Pheochromocytoma, Thyroid Disease, and Hyperparathyroidism

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Pheochromocytomas cause the most dramatic, life-threatening crises in all of endocrinology. The key to diagnosing pheochromocytoma is to suspect it, then to confirm it. Early recognition of the presence of pheochromocytoma is critical to avoiding significant morbidity and mortality. Once suspected, the diagnosis can be confirmed with biochemical testing in virtually all patients. Advances in localization techniques and the availability of various medical and surgical modalities have made successful management more promising than ever before.

PHEOCHROMOCYTOMA

Pathogenesis

Hypertension in pheochromocytoma is a complex process influenced by the sympathetic nervous system (SNS) and circulating catecholamines, and by alterations in cardiovascular response to catecholamines. Patients with pheochromocytoma can be normotensive or only moderately hypertensive despite high circulating levels of catecholamines. Several hypotheses have been proposed to explain the altered response of vascular smooth muscle. These include hypovolemia, increased production of vasodilator agents (such as dopa or prostaglandins), and down-regulation of α-1 adrenergic receptors.

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Despite the presence of several factors that tend to alter vascular smooth muscle responsiveness to circulating catecholamines, sudden and significant rises in arterial pressure are common in patients with pheochromocytoma. These episodes occur even when there are no significant changes in the circulating levels of catecholamines. This may be attributable, in part, to the fact that in pheochromocytoma, the SNS is intact and remains active. Informative clinical data come from studies of the effects of orally administered clonidine in patients with either essential hypertension or pheochromocytoma. Clonidine is a centrally acting α-2 agonist that inhibits neurally mediated catecholamine release. Clonidine decreases blood pressure (BP) in patients with pheochromocytoma and essential hypertension to the same degree. These results suggest that the SNS is intact in pheochromocytoma. In essential hypertension, the fall in BP is associated with decreases in circulating catecholamines, but in pheochromocytoma, there is no change in plasma catecholamine levels. The demonstration that BP in pheochromocytoma was lower despite high levels of circulating catecholamines suggests that the norepinephrine (NE) released from axon terminals of sympathetic postganglionic neurons is biologically more significant than circulating catecholamines. This difference could be related to the easier access of NE released from presynaptic sites to its effector site at effector cells.

Priority of Evaluation

Any patient who has manifestations even remotely suggesting a pheochromocytoma must be properly screened for pheochromocytoma. These manifestations include: 1) episodic symptoms of headaches, tachycardia, and diaphoresis (with and without

Table. Specificity and Sensitivity of Plasma-Free Metanephrines in the Diagnosis of Sporadic and Hereditary Pheochromocytoma

	Sporadic (n=138)	Hereditary (n=76)
Sensitivity (%)	99	97
Specificity (%)	82	96

Data derived from *JAMA*. 2002;287:1427–1434.

hypertension); 2) family history of pheochromocytoma or a multiple endocrine neoplasia syndrome; 3) incidental suprarenal or abdominal masses; 4) unexplained paroxysms of tachyarrhythmias, hypertension during intubation, unexplained hypotension after an operation; 5) adverse cardiovascular responses to ingestion, inhalation, or injection of certain drugs, including anesthetic agents, histamine, glucagon, tyramine, thyrotrophin-releasing hormone, adrenocorticotropic hormone, antidopaminergic agents, naloxone, succinylcholine chloride, phenothiazine, β blockers, guanethidine, tricyclic antidepressants, and mecholyl; and 6) spells or attacks occurring during exercise, twisting or turning of the torso, straining (Valsalva maneuver), coitus, or micturition.

There is no single clinical sign or symptom specific for pheochromocytoma; however, paroxysms of hypertension, severe headaches, palpitations, and diaphoresis occurring in clusters carry a high degree of specificity. Nevertheless, hypertension-related spells may be caused by a variety of clinical disorders unrelated to excess catecholamine production. In addition, only 48% of patients with pheochromocytoma have paroxysmal hypertension, 13% have normal BP, and 8% are completely asymptomatic. For these reasons, the definitive diagnosis of pheochromocytoma rests primarily on the demonstration of excessive and inappropriate catecholamine production.

