Screening for Endocrine Hypertension: An Endocrine Society Scientific Statement

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Hypertension may be the initial clinical presentation for at least 15 endocrine disorders. An accurate diagnosis of endocrine hypertension provides clinicians with the opportunity to render a surgical cure or to achieve an optimal clinical response with specific pharmacologic therapy. It is challenging for the clinician to know when and how to perform case-detection testing for all the endocrine disorders in which hypertension may be the presenting symptom. Herein, we review the different forms of endocrine hypertension, with a focus on prevalence, clinical presentation, guidance on when to perform case detection testing, and currently available case-detection tests. (***Endocrine Reviews*** **38: 103–122, 2017)**

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Abbreviations: ACE, angiotensin-converting enzyme; ACTH, corticotropin; BP, blood pressure; ARR, aldosterone/renin ratio; CAH, congenital adrenal hyperplasia; CPAP, continuous positive airway pressure; CT, computed tomography; DOC, deoxycorticosterone; DHEA-S, dehydroepiandrostenedione-sulfate; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; OSA, obstructive sleep apnea; PA, primary aldosteronism; PPGL, pheochromocytoma and paraganglioma; RAAS, renin-angiotensin-aldosterone system; RVH, renovascular hypertension.

I. Introduction

Hypertension affects 28.6% of adults in United States (1–3). In most, hypertension is primary (essential or idiopathic), but a subgroup of approximately 15% has secondary hypertension (4, 5). More than 50% of children who present with hypertension have a secondary cause (6). In young adults (<40 years old), the prevalence of secondary hypertension is approximately 30% (7). The secondary causes of hypertension include renal causes (*e.g.*, renal parenchymal disease) and endocrine causes. Hypertension may be the initial clinical presentation for at least 15 endocrine disorders (Table 1). An accurate diagnosis of endocrine hypertension provides clinicians with the opportunity to render a surgical cure or to achieve an optimal clinical response with specific pharmacologic therapy (8). Primary aldosteronism (PA) is a disorder that clinicians should consider in most patients with hypertension (9). Herein, we review the different forms of endocrine hypertension with a focus on prevalence, clinical presentation, guidance on when to perform case-detection testing, and currently available case detection tests (Fig. 1).

II. Pheochromocytoma and Paraganglioma

A. Introduction and prevalence

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine chromaffin-cell tumors that usually produce catecholamines and arise from the adrenal medulla (80% to 85%) or from paravertebral ganglia of the sympathetic chain (15% to 20%), respectively (10, 11). Paragangliomas located in the neck and the skull base are usually hormonally inactive; however, some produce dopamine. The prevalence of PPGLs in the general population is extremely low (1.5 to 1.6 per 10,000 persons). The prevalence is higher in patients who present with hypertension (20 to 60 per 10,000 patients). However, it is still a rare neoplasm that a general physician will rarely encounter in clinical practice. In some patient groups, the prevalence is much higher (*e.g.*, 500 PPGLs per 10,000 of patients who also have an incidentally discovered adrenal mass) (12). The diagnosis of PPGL is frequently missed, as the prevalence of PPGLs in autopsy studies is five per 10,000 persons (13, 14).

There are two PPGL biochemical phenotypes: adrenergic and noradrenergic tumors (15, 16). Adrenergic tumors are located in the adrenal medulla and usually produce epinephrine, metanephrine (epinephrine's major metabolite), and varying amounts of norepinephrine. Noradrenergic tumors are located either in the adrenal medulla or are extra-adrenal and produce norepinephrine (predominantly or exclusively) and normetanephrine (norepinephrine's major metabolite). The lack of epinephrine secretion in these latter tumors is due to the absence of the enzyme phenylethanolamine-*N*-methyltransferase in extra-adrenal tumors; this enzyme is essential for converting norepinephrine into epinephrine (17). The biochemical phenotype is important for several reasons. First, it can predict the type of germline mutation [*e.g.*, noradrenergic tumors are more likely to be associated with the hypoxic signaling pathway mutations

