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Hypertension and severe hyperreninemia in a young man

A 29-year-old man presented to the internal medicine clinic for evaluation of hypertension. His blood pressure at 2 separate clinic visits was 152/118 mm Hg and 156/116 mm Hg. He reported home measurements with systolic pressures in the 140s to 150s mm Hg and diastolic pressures in the 90s to 100s mm Hg. His elevated blood pressure was first noted in his late teens and managed with diet and lifestyle changes. He had never been prescribed antihypertensive medication.

His medical history was otherwise normal. He was not taking prescription or over-the-counter medications and said he did not use supplements, tobacco products, alcohol, or drugs. He was unaware of any family history of hypertension. He reported heavy snoring but had not experienced excessive daytime fatigue and was unaware of any apnea.

INITIAL EVALUATION AND MANAGEMENT

On examination, the patient's blood pressure was 156/116 mm Hg, heart rate 90 beats per minute, and body mass index 28.6 kg/m^2. His heart rhythm was regular with no extra heart sounds or murmurs. There was no carotid or abdominal bruit and no elevation in jugular venous pulsation. His lungs were clear to auscultation, with no wheezing or crackles. His extremities were without edema, and no focal neurologic deficits or funduscopic abnormalities were noted.

Laboratory test results

Notable results of initial laboratory testing were as follows:

- Serum potassium 3.5 mmol/L (reference range 3.5–5.0)
- Serum bicarbonate 30 mmol/L (21–31)
- Basic metabolic panel otherwise within normal limits
- Urinalysis with microscopic examination 0–2 red blood cells (0–2), 0–5 white blood cells (0–5), and negative urine protein
- Random urine microalbumin less than 7 mg/L (< 7)
- Hemoglobin, white blood cell count, and platelet count within normal limits
- Total cholesterol 227 mg/dL (< 200)
- High-density lipoprotein cholesterol 48 mg/dL (> 40)
- Low-density lipoprotein cholesterol 143 mg/dL (< 100)
- Triglycerides 182 mg/dL (< 150)
- Hemoglobin A1c 5.5% (4.7–5.6)
- Thyroid-stimulating hormone 1.62 mIU/L (0.55–4.78).

The patient was prescribed lisinopril 20 mg daily. Four weeks later, his blood pressure readings remained above goal, and chlorthalidone 25 mg daily was added. Unattended overnight sleep apnea testing at home revealed a respiratory-event index of 18.3 per hour, consistent with moderate obstructive sleep apnea. Nocturnal continuous positive airway pressure therapy was initiated, and he was encouraged to increase his physical activity and follow a low-sodium diet.

At follow-up 3 months later, his blood pressure was 120/80 mm Hg. Laboratory evaluation revealed a serum potassium of 3.2 mmol/L. Consequently, his chlorthalidone dosage was decreased to 12.5 mg daily and the lisinopril was increased to 40 mg daily. At his next office visit, his blood pressure was 121/70 mm Hg and his potassium had improved to 3.7 mmol/L.

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POSSIBLE SECONDARY HYPERTENSION

1 Which of the following is the most appropriate diagnostic test for this patient?

- ☐ Plasma renin and aldosterone
- ☐ Renal artery angiography
- ☐ Seated plasma fractionated metanephrines
- ☐ Early morning plasma cortisol

Evaluation for identifiable secondary causes of hypertension should be considered in patients diagnosed with hypertension under age 30, those with abrupt onset or sudden worsening of hypertension, and those with severe hypertension (ie, defined as blood pressure > 180/120 mm Hg).[1,2] Screening for secondary hypertension is also recommended in patients with resistant hypertension—defined as uncontrolled hypertension despite 3 antihypertensive drugs including 1 diuretic—or controlled hypertension requiring 4 medications.[1] Testing for specific forms of secondary hypertension can be guided by the history, physical examination, and basic laboratory results.[1,2]

Primary aldosteronism is a common cause of secondary hypertension, with a prevalence of about 10% to 20% in patients with hypertension.[3–5] Screening is recommended in those who present with severe or resistant hypertension, hypertension and spontaneous or diuretic-induced hypokalemia, hypertension with an adrenal lesion, hypertension with atrial fibrillation, or hypertension with obstructive sleep apnea.[1,3,6,7]

The first step in screening for primary aldosteronism is to assess plasma renin and aldosterone levels and calculate the aldosterone-to-renin ratio (ARR).[6,7] Primary aldosteronism is more prevalent than was previously realized and often goes undiagnosed.[3,5] Our patient has multiple indications to screen for primary aldosteronism, including hypertension with hypokalemia and hypertension with obstructive sleep apnea.

