Diagnosis of a Pheochromocytoma

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ABSTRACT: Although rare, pheochromocytomas are potentially lethal tumors. Thus, it is important that physicians be able to diagnose these tumors. The definitive diagnosis of a pheochromocytoma rests on demonstrating catecholamine overproduction. Once the diagnosis is established, computed tomography scan, magnetic resonance imaging, and metaiodobenzylguanidine studies are utilized for localizing the tumor. This paper reviews the biochemical and radiologic studies useful for evaluating a patient for the possibility of a pheochromocytoma. **KEY INDEXING TERMS:** Pheochromocytoma; Adrenal tumor; Hypertensive crisis. **[Am J Med Sci 2005;329(1):18–21.]**

Pheochromocytomas are tumors that arise from the chromaffin cells of the adrenal medulla. They are an uncommon cause of hypertension; about 1 in 1000 people with hypertension has a pheochromocytoma.[1] Although they have only about a 5% incidence of malignancy, these tumors are associated with a high risk of morbidity and mortality from cardiovascular complications.[1,2] A lethal hypertensive paroxysm is a well known catastrophe for which people with a pheochromocytoma are potentially at risk. Thus, recognition that a patient has a pheochromocytoma is critical because surgical excision of the tumor can be a life-saving procedure.

A sporadic pheochromocytoma is usually suspected because of signs and symptoms of excessive catecholamines produced by the tumor. The classic triad of symptoms is headache, palpitations, and sweating.[3] This symptom complex in someone with hypertension has a high specificity (93.8%) and sensitivity (90.9%) for the diagnosis of a pheochromocytoma.[3,4] In some patients with a pheochromocytoma, however, the tumor may not produce signs or symptoms.[5,6] Detection of an asymptomatic pheochromocytoma is especially likely in patients who are undergoing routine screening for a pheochromocytoma as part of the workup of an incidentally found adrenal mass or a familial syndrome that predisposes to a pheochromocytoma such as multiple endocrine neoplasia type 2, von Hippel-Landau disease, or neurofibromatosis.

Diagnosis of a pheochromocytoma is confirmed by biochemical evidence in the plasma or urine of catecholamine production by the tumor.[2] Radiologic studies are then used to localize the pheochromocytoma.

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Biochemical Diagnosis of a Pheochromocytoma

Establishing the diagnosis of a pheochromocytoma requires biochemical evidence of catecholamine overproduction. Catecholamines can undergo metabolism from norepinephrine and epinephrine to normetanephrine and metanephrine, respectively, by the intracellular enzyme system catechol-o-methyl transferase.[1] Thus, the diagnosis of a pheochromocytoma could be confirmed by the presence of increased concentrations of either catecholamines or their metabolites.

Biochemical screening has usually involved measurement of 24-hour urine excretion of catecholamines and total metanephrines.[2] In the past, plasma catecholamines were also advocated as a screening test.[1] More recently, plasma metanephrine measurements have been introduced into the biochemical evaluation of a pheochromocytoma.[7,8] Fractionated plasma metanephrines appear to be a product of catecholamine metabolism within a pheochromocytoma. They have been found to have high sensitivity for detecting a pheochromocytoma.[7,8] It is thought that measurements of plasma metanephrines are diagnostically superior to measurements of serum catecholamines because levels of these metabolites reflect a universal feature of pheochromocytomas, continuous metabolism of catecholamines within the tumor, whereas catecholamine release is more variable.[1,8]

A direct comparison of plasma free metanephrines with biochemical tests commonly used to diagnose a pheochromocytoma was made by Lenders et al[8] in a large group of subjects tested because of signs or symptoms suggesting a pheochromocytoma or risk factors for a pheochromocytoma. The sensitivity was highest for plasma free metanephrines (99%). Other

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sensitivities were 97% for urine fractionated metanephrines, 86% for urine catecholamines, 84% for plasma catecholamines, 77% for urine total metanephrines, and 64% for urine vanillylmandelic acid.[8] Specificity was highest for urine vanillylmandelic acid (95%). Other specificities were as follows: 93% for urine total metanephrines, 89% for plasma free metanephrines, 88% for urine catecholamines, 81% for plasma catecholamines, and 69% for urine fractionated metanephrines.[8] Sawka et al[7] compared diagnostic efficacy of fractionated plasma metanephrine measurements with measurements of 24-hour urine total metanephrines and catecholamines. They confirmed the high diagnostic sensitivity of fractionated plasma metanephrines (97% compared with a sensitivity of 90% for urine total metanephrines and catecholamines), and they reported a high specificity for the urine studies (98% versus 85% for plasma fractionated metanephrines).[7]

It is clear that fractionated plasma metanephrines are highly sensitive (97–99%) for diagnosing a pheochromocytoma. Normal levels of fractionated plasma metanephrines, even in a patient at high risk for having a pheochromocytoma, would effectively exclude a pheochromocytoma.[8] Such good sensitivity may be at the risk of a lower specificity (85–89%). Because pheochromocytoma is such a rare tumor, the frequency of false-positive test results could be a drawback to measuring fractionated plasma metanephrines in everyone being tested. Because of the low prevalence of pheochromocytoma in patients tested, false-positive results with this test could exceed true-positive results.[7] This in turn would lead to problems as physicians try to sort the patients who truly have a pheochromocytoma from those who do not.

