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Pheochromocytoma: Current Perspectives in the Pathogenesis, Diagnosis, and Management

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ABSTRACT

Pheochromocytomas (pheo) cause the most dramatic, life-threatening crises in all of endocrinology. A proper screening for pheo must be performed in any patient who has: 1) episodic headaches, tachycardia, and diaphoresis; 2) family history of pheo or multiple endocrine neoplasia; 3) incidental suprarenal mass; 4) paroxysms of tachyarrhythmias or hypertension; 5) adverse cardiovascular responses to anesthetic agents, histamine, phenothiazine, tricyclic antidepressants, etc); and 6) spells occurring during exercise, straining, etc. The key to diagnosing pheo is to suspect it, then to confirm it. Early recognition of its presence is critical to avoiding significant morbidity and mortality. Once suspected, the diagnosis can be confirmed with biochemical testing in virtually all patients. The combination of resting plasma catecholamines $\geq$2000 pg/mL and urinary metanephrines $\geq$1.8 mg/24h has a diagnostic accuracy of 98% in both sporadic and hereditary pheos. When available, measurement of plasma free metanephrines should be performed especially in hereditary pheos. Provocative (glucagon) and suppression tests (clonidine) may be necessary when baseline measurements are inconclusive. CT and MRI are equally sensitive for localization (98% and 100%, respectively), but have lower specificities (70% and 67%). MIBG is 100% specific, but less sensitive (78%). The availability of various medical (selective alpha-1- and beta-adrenergic receptor antagonists, calcium channel blockers) and surgical modalities have made successful management more promising than ever before. **(Arq Bras Endocrinol Metab 2004;48/5:746-750)**

Keywords: Pheochromocytoma; Hypertension; Catecholamines; Metanephrines; Adrenergic receptor antagonists; Calcium channel blockers

RESUMO

Feocromocitoma: Perspectivas Atuais em Patogênese, Diagnóstico e Manuseio

Feocromocitoma (feo) causa a mais dramática crise com risco de morte em toda a endocrinologia. Screening apropriado deve ser feito em qualquer paciente que tenha: 1) episódios de cefaléia, taquicardia e sudorese; 2) história familiar de feo ou neoplasia endócrina múltipla; 3) massa adrenal incidental; 4) paroxismos de taquiarritmia ou hipertensão; 5) resposta cardiovascular adversa a agentes anestésicos, histamina, fenotiazina, antidepressivos tricíclicos, etc); e 6) crises durante exercício, esforço, micção, etc. A chave para o diagnóstico do feo é: primeiro suspeitá-lo e depois confirmá-lo. O reconhecimento precoce de sua presença é crítico para se evitar maior morbidade e mortalidade. Quando suspeitado, o diagnóstico pode ser confirmado por testes bioquímicos em todos os pacientes. A combinação de catecolaminas plasmáticas em repouso $\geq$2000 pg/mL e metanefrinas urinárias $\geq$1,8 mg/24h tem acurácia diagnóstica de 98%, tanto no feo esporádico como hereditário. Quando disponível, metanefrinas plasmáticas livres devem ser dosadas, especialmente na suspeita de feo hered-

itário. Testes provocativos (glucagon) e supressivos (clonidina) podem ser necessários quando a avaliação bioquímica basal é inconclusiva. TC (98%) e RM (100%) são igualmente sensíveis para localização, mas têm baixa especificidade (70% e 67%). MIBG é 100% específica, mas menos sensível (78%). A disponibilidade de vários medicamentos (antagonistas seletivos dos receptores adrenérgicos alfa-1 e beta e bloqueadores do canal de cálcio) e de modalidades cirúrgicas têm tornado o manuseio bem sucedido mais promissor do que nunca. **(Arq Bras Endocrinol Metab 2004;48/5:746-750)**

Descritores: Feocromocitoma; Hipertensão; Catecolaminas; Metanefrinas; Antagonistas do receptor adrenérgico; Bloqueadores de canal de cálcio

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.