Renal vascular disease is another relatively common cause of secondary hypertension, with a prevalence of about 1% to 8% in patients with hypertension.[4] Atherosclerotic vascular disease is responsible for approximately 90% of cases of renal artery stenosis and typically affects patients over age 50 who have other vascular comorbidities or risk factors.[1] Fibromuscular dysplasia is a less common cause of renal artery stenosis in younger patients, usually women.[8] In a young man like our patient, renal artery stenosis is statistically less likely than primary aldosteronism. Screening for renal vascular disease could still be considered, but the initial screening test should be noninvasive imaging such as renal vascular duplex ultrasonography, magnetic resonance angiography of the abdomen, or computed tomographic angiography of the abdomen. Renal artery angiography is a confirmatory test that could be considered depending on initial imaging findings.[1]

Pheochromocytoma is a rare cause of secondary hypertension, with a prevalence of 0.1% to 0.6%.[1] Screening should be considered in patients with resistant hypertension, blood pressure lability, headache, sweating, palpitations, pallor, or a positive family history for pheochromocytoma, and in those with an adrenal lesion.[1] The pretest probability of pheochromocytoma in our patient is much lower than for primary aldosteronism or renal vascular disease.

Checking for plasma fractionated metanephrines is appropriate if there is high suspicion of pheochromocytoma. However, plasma metanephrines should be assessed only under standard conditions, with the patient in the supine position with an indwelling intravenous cannula. Measurements taken while the patient is seated are associated with a high rate of false-positive results. Alternatively, metanephrines and fractionated catecholamines can be assessed on a 24-hour urine collection.[9]

Hypercortisolism is a rare cause of secondary hypertension, with a prevalence of less than 0.1%.[1] Signs and symptoms may include weight gain, central obesity, facial plethora, proximal muscle weakness, striae, bruising without trauma, hirsutism, dorsal and supraclavicular fat pads, mental health problems, menstrual irregularities, hyperglycemia, and early-onset osteoporosis.[1,10] Screening for hypercortisolism can be done with an overnight 1-mg dexamethasone suppression test, 24-hour urine-free cortisol test, or late-night salivary cortisol testing.[11] An unsuppressed early morning cortisol test is sometimes used in case-detection of adrenal insufficiency but would not be useful in screening for cortisol excess.

CASE CONTINUED: PLASMA RENIN

Our patient was initially started on lisinopril monotherapy. A second agent, chlorthalidone, was added when blood pressure remained above goal after 4 weeks. Consensus guidelines recommend that for patients who present with blood pressure more than 20/10 mm Hg above goal, initial antihypertensive therapy should consist of 2 agents of different classes rather than monotherapy.[1] In our patient, it would have been appropriate to start treatment with combination drug therapy rather than waiting 4 weeks to start the second drug.

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TABLE 1
Effects of antihypertensive drug classes on plasma renin and aldosterone

Medication class	Effect on plasma renin	Effect on plasma aldosterone
Beta-blockers	Decrease	Moderate decrease
Central agonists (eg, clonidine, alpha-methyldopa)	Decrease	Moderate decrease
Potassium-wasting diuretics	Increase	No change or moderate increase
Potassium-sparing diuretics	Increase	Moderate increase
Angiotensin-converting enzyme inhibitors	Increase	Moderate decrease
Angiotensin receptor blockers	Increase	Moderate decrease
Dihydropyridine calcium channel blockers	Moderate increase	No change or moderate increase
Renin inhibitors	Moderate decrease or increase[a]	Moderate decrease

[a]Renin inhibitors lower plasma renin activity but raise plasma renin concentration.

Based on information in reference 6.

Our patient's plasma renin concentration (PRC) was found to be 1,971 pg/mL (4.2–52.2), and the plasma aldosterone concentration was 11.3 ng/dL (< 35.3).