Sawka et al[7] have recommended fractionated plasma metanephrines as the test of choice in patients at high risk for having a pheochromocytoma, such as those with a predisposing familial syndrome, vascular adrenal mass, or prior history of a pheochromocytoma. In the more common clinical setting of looking for a sporadic pheochromocytoma, they suggest that 24-hour urine metanephrines and catecholamines may provide an adequate sensitivity with a lower rate of false-positive results.[7] The study of Sawka et al did not include measurement of urine fractionated metanephrines. A spectrophotometric technique was used to measure urine total metanephrines. This method has been replaced in many laboratories by a technique involving liquid chromatography that allows for measurement of normetanephrine and metanephrine individually (ie, fractionated metanephrines).[9] Therefore, the sensitivities and specificities may not be directly applied to those using the newer assay.

A combination of tests has been suggested as a way to overcome the problem of false-positive results with fractionated plasma metanephrines.[10,11] Eisenhofer et al[10] have shown the benefit of using clonidine suppression as a confirmatory test in patients with elevated plasma free metanephrines. Sawka et al[11] evaluated several algorithms for screening for a pheochromocytoma. They suggested that a protocol incorporating the measurement of 24-hour urine metanephrines and catecholamines in patients with "borderline" elevations of fractionated plasma metanephrines was the least costly approach and, at the same time, had a reasonable level of sensitivity for diagnosing a pheochromocytoma.

Table 1. Drugs that May Interfere with Measurement of Catecholamines and Metanephrines[1,2,20,23]

Acetaminophen
Benzodiazepines
Buspirone
Catecholamines and related drugs
Diuretics
Levodopa
Sympathomimetics
Tricyclic antidepressants
Vasodilators

Interference with Test Results

Various methods have been used for measuring catecholamines and their metabolites. Sensitivity and reliability are best with techniques involving high-pressure liquid chromatography/mass spectrometry methods.[2,12] Quantification with these newer methods is less likely to have interference from drugs that a patient may be taking than are the older colorimetric or fluorometric methods. Nevertheless, drug-induced alterations of test results are perhaps the most common cause of false-positive or erroneous interpretations of catecholamine measurements.

Drug influence can occur by several mechanisms: the drug can interfere with the assay in vitro; the drug can directly cause changes in catecholamine levels by affecting the synthesis, release, or metabolism of catecholamines; or the drug can contain catecholamines that are then measured in the assay (Table 1).

Drugs with prolonged half-lives, such as tricyclic antidepressants and levodopa, may need to be discontinued for 2 to 3 weeks before accurate measurements can be made.[13] Caffeine and nicotine both increase catecholamine levels and should be avoided.[8]

Biologic variation in plasma catecholamine concentrations can be substantial and can affect test results.[1] For example, plasma epinephrine increases as much as 100-fold during hypoglycemia; norepinephrine increases two- to threefold when a person stands; and plasma levels of both catecholamines increase at least several-fold during vigorous exercise.[1] A significant event such as an acute myocardial infarction causes a marked elevation of plasma catecholamines.[14,15] More subtle elevations also occur with chronic diseases such as hypothyroidism, congestive heart failure, and chronic obstructive pulmonary disease.[1] Concentra-

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tions of catecholamines can increase with alcohol or clonidine withdrawal, essential hypertension, or anxiety.[12–14,16,17]

Catecholamine and catecholamine metabolite excretions are subject to the same sources of biologic variations that apply to plasma catecholamine levels; however, because these variations in catecholamine release are usually brief, their effect on 24-hour urine excretion is relatively small.[1] Major stress should be avoided during these collections, as conditions known to produce stable elevations in plasma catecholamine levels will produce corresponding elevations in urine catecholamine and metabolite excretion.[1] Although plasma free metanephrines are less sensitive to changes in sympathoadrenal activity than are levels of parent amines, these metabolites are influenced by many of the same stimuli and drugs that influence plasma catecholamines.[8]

Measurement of urine catecholamines and metanephrines may not be valid in patients with advanced renal insufficiency.[12] In addition, plasma catecholamines may be affected. It would be normal for patients on hemodialysis to have plasma norepinephrine and dopamine levels three times and two times, respectively, the upper limit of normal.[12] Therefore, concentrations of plasma catecholamine levels more than three times the upper limit of normal in patients with renal failure would be suspicious for a pheochromocytoma.[12]

Sampling Collection

Urine samples for catecholamine determinations are commonly collected in refrigerated containers to which HCl has been added because catecholamines are more stable at low temperature and low pH.[1] Urine samples for metanephrines do not need to be acidified, but the analytic methods are compatible with this form of collection if catecholamines are also to be measured.[1] The creatinine level should also be measured to help detect an inadequate collection.