Table 1. Endocrine Causes of Hypertension

Etiology
Adrenal-dependent causes
1. Pheochromocytoma and sympathetic paraganglioma
2. Primary aldosteronism
3. Hyperdeoxycorticosteronism
a. Congenital adrenal hyperplasia
i. 11β-Hydroxylase deficiency
ii. 17α-Hydroxylase deficiency
b. Deoxycorticosterone-producing tumor
c. Primary cortisol resistance
4. Cushing syndrome
Apparent mineralocorticoid excess/11β-hydroxysteroid dehydrogenase deficiency
1. Genetic
2. Acquired
a. Licorice or carbenoxolone ingestion
b. Cushing syndrome
Parathyroid-dependent causes
1. Hyperparathyroidism
Pituitary-dependent causes
1. Acromegaly
2. Cushing syndrome
Secondary hyperaldosteronism
1. Renovascular hypertension
Thyroid-dependent causes
1. Hypothyroidism
2. Hyperthyroidism
Complex effects
1. Obstructive sleep apnea

([cluster 1: von Hippel Lindau and succinate dehydrogenase mutations), and adrenergic tumors are more likely to be associated with kinase signaling pathway mutations (cluster 2: multiple endocrine neoplasia type 2 and neurofibromatosis type 1)]. Second, patients with adrenergic tumors may have more paroxysmal symptoms than those with noradrenergic tumors (17, 18).

B. Clinical presentation

The clinical presentation of patients with PPGLs varies widely from no symptoms, to minor discrete symptoms, to catastrophic life-threatening clinical conditions (10, 19). In general, one of every 10 patients with PPGL is completely asymptomatic; this asymptomatic subgroup is much larger in those patients with incidentally discovered adrenal masses or those tested during family screenings. When present, the classic triad of pounding headache, profuse sweating, and palpitations occurs in spells that last from several minutes to 1 hour. There is complete relief of symptoms between spells. The frequency of spells may vary from several times a day to a few times per month, occurring either spontaneously or being provoked by a variety of physical or chemical triggers, such as general anesthesia, micturition, and medications *(e.g.,* β-adrenergic inhibitors, tricyclic antidepressants, glucocorticoids) (20, 21). Enhanced blood pressure (BP) variability is reflected by paroxysmal hypertension in about 35% of the patients. Other patients may experience severe high BP peaks, sometimes superimposed on sustained hypertension and potentially evolving into a hypertensive crisis. These high BP surges, and the underlying episodes of tumoral catecholamine release, are thought to be responsible for the high prevalence of cardiovascular emergencies, such as myocardial infarction, stroke, and heart failure (22, 23).

C. Who should be screened?

Routine biochemical screening of all new hypertensive patients for PPGL is not cost effective and, therefore, is not recommended. Clinicians should base biochemical testing for PPGL on clues that suggest the possibility of excess catecholamine secretion. In particular, clinicians should consider any paroxysmal signs or symptoms as a red flag. Since missing the diagnosis can have fatal consequences, even slight clinical suspicion of PPGL should prompt biochemical testing, irrespective of BP level (Table 2). For example, most patients with an incidentally discovered adrenal mass should have biochemical testing for PPGL (24). In addition, patients with known PPGL-causing germline mutations should have periodic biochemical testing (25). Clinicians should also consider case-detection testing in family members of newly diagnosed patients with PPGL.

D. Case-detection tests

Biochemical testing should generally precede imaging procedures because only solid evidence of excess production of catecholamines can justify performing expensive imaging procedures. Initial biochemical testing for PPGLs should include measuring plasma free or urinary fractionated metanephrines (25). Because of their very high sensitivities, normal values for these tests exclude a PPGL with high reliability. Exceptions include very small tumors that may be missed, as might be the case in asymptomatic patients tested because of a hereditary predisposition. Diagnostic accuracy is not significantly different between plasma and 24-hour urinary tests, particularly when assays use liquid chromatography with tandem mass spectrometry (26, 27). The explanation for this high sensitivity is the continuous secretion of intratumorally produced metanephrines, which contrasts with the episodic exocytotic secretion of their parent catecholamines. Conversely, elevated test results of fractionated metanephrines are not fully specific for the presence of a PPGL and, therefore, do not prove that a patient has a PPGL.

Other available biochemical tests, such as those for plasma or urinary catecholamines, urinary vanillylmandelic acid, and urinary chromogranin A, have inferior diagnostic value as compared with plasma free and urinary fractionated metanephrines.

Figure 1.