2 Which of the following causes of secondary hypertension is not associated with hyperreninemia?

- ☐ Juxtaglomerular cell tumor
- ☐ Renal artery stenosis
- ☐ Primary aldosteronism
- ☐ Scleroderma renal crisis

The enzyme renin is secreted by the juxtaglomerular apparatus, a specialized group of cells in the afferent arterioles of glomeruli. The renin-angiotensin-aldosterone system plays a central role in blood pressure regulation. Briefly, increased renin-angiotensin-aldosterone system activity raises blood pressure via arterial vasoconstriction and retention of sodium by the renal tubules. Normal physiologic stimuli for renin release include decreased renal arteriolar pressure sensed by baroreceptors, sodium and chloride depletion sensed by the macula densa in the distal renal tubules, and sympathetic (beta-1-adrenergic) activity. Renin secretion is regulated via negative feedback by angiotensin II.[12]

Primary aldosteronism is classically associated with low plasma renin. In fact, suppressed plasma renin is a criterion for the diagnosis of primary aldosteronism: autonomous aldosterone production leads to pathogenic sodium retention and volume expansion, resulting in negative feedback on renin secretion.[3,6]

Juxtaglomerular cell tumor, or reninoma, is a rare cause of secondary hypertension and hypokalemia. It leads to "primary" hyperreninemia via direct renin secretion from tumor cells.[13] "Secondary" hyperreninemia can be seen with any process that decreases renal arteriolar perfusion pressure, including renal artery stenosis, malignant hypertension, scleroderma renal crisis, and renal thrombotic microangiopathy. Hyperreninemia can occur secondary to excessive sympathetic activation, as in pheochromocytoma.[14] Secondary hyperreninemia can also be seen in the setting of sodium depletion, as occurs in salt-wasting disease states like Bartter or Gitelman syndrome or adrenal insufficiency. However, these are generally not associated with hypertension.

Measurement of plasma renin

Clinical measurement of plasma renin is mainly indicated in screening for primary aldosteronism. A high renin level is not specific to any one form of secondary hypertension. Two common assays are used to measure plasma renin:

- The plasma renin activity (PRA) assay quantifies renin in terms of its enzymatic activity expressed as the amount of angiotensin I generated per unit of time
- The PRC assay, sometimes referred to as the direct renin concentration, measures the mass of active renin directly.

PRA accounts for endogenous angiotensinogen levels and has less variation due to exogenous estrogen,

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TABLE 2
Trend of plasma renin and aldosterone laboratory values in our patient

	Initial results while taking lisinopril and chlorthalidone	Rechecked 6 weeks later, with no medication changes	Rechecked after 4 weeks of verapamil monotherapy
Plasma renin concentration (reference range 4.2–52.2 pg/mL)	1,971 pg/mL	1,253 pg/mL	14.8 pg/mL
Plasma aldosterone concentration (< 35.3 ng/dL)	11.3 ng/dL	17.1 ng/dL	10.1 ng/dL

menstruation, pregnancy, and liver dysfunction. PRC correlates well with PRA, and many laboratories have adopted it because it is easier and less expensive to perform than PRA.[15] Our institution measures PRC via chemiluminescent immunoassay.

CASE CONTINUED: NEPHROLOGY REFERRAL

Further workup was pursued to evaluate possible causes of hypertension and hyperreninemia. Renal vascular duplex ultrasonography did not demonstrate evidence of renal artery stenosis. Contrast-enhanced computed tomography of the abdomen showed normal kidneys and adrenal glands without focal lesions. Plasma fractionated metanephrines were normal. The patient was referred to our nephrology hypertension clinic for further evaluation of elevated plasma renin. Repeat laboratory evaluation about 6 weeks after the initial check showed a PRC of 1,253 pg/mL and a plasma aldosterone concentration of 17.1 ng/dL. A "washout" of medications that affect plasma renin levels was pursued.

3 Which class of antihypertensive medication is not associated with an increase in plasma renin levels?

- ☐ Angiotensin-converting enzyme (ACE) inhibitors
- ☐ Angiotensin receptor blockers (ARBs)
- ☐ Thiazide and thiazide-like diuretics
- ☐ Direct renin inhibitors
- ☐ Beta-blockers

Many antihypertensive agents alter renin and aldosterone levels (**Table 1**).[6] When possible, screening for primary aldosteronism should be done in the absence of interfering medications.[6] For patients already on antihypertensive therapy, however, withdrawal of these medications may not be feasible, and delaying testing for medication washout can lead to missed screening opportunities. To improve case-detection rates, some authors have recommended a simplified approach in which patients who meet criteria for screening have their plasma renin and aldosterone levels checked without adjustment of existing medications.[3,16,17] At the time of initial screening, our patient was taking lisinopril and chlorthalidone, both of which can increase plasma renin levels.