Recommendations for Biochemical Testing

The availability of tests in any given center will necessarily determine the nature of the investigation in an individual patient and debate over the relative merits of various tests will continue. When performed under appropriate clinical settings, currently available tests can establish the diagnosis in greater than 95% of cases. For example, the combination of resting plasma catecholamines (NE + epinephrine [E]) ≥2000 pg/mL and urinary metanephrines (MNs) (normetanephrines + MN) ≥1.8 mg/24 h has a diagnostic accuracy of close to 98% in both sporadic and hereditary pheochromocytoma. In 109 confirmed cases in which all four tests were performed, we found (personal observations) that assays of plasma catecholamines and urinary MNs have the lowest false-negative rates (7%), and assays of urinary NE + E the next higher (14%). Urinary vanillylmandelic acid measurements have a high false-negative rate (41%) and should not be used for screening purposes; however, all four tests have excellent specificity when elevated. When available, the measurement of plasma-free MNs should be performed, especially when hereditary pheochromocytoma is suspected. It has a reported test specificity and sensitivity of 97% and 96%, respectively, in this patient population. In sporadic pheochromocytoma, the test has a reported sensitivity of 99%, but a specificity of only 82% (Table). The test specificity of urinary total MNs is higher at 89%.

Because pheochromocytomas are a heterogeneous group of hormone-secreting tumors with variable metabolism, it is prudent to recommend that for 100% diagnostic accuracy, multiple tests should be performed, combining all tests to achieve the highest specificity and sensitivity. Whether the measurement of plasma-free MNs should be the sole diagnostic test for pheochromocytoma remains to be determined.

Pharmacologic Testing

Basal concentrations of plasma catecholamines are usually several-fold higher in patients with pheochromocytoma than in other subjects, even taking into account normal variations due to postural change, exercise, and emotional arousal. When blood specimens are drawn under standardized conditions, a total plasma catecholamine ≥2000 pg/mL is diagnostic of pheochromocytoma; one <500 pg/mL essentially rules it out. Concentrations in between, especially those exceeding 1000 pg/mL in medically stable patients, suggest the need for further testing and confirmation by pharmacologic evaluation. In such cases, the goal is to separate pheochromocytoma patients with relatively low levels of biosynthetic activity from non-pheochromocytoma patients with increased sympathetic outflow. Either a stimulation test to provoke catecholamine secretion from a tumor with low secretory activity or a suppression test to inhibit sympathetic outflow is usually employed.

A provocative test is used (usually glucagon) when the clinical findings are highly suggestive of pheochromocytoma, but the BP is normal or slightly increased and plasma catecholamines are between 500 and 1000 pg/mL. If a sudden rise in BP is a concern, a calcium channel antagonist can be used to blunt the hypertensive response without

interference with plasma catecholamine determinations. A positive glucagon stimulation test requires at least a three-fold increase and/or more than 2000 pg/mL in total plasma catecholamines. The glucagon test has a high specificity (100%) but low sensitivity (81%). A suppression test (clonidine) is used in patients with plasma catecholamines between 1000 and 2000 pg/mL, with or without hypertension. A normal clonidine suppression test requires a fall of plasma catecholamines from baseline of at least 50% and below 500 pg/mL. When the test is performed in patients with plasma catecholamines ≥1000 pg/mL, the false-positive and false-negative rates are 2%.

Clinical Situations That May Alter Measured Levels of Catecholamines and Metabolites

Certain clinical situations may increase both plasma catecholamine and urine catecholamine metabolites to levels often seen in the presence of pheochromocytoma. These disorders include: 1) acute clonidine withdrawal; 2) acute alcohol withdrawal; 3) monotherapy with pure arterial vasodilator, hydralazine, or minoxidil; 4) acute myocardial ischemia or infarction; 5) acute cerebrovascular accident; 6) cocaine abuse; and 7) severe congestive heart failure (class III or IV). IV administered dopamine, oral dopaminergic drugs, and acute hypoglycemia produce significant elevations in plasma E concentrations. Drugs that inhibit central sympathetic outflow (e.g., clonidine, methyldopa, bromocriptine, and haloperidol) decrease plasma catecholamines in normal and hypertensive subjects, but have little effect on the excessive catecholamine secretion by pheochromocytoma. Blood samples should be collected using a large bore-scalp vein needle with patients fasting overnight and supine for at least 20 minutes before sampling.

Labetalol, a commonly used antihypertensive agent, can increase plasma catecholamines and urinary MNs determined by high-performance liquid chromatography to values seen in pheochromocytoma patients. In addition, a urinary metabolite of buspirone, an anxiolytic drug, is artificially measured as MN, resulting in marked increase in measured MN excretion.

The measurement of plasma-free MNs is influenced by many of the same stimuli and drugs that influence plasma catecholamines. In addition, acetaminophen has been shown to cause spurious increases in plasma-free MNs. Patients should be instructed to avoid taking this drug for at least 5 days before blood sampling.

