

Screening for Endocrine Hypertension

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Hypertension is one of the most common reasons for patient visits.¹ According to the US Preventive Services Task Force, more than 70 million individuals older than 20 have hypertension, which is defined as a blood pressure (BP) of $\geq 130/85$ mm Hg.² Essential hypertension is the most common form of this condition; most affected patients will show improvement with evidence-based pharmacologic treatment, lifestyle modifications, and risk factor reductions.

For patients with refractory hypertension, however, identifying what steps to take in screening and diagnosis can be daunting for clinicians. It is important to identify cases of *secondary* hypertension, because if it is left undiagnosed and untreated, serious complications—such as cardiovascular and renal disease—are likely to occur.^{3,4}

Secondary hypertension can be caused by myriad disease states and disorders, including endocrine disorders, renal disease, neurologic disorders, acute stress, and drug-induced hypertension.⁵ Endocrine hypertension is most commonly caused by adrenal gland disorders, including primary aldosteronism, Cushing syndrome, and pheochromocytoma. (Of note, Cushing *syndrome* is caused by glucocorticoid-secreting adrenal tumors, while Cushing *disease* is a condition in which there is glucocorticoid excess caused by oversecretion of pituitary adrenocorticotropic hormone.⁶ Cushing disease is more common than Cushing syndrome, which is rare.⁷) While nonadrenal endocrine disorders are not as common, they pose significant health issues, including growth hormone excess or deficiency, thyroid disorders, testosterone deficiency, obesity, insulin resistance, and metabolic syndrome.⁸

Understanding the endocrine causes of hypertension is a valuable resource for clinicians to have in their toolbox. Although the negative consequences of endocrine disorders are significant, these conditions

are often recognizable, and pharmacologic treatment and/or surgical interventions can potentially resolve or improve hypertension and reduce risk for other comorbidities. This article summarizes screening and diagnosis guidelines for several possible causes of endocrine hypertension: primary aldosteronism, Cushing syndrome, and pheochromocytoma.

PRIMARY ALDOSTERONISM

Primary aldosteronism occurs in 5% to 10% of all hypertensive patients and is a common cause of secondary and endocrine hypertension (although in younger—particularly female—patients, it most commonly causes renal artery stenosis).^{9,10} Historically, primary aldosteronism was considered rare and not generally included in a differential diagnosis for patients presenting with resistant hypertension. However, clinical investigations have indicated that primary aldosteronism is more prevalent than previously thought.¹¹

Patients develop this condition when there is increased aldosterone production independent of the renin-angiotensin system. The resulting sodium retention can lead to hypertension, hypokalemia, and high plasma aldosterone/renin ratio (ARR).¹² Clinical findings and symptoms can be vague, increasing the difficulty in identifying primary aldosteronism as the diagnosis. Patients may be asymptomatic, with the only abnormal lab finding being hypokalemia (an infrequent finding, affecting < 25% of patients).¹³ If hypokalemia is present, symptoms can include nocturia, polyuria, muscle weakness, cramps, paresthesias, and palpitations.¹¹

The Endocrine Society has identified 8 characteristics that increase the likelihood of primary aldosteronism. Patients require further screening if they

1. Have a sustained elevated BP (≥ 150 mm Hg [systolic] and/or 100 mm Hg [diastolic])
2. Have hypertension (BP > 140/90 mm Hg) that is resistant to 3 conventional antihypertensive drugs, including a diuretic
3. Have controlled BP (BP < 140/90 mm Hg) with ≥ 4 antihypertensive drugs



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4. Have hypertension and spontaneous or diuretic-induced hypokalemia
5. Have hypertension and adrenal incidentaloma
6. Have hypertension and obstructive sleep apnea
7. Have hypertension and a family history of early-onset hypertension or a cerebrovascular accident at a young age (< 40 years)
8. Are hypertensive and a first-degree relative of a patient with primary aldosteronism.¹⁴

The most reliable screening test for primary aldosterone is the ARR, although false-negative and false-positive results are possible.¹¹ False-negative results can be caused by dietary salt restriction, hypokalemia, and use of medications including diuretics, calcium channel blockers, ACE inhibitors, and angiotensin receptor antagonists. Use of β -adrenergic blockers, α -methyl dopa, or NSAIDs can cause false-positive results.¹⁵ Patients should be encouraged to follow a liberal sodium diet before ARR testing, and efforts to correct hypokalemia should be implemented. Before ARR is measured, diuretics (specifically spironolactone) should be stopped for at least 4 weeks; other possible interfering medications should be stopped for at least 2 weeks.¹⁶

The ARR should be obtained multiple times to confirm elevated readings.¹⁶ Reference ranges vary, but generally plasma aldosterone concentrations > 20 ng/dL and plasma renin activity < 1 ng/mL/h indicate whether confirmatory testing should be completed.¹⁴ Further confirmatory testing can be achieved with efforts to suppress plasma aldosterone to < 10 ng/dL after an IV infusion of 2 L isotonic saline over 4 hours.¹² Oral sodium load is used as well and usually before IV infusion.