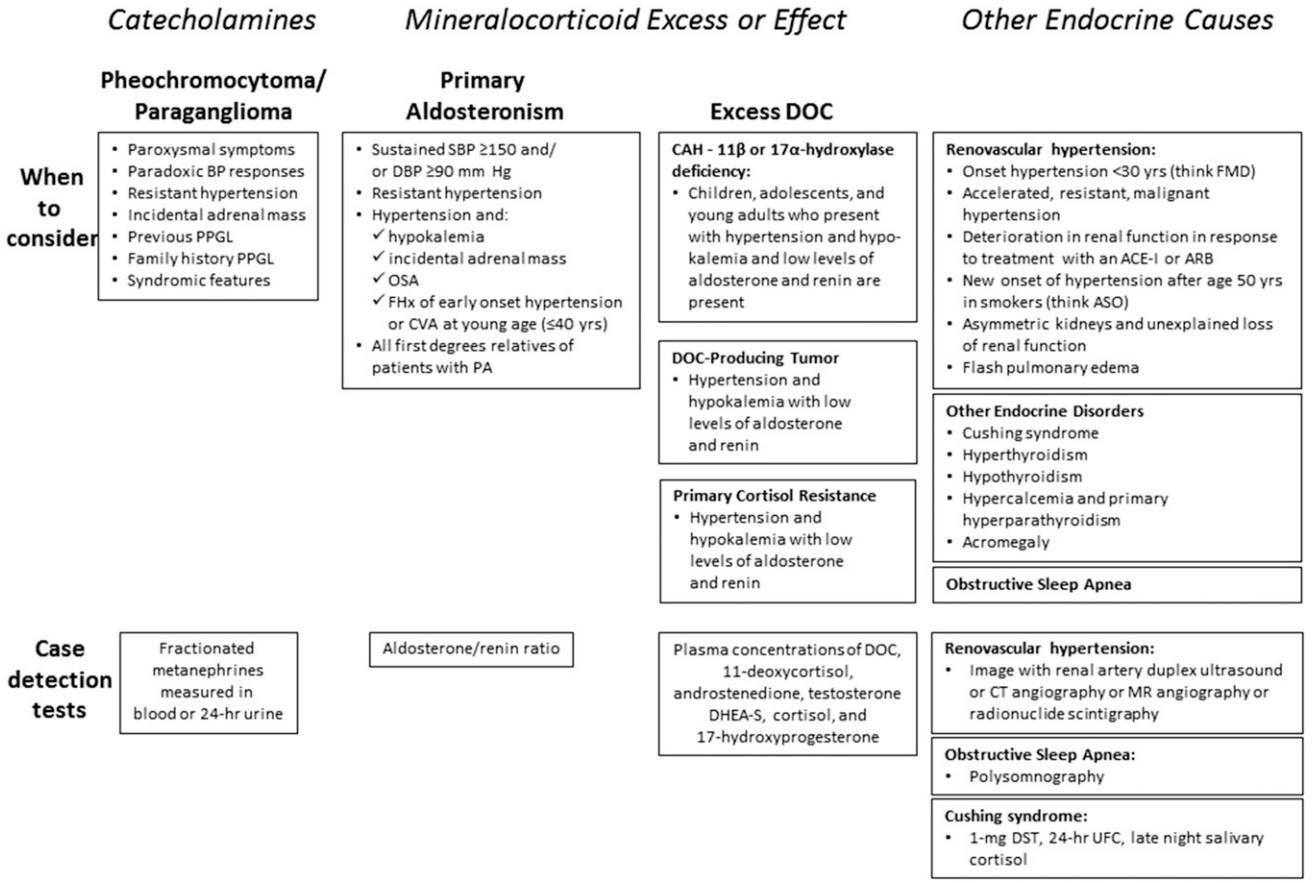

Figure 1. When to consider and how to test for endocrine hypertension. ARB, angiotensin II receptor blockers; ASO, arterial switch operation; CT, computerized tomography; CVA, cerebrovascular accident; DBP, diastolic blood pressure; DST, dexamethasone suppression test; FMD, fibromuscular dysplasia; FHx, family history; MR, magnetic resonance; SBP, systolic blood pressure; UFC, urinary free cortisol.

Preanalytical conditions

Clinicians should take several precautions regarding biochemical testing. They should assess coexisting conditions associated with increased sympathetic activity, such as occult or overt heart failure, renal failure, and hypoglycemia. Increased sympathetic activity may result in false-positive test results, thus limiting the positive predictive value of a positive test result. A more commonly occurring example is clinicians sampling blood from patients who are in the seated position and have not had preceding rest. To minimize the risk of false-positive test results of plasma free metanephrines, clinicians should draw blood samples from an indwelling cannula after patients have had supine rest for at least 30 minutes. If taking a blood sample after supine rest is not feasible, measuring 24-hour urinary fractionated metanephrines provides an excellent alternative test.