Localization

Biochemical confirmation of the diagnosis should be followed by radiologic evaluation to locate the tumor, not the other way around. An understanding of the clinicopathologic behavior of these tumors may help localize them more precisely. Adrenal tumors are common in patients 60 years of age or older, are rarely associated with extraadrenal tumors, and may be bilateral when occurring in patients with familial syndromes. On the other hand, extra-adrenal tumors are predominant tumors in patients younger than 20 years old, are often multifocal, and rarely if ever are associated with familial syndromes. Thus, age and the presence or absence of family history are important considerations when determining the type and location of pheochromocytomas. Most tumors (95%) occur within the abdomen. The most common extra-adrenal locations are the superior and inferior para-aortic areas (75% of extra-adrenal tumors), the bladder (10%), the thorax (10%), and the head, neck, and pelvis (5%).

Computed tomography and magnetic resonance imaging are equally sensitive (98% and 100%, respectively) but have lower specificities of 70% and 67%, respectively. Metaiodobenzylguanidine has excellent specificity (100%) but sensitivity of only 78%. In the biochemically confirmed patient, magnetic resonance imaging provides the highest sensitivity among current imaging techniques. Pheochromocytomas appear hyperintense to the liver on T_2 weighted image, whereas benign tumors appear isointense. If no tumor is detected, metaiodobenzylguanidine scintigraphy should be employed. Arteriography and/or venous sampling for plasma concentrations are hardly ever indicated, except in situations where the clinical and biochemical evidence points strongly to pheochromocytoma, yet the noninvasive techniques persistently fail to localize the tumor sites.

Treatment Considerations

The management of pheochromocytoma has been dominated by efforts to prevent hypertensive episodes and associated complications and to diminish the magnitude of postoperative hypotension. For control of BP, the use of α-blocking agents has been advocated. The theoretical advantages of phenoxybenzamine (a nonspecific, α-blocking agent) relate to its ability to permit vascular volume repletion and to block α receptors that noncompetitively make it difficult for released catecholamines to overcome the blocking effect; however, phenoxybenzamine produces significant orthostatic hypotension and

reflex tachycardia. Moreover, it may prolong and contribute to the hypotension that follows removal of the tumor. Finally, despite adequate α blockade, total elimination of cardiovascular disturbances is seldom achieved, and significant elevations of BP are to be anticipated during manipulation of the tumor. Selective postsynaptic α-1 adrenergic receptor antagonists (prazosin, terazosin, and doxazosin) have been used to circumvent some of the disadvantages of phenoxybenzamine. This class of drugs does not produce reflex tachycardia and has a shorter duration of action, permitting more rapid adjustment of dosage. Labetalol, an α-adrenergic and β-adrenergic blocker, was reported effective in the control of BP and clinical manifestations associated with pheochromocytoma. Its safety has been questioned, however, because it has precipitated hypertensive crises in some patients.

Calcium channel blockers have also been successful in controlling BP in pheochromocytoma. These agents do not produce hypotension or orthostatic hypotension; therefore, they may be used safely in patients who are normotensive but have occasional episodes of paroxysmal hypertension. Calcium channel blockers are useful agents in managing cardiovascular complications because they may also prevent catecholamine-induced coronary vasospasm and myocarditis. In addition, they have none of the complications associated with chronic use of phenoxybenzamine and they can prevent the hypertensive response to provocative challenge. It is likely that they reduce arterial pressure by inhibiting NE-mediated increases in intracellular calcium in vascular smooth muscle, not by decreasing catecholamine synthesis in tumors.

Patients with pheochromocytoma have a high plasma volume requirement both during and after surgery. Expansion of intravascular volume either with plasma volume expanders or 2 L normal saline the evening before surgery with generous replacement of blood lost during the procedure greatly reduces the frequency and severity of postoperative hypotension. Persistence of hypotension may be caused by hemorrhage, persistent venodilation, inadequate volume repletion, or residual effects of preoperative α-adrenergic blockade with phenoxybenzamine. Fluids should be administered first, keeping in mind that these patients require large amounts of volume after tumor resection. Pressor agents are not usually effective in the presence of persistent hypovolemia. In addition, it is often difficult to withdraw vasopressors once they have been initiated.

The crisis of pheochromocytoma may be associated with signs and symptoms suggestive of acute myocardial infarction or congestive heart failure. In this situation, sodium nitroprusside should be used to obtain a gradual and controlled reduction of BP. The drug has a favorable hemodynamic effect because of its ability to decrease both preload and afterload. Beta-adrenergic blockade is added as needed to control tachycardia or tachyarrhythmias. Esmolol hydrochloride, an IV administered selective β-1 receptor antagonist, is used when β blockade of rapid onset and short duration is desired, or in critically ill patients in whom adverse effects of bradycardia, heart failure, or hypotension may necessitate rapid withdrawal of the drug. For treatment of supraventricular tachycardia, lidocaine may be used if β blockade is absolutely contraindicated. Alternatively, amiodarone hydrochloride may be useful.