CUSHING SYNDROME

Cushing syndrome is caused by excess circulating levels of glucocorticoids and affects < 0.1% of the world population.¹⁷ Signs and symptoms include centripetal obesity, moon facies, facial plethora, easy bruising, buffalo hump (or posterior cervical fat pad), hirsutism, and wide-purple striae.¹⁸ Up to 80% of these patients also have hypertension.¹⁹ If these patients have chronic exposure to high levels of glucocorticoid (the most common source being therapeutic administration of exogenous glucocorticoids), multiple complications can occur.^{6,20}

The Endocrine Society Clinical Practice Guideline recommends the following patient groups be tested for Cushing syndrome:

1. Young patients with unusual medical conditions, such as osteoporosis and resistant hypertension
2. Patients with classic signs and symptoms, such as easy bruising, weight gain, facial plethora, and purple striae
3. Children with decreasing height percentile and increasing weight
4. Patients with adrenal incidentaloma compatible with adenoma.¹⁸

If Cushing syndrome is suspected, 1 of the following 3 initial tests can be completed: 24-hour, urine-free cortisol and creatinine; late-night salivary cortisol; or 1-mg overnight dexamethasone suppression test. Two of these tests must have abnormal results for confirmation before appropriate pituitary or adrenal imaging. If a patient has clinical features indicating Cushing syndrome but test results are normal, he or she should be referred to an endocrinologist. If a patient has ≥ 2 normal tests and probability of Cushing syndrome is unlikely, patients should be recommended for follow-up in 6 months to evaluate for any worsening of symptoms.¹⁸

PHEOCHROMOCYTOMA

Pheochromocytoma is a condition in which there is secretion of excess catecholamines, epinephrine, norepinephrine, and dopamine due to a tumor of the adrenal medulla.²¹ This is a rare disease and accounts for only 0.2% to 0.6% of all causes of hypertension.²² Hypertension (persistent or paroxysmal) is the most common finding for patients with pheochromocytoma, with 80% to 90% presenting with this finding.²³ It is important to note that approximately 10% of these patients will be normotensive. Three of the condition's classic symptoms are headache, sweating, and palpitations.²⁴ Additional symptoms include anxiety, sense of impending doom, fever, nausea, or vomiting.²¹

If left untreated, there is risk for hypertensive retinopathy, nephropathy, myocardial infarction, stroke from cerebral infarction, intracranial hemorrhage, or embolism.²⁵ Due to the high rate of morbidity and mortality with untreated pheochromocytoma, laboratory testing should be initiated immediately upon suspicion of this diagnosis or if the patient has relevant family history.¹¹

Patients should be screened for pheochromocytoma if they have ≥ 1 of the following factors:

1. Resistant hypertension and hyperadrenergic

symptoms (palpitations, perspiration, pallor, or headache)

2. Family history of pheochromocytoma
3. Any genetic syndrome with a known association to pheochromocytoma
4. An adrenal mass that is > 4 cm, is cystic, or has hemorrhagic changes.¹⁹

Pheochromocytoma is diagnosed by identifying high concentrations of plasma-free metanephrines or 24-hour fractionated metanephrines and catecholamines. Some medications can interfere with the accuracy of lab results and therefore may need to be temporarily stopped; it is important to check the specific lab guidelines and review the patient's medication lists before tests are ordered and conducted.²⁵

ALWAYS SCREEN THE PATIENT

Although the causes of endocrine-related hypertension are very rare, screening for endocrine hypertension in patients who present with signs and symptoms of these conditions can greatly improve their lives. The endocrine disorders discussed in this article can be treated or controlled with appropriate diagnosis and treatment. In addition, resolving uncontrolled hypertension by addressing endocrine disorders can reduce the risk for long-term sequelae. It is important for clinicians to consider referral to an endocrine specialist if a patient has endocrine-related hypertension. In particular, patients with pheochromocytoma require quick referral due to a risk for high morbidity and mortality if left untreated.¹¹

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