ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What is the best diagnostic approach when pheochromocytoma is suspected?

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A: The definitive diagnosis of pheochromocytoma rests primarily on the demonstration of excessive catecholamine production, best achieved with a resting plasma catecholamine assay plus a total urinary metanephrine assay, since no single clinical sign or symptom is pathognomonic. This is best followed by magnetic resonance imaging (MRI) to locate the tumor.

COMMON SIGNS AND SYMPTOMS

Because missing the diagnosis can have tragic consequences, such as stroke or death, any patient with manifestations even remotely suggesting pheochromocytoma must be properly screened for it. Features that should raise suspicion include:

- Paroxysmal symptoms consisting of hypertension, intense headaches, diaphoresis, tachycardia, and palpitations
- A paradoxical response to antihypertensive therapy, especially to beta-blockers or guanethidine
- A hypertensive response to anesthesia, naloxone, metoclopramide, thyrotropin-releasing hormone (used as a diagnostic agent), tricyclic antidepressants, glucagon, micturition, or pregnancy
- Indeterminate suprarenal masses noted on a computed tomographic scan of the abdomen
- A hyperdynamic circulatory state
- Malignant or refractory hypertension
- A family history of either pheochromocytoma or multiple endocrine neoplasia (MEN)
- Mucocutaneous lesions (neurofibromatosis).

However, only 48% of patients have paroxysmal hypertension, 13% have normal blood pressure, and 8% have no symptoms.

BIOCHEMICAL TESTS

Biochemical testing, if done carefully, can establish the diagnosis in more than 95% of cases. Demonstration of resting plasma catecholamine (norepinephrine and epinephrine) levels greater than 2,000 pg/mL, urinary total metanephrine levels greater than 1.8 mg/24 hours, and urinary norepinephrine levels greater than 156 µg/24 hours suggests the diagnosis of pheochromocytoma.

Combining assays increases sensitivity

Because of the serious consequences of missing the diagnosis, a test with the lowest possible false-negative rate should be used. Currently, this means using the combination of a resting plasma catecholamine assay and a total urinary metanephrine assay, which has a false-negative rate of 2.7%. Taken individually, plasma catecholamine and total urinary metanephrine assays have a false-negative rate of 7%, urinary norepinephrine and epinephrine assays a rate of 14%, and the urinary vanillylmandelic acid assay a rate of 41%.

Patients with plasma catecholamine levels between 1,000 and 2,000 pg/mL and urinary metanephrine levels between 1.3 and 1.8 mg/24 hours may have neurogenically mediated catecholamine release and will require a suppression test (eg, with oral clonidine). This will cause these levels to fall by about 50% from baseline in patients with neurogenically mediated catecholamine release, but not in patients with pheochromocytoma.

Patients who are highly suspected of having pheochromocytoma and who have plasma catecholamine levels of 1,000 pg/mL or less and urinary metanephrine levels of 1.3 mg/24

The diagnosis rests on proving catecholamine overproduction

hours or less require a provocative test (eg, with glucagon injection). This will cause plasma catecholamines to rise by two and a half fold if pheochromocytoma is present. Blood pressure may or may not change.

Patients with overt symptoms and normal or slightly increased plasma catecholamine and 24-hour urinary metanephrine values are unlikely to have pheochromocytoma. On the other hand, some patients with pheochromocytoma may remain asymptomatic despite high plasma catecholamine and 24-hour urinary metanephrine values. Clinical judgment dictates whether other biochemical tests should be performed to confirm or rule out other conditions that mimic the disease.

DIFFERENTIAL DIAGNOSIS

Other conditions in which both plasma catecholamine and urinary metanephrine levels may be elevated to a degree usually encountered in pheochromocytoma include:

- Acute clonidine withdrawal
- Acute alcohol withdrawal
- Vasodilator therapy with hydralazine or minoxidil
- Acute myocardial ischemia or infarction
- Acute cerebrovascular accident
- Cocaine abuse
- Severe congestive heart failure

Intravenous dopamine, dopaminergic drugs, and acute hypoglycemia can produce significant elevations of plasma epinephrine (labetalol can increase levels for 7 to 10 days)

Once biochemical tests are positive, MRI is the next step

Phenylpropanolamine abuse can increase levels of urinary metanephrines (assayed by high-performance liquid chromatography) but not of plasma catecholamines (assayed by the radioenzymatic technique).

However, patients should not undergo localization procedures unless pheochromocytoma has been confirmed by biochemical testing and other conditions that can increase catecholamine levels have been ruled out.

CONFIRMING THE DIAGNOSIS

Once biochemical testing suggests pheochromocytoma, MRI is the next step. It provides the highest sensitivity of current imaging techniques. If MRI detects no tumor in the neck, chest, or pelvis, then metaiodobenzylguanidine (MIBG) scintigraphy should be used. In rare instances, the octreotide scan is positive when MIBG scintigraphy is negative. Arteriography and vena cava sampling for catecholamine concentrations are rarely indicated.

SUGGESTED READING

Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. Endocr Rev 1994; 15:356–368.

Bravo EL, Gifford RW Jr, Manger WM. Adrenal medullary tumors: pheochromocytoma. In: Mazzaferri EL, Samaan NA, editors. Endocrine Tumors. Boston: Blackwell Scientific Publishers, 1993:1426–1448.

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