HYPOTHYROID DISEASE

The prevalence of hypertension in hypothyroid patients is approximately three times that in age- and gender-matched euthyroid patients (14.8% vs. 5.5%, $p<0.01$). The degree of thyroid deficiency is associated with increases in diastolic BP. Restoration of normal thyroxine levels via thyroid hormone replacement therapy lowers BP in most hypothyroid patients.

The hypertension is associated with low cardiac index, low stroke volume, and increased systemic vascular resistance. Sympathetic nerve activity is increased (as reflected by increases in plasma NE and in muscle sympathetic nerve activity). Beta-adrenergic receptors are reported to be decreased while α-adrenergic responses are increased. These changes suggest an important role of the SNS activation to account for the increase in systemic vascular resistance and hypertension. After treatment, hemodynamic and neurohumoral abnormalities return to normal. Plasma renin activity is low and increases in response to adequate thyroxine replacement therapy.

HYPERTHYROIDISM

The prevalence of hypertension varies from 20% to 26%. Elevation of diastolic BP is uncommon. Uncomplicated disease is associated with increases in cardiac output, stroke volume, heart rate, mean ejection fraction, blood volume, widened pulse pressure, and decreases in systemic vascular resistance. Despite a hyperdynamic circulation, there is no evidence for increased SNS or adrenomedullary function. Increased β-adrenergic response accounts for the cardiovascular manifestations and the efficacy of β-adrenergic blockers in the management of hyperthyroidism. Plasma renin activity is increased; however, infusion of angiotensin II receptor antagonists does not reduce BP in hypertensive patients.

HYPERPARATHYROIDISM

Hypertension is common in hyperparathyroidism. Patients have increased arterial stiffness and impaired endothelium-mediated vasodilation, which may or may not improve after surgical relief of primary hyperparathyroidism. Moreover, no correlation is found between serum calcium or parathyroid hormone levels and BP. Hypertension usually does not recede after surgical relief.

SUGGESTED READING

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Should We Be Evaluating Blood Pressure Dipping Status in Clinical Practice?

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One of the unique aspects of ambulatory blood pressure (BP) monitoring is its ability to record the diurnal variation of BP. The normal pattern is a decrease of around 10%–20% during the night, which coincides with the hours of sleep, and is commonly referred to as dipping. This pattern is not universal, however, and in some people (about 25% of hypertensives), a non-dipping pattern is seen in which the normal nocturnal fall of pressure is absent. A further classification that some authors have used is to identify people who show an excessive fall of pressure (the extreme dippers whose nocturnal pressure falls more than 20%), or an actual increase (risers).[1] A major question at the present time is the pathological significance of the differences in these patterns, and whether identification of them has clinical relevance. There are several potential ways by which the non-dipping pattern could affect prognosis. First, if the daytime pressure is used as the reference level, non-dippers by definition are exposed to a higher BP load over 24 hours than dippers, which could result in more target organ damage and a more adverse clinical outcome. So if the issue is whether the pattern of the diurnal rhythm of BP matters, comparisons should be made between dippers and non-dippers who have the same 24-hour level of BP. Second, non-dippers will have a more modest early morning surge of BP than dippers. An excessive morning rise is now thought to have pathogenic significance, so by this criterion non-dippers should be at reduced risk.[2] Third, if an excessively low BP during the night is associated with ischemic damage to various organs, non-dippers are less likely to be exposed to this than dippers. The point of these considerations is that if non-dipping does have independent pathological significance, it may be limited to certain specific end points.

The issue is becoming of practical importance because dipping and nighttime BP can only be assessed by 24-hour BP monitoring. In contrast, a good estimate of the average daytime pressure can be provided by self- or home-monitoring. Home monitors are cheaper and more widely available than 24-hour monitors.

Another issue is how the nocturnal BP changes should be expressed. Dipping and non-dipping is a binary classification, and while this may be useful for therapeutic decision making, the chosen limits separating dippers from non-dippers are quite arbitrary. This, of course, is true of just about any definition based on BP levels.

WHAT ARE THE CAUSES OF THE NON-DIPPING PATTERN?

Since all definitions of dipping and non-dipping rely on some measure of the differences between daytime and nighttime pressures, it is clear that both components will influence the classification. The nocturnal BP is mainly influenced by two factors: assuming the horizontal posture, and going to sleep. Likewise, the daytime BP level will depend on posture and activity. This has been well illustrated in a 2-day study combining activity monitoring and BP monitoring, when subjects were relatively active during 1 day and inactive during

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