5.9% (10 patients) had pheochromocytoma. The 24-hour urinary VMA was the sole confirmatory test used in this study. Urinary VMA has poor sensitivity, so it is possible that some pheochromocytoma patients without the triad were missed.

DR. MADIAS: Are there any known differences in the biology of tumors in patients who have sustained, as opposed to episodic, hypertension?

DR. BRAVO: Norepinephrine-secreting tumors usually are associated with sustained hypertension. Tumors that secrete relatively large amounts of epinephrine together with norepinephrine are associated with episodic hypertension. Pure epinephrine-secreting tumors can produce hypotension rather than hypertension. Large (>50 g) cystic pheochromocytomas often are asymptomatic because the secreted catecholamines are metabolized within the tumor, and therefore only a small amount, if any, of free catecholamines is released into the circulation. However, sudden catecholamine release, either spontaneous or provoked, can occur in these tumors and cause marked hypertension in an otherwise-normotensive patient. Small tumors (\leq 50 g) have a high metabolic turnover rate and release free catecholamines into the circulation, producing persistent signs and symptoms.

DR. MICHAEL MONAHAN (*Fellow in Nephrology, New England Medical Center*): Do you think the increased use of ambulatory blood pressure monitoring will help identify patients who have unsuspected pheochromocytoma by finding labile hypertension?

DR. BRAVO: I doubt it very much. Labile hypertension is so common that one would end up with very high false-positive

rates. The cost, time, effort, and low yield do not justify the use of ambulatory blood pressure monitoring to screen patients.

DR. MONAHAN: A group from Scotland described the use of a clonidine suppression test that measured urinary catecholamines in an overnight sample [82], but I haven't seen a followup on that test. Would this test add any diagnostic information to a serum clonidine suppression test?

DR. BRAVO: Neurogenic tone is normally reduced at night. The administration of clonidine at night might further suppress any remaining neurogenic activity. Thus, one might differentiate more reliably patients with pheochromocytoma from other hypertensives with increased neurogenic activity. The study you allude to reported that the test identified all 12 patients in whom pheochromocytoma was present. It is uncertain what diagnostic information this test adds to the standard clonidine suppression test, as the two tests were not directly compared in the same patient population. A major drawback of the test is that it requires hospitalization with carefully timed collection of urine samples.

DR. MADIAS: I would like to return to an earlier question. You have a referred population that has been subjected to an exhaustive workup for the diagnosis of pheochromocytoma. You should be able to derive from that population the sensitivity and specificity of combinations of clinical symptoms in diagnosing pheochromocytoma. Have you carried out this exercise? If so, how does your experience compare with the results of the French study you cited?

DR. BRAVO: Our patients were referred to us because of signs and symptoms strongly suggestive of pheochromocytoma. In this highly selected group, the prevalence rate of the disease was about 41%; thus, signs and symptoms alone were poor predictors of the presence of pheochromocytoma in this group. I have no idea how common the triad (of headaches, sweating attacks, and tachycardia) was in our patients. We haven't yet extracted that information from the charts. It will be interesting to find out.

DR. HARRINGTON: You mentioned that some of your patients had orthostatic hypotension. If I understood you correctly, tilt-table testing was not able to detect differences between those susceptible to hypotension and those not susceptible. My question is, were there any differences in norepinephrine or epinephrine blood levels between these two populations? If not, what's your speculation for the difference?

DR. BRAVO: There are no differences in the type of catecholamine secreted between patients susceptible to postural hypotension and those who are not. Neither are there any significant differences in intravascular volume or basal hemodynamic characteristics. Patients susceptible to postural hypotension are unable to increase their peripheral vascular resistance in response to head-up tilt. It is unclear why some patients have this hemodynamic abnormality and some do not. It would be interesting to determine whether tumor removal corrects this hemodynamic abnormality.

DR. MADIAS: In view of the "catecholamine hypothesis" for the pathogenesis of left-ventricular hypertrophy, do patients with pheochromocytoma express inordinate rates of echocardiographically diagnosed left-ventricular hypertrophy?

DR. BRAVO: As I mentioned, the prevalence of left-ventricular hypertrophy is no higher in patients with pheochromocytoma

than in patients with essential hypertension despite tenfold higher plasma catecholamine values in the former.

DR. HARRINGTON: Excluding patients with the MEA syndrome, do we know anything about what makes an individual more likely to develop a pheochromocytoma?

DR. BRAVO: No information is available on sporadic pheochromocytoma.

DR. HARRINGTON: Are there any HLA linkages with pheochromocytoma, or are we still in the dark?