For plasma measurements, blood must be drawn after an overnight fast and after at least 15 minutes in the supine position.[1] Because the stress of the venipuncture elevates catecholamines, some practitioners advocate sampling blood through an indwelling catheter that has been in place for 20 minutes.[1,12]

Radiologic Studies

Once biochemical testing has established the possibility of a pheochromocytoma, magnetic resonance imaging (MRI) or computed tomography (CT) scan of the abdomen should be done to locate the tumor.[12]

Pheochromocytomas are usually located within the adrenal gland; about 10% of the tumors are located outside of the adrenal gland.

Most pheochromocytomas within the adrenal gland have a diameter of at least 3 cm.[18] CT scan can detect an adrenal pheochromocytoma that is at least 0.5 to 1.0 cm in diameter.[18] The CT scan has a sensitivity of greater than 90% for detecting a pheochromocytoma in the adrenal gland; however, its sensitivity for detecting an extra-adrenal pheochromocytoma is lower.[19]

Table 2. Drugs that May Interfere with MIBG Study[20,21,23]

Calcium channel blockers
Cocaine
Guanethidine
Labetolol
Reserpine
Sympathomimetics
Tricyclic antidepressants

MIBG, Metaiodobenzylguanidine.

Scintigraphy using metaiodobenzylguanidine (MIBG) provides information complementary to CT scan and MRI images. MIBG is a guanethidine analogue that resembles norepinephrine in its molecular structure.[20,21] Iodine isotopes, ^{131}I or ^{123}I, are used for radioactive labeling.[18] Like norepinephrine, MIBG is taken up by sympathomedullary tissues, mainly by a noradrenergic transporter system, and then actively transferred into catecholamine storage vesicles.[15,21] When these vesicles are present in sufficient amounts, as with a pheochromocytoma, scintigraphic images from the distribution of MIBG can be detected.[13] The MIBG scan has a sensitivity of 77% to 90% and specificity of 88% to 99% for localizing a pheochromocytoma.[12,18–20] Thus, it is superior in specificity to other radiologic studies; however, it is not a sensitive enough test to exclude a pheochromocytoma.[19]

False-positive results with an MIBG scan have rarely been reported.[18,22] False-negative results are a much more common problem. Reasons for a false-negative test result could include rapid turnover of radionuclide within the tumor and variability in the tumor's capacity to take up the MIBG.[22] In addition, drugs that block the uptake or deplete the contents of the storage vesicles can interfere with the distribution of the MIBG and cause a false-negative result[13,18,20,23] (Table 2).

Although labetalol does interfere with the MIBG study, other alpha-blocking and beta-blocking drugs do not appear to affect the distribution of MIBG.[21] The effect of labetalol on reducing a pheochromocytoma's uptake of MIBG persists for 36 hours after its discontinuation.[21] Thus, it is recommended that labetalol be discontinued at least several days before the patient undergoes study with MIBG.[14,21]

Calcium channel blockers are among other drugs that interfere with the MIBG scan. The mechanism for this is unknown.[21]

Some practitioners have recommended that intravenous contrast material in general should not be given to a patient suspected of having a pheochromocytoma without prior treatment with alpha-blockade.[24,25] The concern is that the intravenous

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contrast material could stimulate a rise of plasma epinephrine levels and potentially precipitate a hypertensive crisis.[25]

Prior to the availability of the CT scan, angiography was often performed to evaluate a suspected pheochromocytoma.[26,27] This procedure had significant morbidity and mortality when done in someone with a pheochromocytoma.[26,27] It was believed that trauma to the tumor from the procedure or contrast material entering the tumor could stimulate an outpouring of catecholamines from the tumor, causing wide fluctuations of blood pressure or a hypertensive crisis.[26,27] Preparation of patients with the alpha-blocker phenoxybenzamine prior to the procedure reduced the occurrence of such complications.[27] Although hypertensive crisis has been reported after angiography, no report could be found suggesting that intravenous contrast for a CT scan has caused such a problem.[26,28] In addition, plasma catecholamine levels did not rise in a series of patients with a pheochromocytoma who received intravenous nonionic contrast material.[18] Thus, contrast-enhanced CT scan does not appear to increase the risk of hypertensive crisis.[18]

Summary

Making the diagnosis of a pheochromocytoma depends on having a clinical suspicion for it and then confirming the diagnosis biochemically. Measurement of plasma free metanephrines is the biochemical test with the highest sensitivity for diagnosing a pheochromocytoma. However, physicians need to be aware of the possibility of false-positive results with this test, particularly when testing someone who is at low risk for having this tumor. It is important for the physician to consider the circumstances under which the testing was done and the drugs the patient was taking during the testing, as these factors can influence test results. The CT scan, MRI, and MIBG studies all have utility in localizing a pheochromocytoma. When interpreting MIBG scan results, the physician must keep in mind the possibility of certain medications interfering with the results.

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