PATHOGENESIS

The 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 alpha-1 adrenergic receptors.

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 alpha-2 agonist that inhibits neurally mediated catecholamines release. Clonidine decreases blood pressure in patients with pheochromocytoma to the same degree. These results suggest that the SNS is intact in pheochromocytoma. In essential hypertension, the fall in blood pressure is associated with decreases in circulating catecholamines, but in pheochromocytoma, there is no change in plasma catecholamine levels. The demonstration that blood pressure in pheochromocytoma was lowered despite 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 difference could be related to the easier access of norepinephrine 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 hypertension); 2) family history of pheochromocytoma or a multiple endocrine neoplasia (MEN) syndrome; 3) incidental suprarenal or abdominal masses; 4) unexplained paroxysms of tachyarrhythmias, hypertension during incubation, 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, adrenocorticotrophic hormone, antidopaminergic agents, naloxone, succinylcholine chloride, phenothiazine, beta-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 blood pressure, 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 [norepinenephrine (NE) plus epinephrine (E)] ≥ 2000 pg/mL and urinary metanephrines (NMN + 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 whom all four tests were performed, we found (personal observations) that assays of plasma catecholamines and urinary metanephrines have the lowest false-negative rates (7%), and assays of urinary NE + E, the next higher (14%). Urinary VMA 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 metanephrines 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%. The test specificity of urinary total metanephrines is higher at 89%.

Because pheochromocytomas are a heterogeneous group of hormone-secreting tumors with variable metabolism, it is prudent to recommend that for100% diagnostic accuracy, multiple tests should be performed combining tests to achieve the highest specificity and sensitivity. Whether the measurement of plasma free metanephrines 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 (usually glucagon) is used when the clinical findings are highly suggestive of pheochromocytoma, but the blood pressure is normal or slightly increased and plasma catecholamines are between 500 and 1000 pg/ml. If a sudden rise in blood pressure 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 3.0-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 catecholamines 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, 7)severe congestive heart failure, class 3 or 4. Intravenously 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, 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 nee-

dle 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 HPLC 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 metanephrines 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 metanephrines and subjects should be instructed to avoid taking this drug for at least 5 days prior to 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 or older, are rarely associated with extraadrenal tumors and may be bilateral when occurring in patients with familial syndromes. On the other hand, extraadrenal tumors are predominant tumors in patients younger than 20 years old, are often multifocal and rarely, if ever, 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 extraadrenal locations are the superior and inferior paraortic areas (75% of extraadrenal tumors), the bladder (10%), the thorax (10%), and the head, neck and pelvis (5%).

CT and MRI are equally sensitive (98% and 100%, respectively), but have lower specificities of 70% and 67%, respectively. MIBG has excellent specificity (100%), but sensitivity of only 78%. In the biochemically-confirmed patient, MRI 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, MIBG 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 blood pressure, the use of alpha-blocking agents has been advocated. The theoretical advantages of phenoxybenzamine (a nonspecific, alpha-blocking agent) relate to its ability to permit vascular volume repletion and to block alpha receptors that noncompetitively make it difficult for release 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 alpha-blockade, total elimination of cardiovascular disturbances is seldom achieved, and significant elevations of blood pressure are to be anticipated during manipulation of the tumor. Selective postsynaptic alpha-1 adrenergic receptor antagonists (prazosin, terazosin, 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 and decreasing the alpha-adrenergic and beta-adrenergic blocker, was reported effective in the control of blood pressure 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 blood pressure in pheochromocytoma. These agents do not produce hypotension or orthostatic hypotension and therefore 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 norepinephrine-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 alpha-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 MI or congestive heart failure. In this situation, sodium nitroprusside should be used to obtain a gradual and controlled reduction of blood pressure. 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 intravenously administered selective beta-1 receptor antagonist, is used when beta-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 beta-blockade is absolutely contraindicated. Alternatively, amiodarone hydrochloride may be useful.

SUGGESTED READINGS

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