DR. BRAVO: No HLA linkages have been reported.

DR. RONALD PERRONE (*Division of Nephrology, New England Medical Center*): In view of the differential effect of alpha- and beta-receptor stimulation on potassium movement into cells, do you find that plasma potassium correlates with the output of the tumor? Is it useful in any way?

DR. BRAVO: The acute systemic administration of epinephrine decreases extracellular potassium by shifting potassium intracellularly. Therefore, it has been postulated that pheochromocytoma patients might exhibit hypokalemia. However, in our experience it is rare to see hypokalemia in these patients, even in those with predominant epinephrine-secreting tumors. When it does occur, it usually is associated with secondary aldosteronism.

DR. HARRINGTON: As an inveterate potassium skeptic, I'm delighted to hear that!

DR. PAUL KURTIN (*Director, Dialysis Unit, Division of Nephrology, New England Medical Center*): In terms of the glucagon stimulation test, are there any practical things we should know? Should we be aware of any side effects when we administer the glucagon?

DR. BRAVO: The most important side effect associated with the glucagon stimulation test is the rapid rise in blood pressure, which is readily counteracted with phentolamine. Alternatively, the rise in blood pressure can be prevented by the administration of oral nifedipine 30 minutes before testing.

DR. MADIAS: We reported a patient with pheochromocytoma in whom severe lactic acidosis featured prominently in the clinical presentation [83]. High concentrations of epinephrine and norepinephrine have the potential for generating substantial hyperlactatemia on the basis of their metabolic and vasoconstrictor effects; both these influences result in overproduction and underutilization of lactate.

DR. BRAVO: Severe lactic acidosis is an uncommon manifestation of pheochromocytoma, but it is a potential complication in patients with severe peripheral vasoconstriction.

DR. ALAN MURRAY (*Fellow in Nephrology, New England Medical Center*): What approach do you advise for the evaluation of the asymptomatic adrenal mass identified by CT scan or MRI?

DR. BRAVO: All patients with incidental adrenal adenomas should have a thorough clinical evaluation to rule out malignancy and to determine whether the mass is functional. Parameters used to reach a therapeutic decision include: (1) tumor extent and size on CT, (2) hormonal assessment, and (3) MRI. I recommend the following guidelines: (1) Tumors should be resected if they are larger than 6.0 cm in diameter, if they are functional, or even if they are less than 6.0 cm diameter and nonfunctional but have an MRI T₂ signal intensity greater than 3.0 (adrenal versus liver). (2) Nonfunctional tumors less than 6.0 cm in diameter but which have an MRI T₂ signal intensity

greater than 1.4 but less than 3.0 should have cytologic aspiration before one decides on resection. (3) Nonfunctional tumors less than 6.0 cm in diameter with an MRI T₂ signal intensity less than or equal to 1.4 should have studies yearly and should be resected if they grow by 1.0 cm/year.

DR. KURTIN: Would you please elaborate on the relationship between the size of the tumor and symptoms, whether cystic tumors are more or less symptomatic compared with solid, and the relationship among patient age, tumor size, and symptoms?

DR. BRAVO: Small tumors (< 50 g) produce more symptoms than do large tumors (> 50 g). Children are more prone to develop dilated cardiomyopathy, have fewer malignant tumors and more extra-adrenal tumors, have greater bilaterality and multiplicity of tumors, and to have an increased incidence of multiple endocrine neoplasia and familial disease. Elderly subjects (> 65 years) have less pronounced clinical manifestations, perhaps because of decreased beta-adrenergic responsiveness associated with aging.

DR. GEETHA NARAYAN (*Division of Nephrology, St. Elizabeth's Hospital of Boston, Brighton, Massachusetts*): Is a level of plasma catecholamines that is greater than or equal to 2000 pg/ml diagnostic even when obtained as a random drawing, or only when it is obtained under carefully controlled conditions as generally recommended, that is, with the patient resting in a quiet room with an indwelling venous catheter for a few minutes before drawing the sample?

DR. BRAVO: Any plasma catecholamine value that is obtained under less than optimal, standardized conditions has very little clinical utility. It is important that one record the blood pressure at the time of blood sampling because if the plasma catecholamine level is less than 1000 pg/ml and the patient is markedly hypertensive, the diagnosis of pheochromocytoma is not likely. On the other hand, a plasma catecholamine level of 1000 pg/ml or less in the presence of a normal blood pressure does not rule out the disorder. As previously shown, however, blood pressure can be normal despite high circulating catecholamine levels in active pheochromocytoma.

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