ACE inhibitors and ARBs increase plasma renin by blocking the negative feedback of angiotensin II on renin secretion. Downstream, angiotensin II-mediated aldosterone secretion is diminished.[18] This rise in renin and drop in aldosterone can significantly decrease the ARR and lead to a false-negative screening result in patients with primary aldosteronism.[7,19]

Diuretics lead to increased renin secretion in compensation for natriuresis and reduced blood volume. Aldosterone is increased to a lesser degree, which can also result in a false-negative ARR.[7]

Direct renin inhibitors block the enzymatic activity of renin and prevent formation of angiotensin I and subsequently angiotensin II. This means that the observed effect of direct renin inhibitors on plasma renin varies depending on which assay is used. The PRA (measuring the amount of angiotensin I generated per unit time) decreases, while conversely the PRC (measuring the mass of renin present in plasma) increases due to reduced negative feedback by angiotensin II.[20]

Dihydropyridine calcium channel blockers have been associated with increased plasma renin in some studies,[19,21] while others reported a less significant effect.[18] Expert consensus guidelines still list this class among those that can confound renin and aldosterone measurements.[6,7] The mechanism by which dihydropyridine calcium channel blockers could increase renin is not fully understood, but may involve effects

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on renal arteriolar baroreceptors, sympathetic activity, and the secondary natriuresis induced by this class.[12,19]

Beta-blockers and central alpha-2 agonists lead to a reduction in plasma renin by the inhibition of beta-adrenergic activity.[6,18] Aldosterone levels are reduced to a lesser extent, which can lead to a false-positive ARR.[7]

When medication adjustment is feasible, expert consensus guidelines recommend the substitution of antihypertensive drugs that have a minimal effect on plasma renin and aldosterone. These include hydralazine, nondihydropyridine calcium channel blockers, and alpha-2 adrenergic blockers. Medications that can interfere with renin and aldosterone measurements should be discontinued for at least 4 weeks.[6,7]

CASE CONCLUDED

In our patient, lisinopril and chlorthalidone were stopped, and acceptable blood pressure control was maintained using verapamil. Four weeks after these changes, the patient's PRC was rechecked and found to be within the normal range at 14.8 pg/mL (**Table 2**), indicating that the initial high PRC was secondary to combination ACE inhibitor and diuretic therapy.

The confounding effects of ACE inhibitors and diuretics on plasma renin and aldosterone levels are well recognized, but the magnitude of renin elevation in our patient was significantly higher than what has previously been reported. In prospective studies of normotensive volunteers and patients with essential hypertension, initiation of an ACE inhibitor or ARB has been associated with an average 4-fold to 6-fold increase in plasma renin.[21,22] In a recent meta-analysis of randomized controlled trials in patients with hypertension, the standardized mean increase in plasma renin after starting a thiazide or thiazide-like diuretic was about 1.5 times baseline, and the highest reported mean increase was about 7 times baseline.[23]

Our patient's initial PRC was more than 37 times the upper limit of normal, comparable to levels reported in association with reninoma.[13] It is understandable that this finding prompted imaging and nephrology referral.

TAKE-HOME POINTS

Primary aldosteronism is an underrecognized and treatable cause of secondary hypertension. Checking plasma renin and aldosterone levels without first adjusting medication may improve case-detection rates.[3,16,17] Results can still be reliably interpreted if renin is in the suppressed range.[19] In fact, a suppressed renin while on ACE inhibitor, ARB, or diuretic therapy should increase suspicion for primary aldosteronism.[3,24] However, when renin levels are not suppressed, a medication effect should be considered.

With broader application of screening for primary aldosteronism, it is critical to understand the effects of medications on plasma renin and aldosterone levels. As shown in our patient, ACE inhibitors and thiazide diuretics can lead to extremely high plasma renin levels, comparable to those seen with rare causes of secondary hypertension such as reninoma. Awareness of this possibility is critical when screening for primary aldosteronism in patients taking these medications, especially when taken in combination.

When evaluating a patient with elevated plasma renin—even extremely high levels—the effect of medications should be considered before pursuing additional diagnostic testing. Significant cost, radiation exposure, and psychological stress for the patient may be avoided if plasma renin levels are reassessed after confounding drugs are withdrawn.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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