Patients who consume biogenic amines may also exhibit false-positive test results. However, measuring plasma free metanephrines requires no special dietary precautions. The only exception is the *O*-methylated dopamine metabolite methoxytyramine, which can be spuriously elevated when blood is sampled from patients who are in a nonfasting state (28). Elevated levels of this metabolite have some value in predicting extra-adrenal tumor location (in particular, neck and skull-base paragangliomas) and the presence of metastatic disease (29).

Table 2. When To Perform Biochemical Testing To Screen for Pheochromocytoma or Sympathetic Paraganglioma

Indications for Biochemical Testing
Paroxysmal signs or symptoms suggesting catecholamine excess
Paradoxic BP response to drugs, surgery, or anesthesia
Resistant hypertension
Incidentally discovered adrenal mass (with or without hypertension)
Previous diagnosis of pheochromocytoma or paraganglioma (with annual biochemical testing to detect recurrent disease)
Hereditary predisposition for pheochromocytoma or paraganglioma
Syndromic feature indicating a pheochromocytoma-related hereditary syndrome

Adapted from Lenders *et al.* (25).

When measuring plasma metanephrines, clinicians should collect blood samples in heparinized tubes or tubes with ethylenediaminetetraacetic acid and place these immediately on ice to prevent oxidative degradation (30). When measuring 24-hour urinary fractionated metanephrines, clinicians can use containers without additives. Before storage, technicians should acidify the urine sample to a pH of 4 when it arrives in the laboratory (31). Clinicians should instruct patients carefully about how to collect urine for 24 hours. Measuring urinary creatinine is a useful way to verify that urine collection was complete.

Finally, several drugs can be a source of false-positive test results due to analytical or pharmaco-physiological interference (Table 3). Liquid chromatography with tandem mass spectrometry assays are more specific and experience less from analytical interference by drugs than liquid chromatography with electrochemical detection assays.

Table 3. Medications That Can Cause False-Positive Biochemical Testing for Pheochromocytoma and Sympathetic Paraganglioma

	Plasma		Urine	
Medication	**NMN**	**MN**	**NMN**	**MN**
Tricyclic antidepressants[a]	↑↑	—	↑↑	—
Antipsychotics[a]	↑↑	—	↑↑	—
Buspirone[a]	↑	↑↑	↑	↑↑
MAO inhibitors[a]	↑↑	↑↑	↑↑	↑↑
Sympathomimetics[a]	↑	↑	↑	↑
Cocaine[a]	↑↑	↑	↑↑	↑
Levodopa[b]	↑	↑	↑↑	↑
Phenoxybenzamine[c]	↑↑	—	↑↑	—
Acetaminophen[d]	↑↑	—	↑↑	—
Labetalol[d]	—	—	↑↑	↑↑
Sotalol[d]	—	—	↑↑	↑↑
α-methyldopa[d]	↑↑	—	↑↑	—
Sulphasalazine[d]	↑↑	—	↑↑	—

Adapted from Lenders *et al.* (25).

Abbreviations: —, no change; MAO, monoamine oxidase; MN, metanephrine; NMN, normetanephrine.

[a] Pharmacodynamic interference affects all analytical methods.

[b] There is analytical interference with some liquid chromatography with electrochemical detection assays and pharmacodynamic interference increases measured levels of dopamine and the dopamine metabolite methoxytyramine.

[c] There is pharmacodynamic interference during the first few days of medication initiation.

[d] There is analytical interference for some but not all methods using liquid chromatography with electrochemical detection; these drugs do not cause false-positive testing in tandem mass spectroscopy assays.

Reference values

To obtain optimal diagnostic accuracy, each laboratory should establish reference values for plasma free and 24-hour urinary fractionated metanephrines, taking into account patient-specific characteristics, such as age and sex. Specifically, the upper cutoff level of plasma free normetanephrine is higher in older patients (32, 33). There is no such effect for metanephrine or methoxytyramine.

Interpretation of test results

If a test result of plasma free or 24-hour urinary fractionated metanephrines in a symptomatic patient is within the normal range, clinicians can exclude a PPGL, provided that urine collection is complete and blood sampling was performed correctly. In asymptomatic patients, as in those who are carriers of one of the susceptibility genes, a single normal test result cannot definitely exclude a PPGL; in these cases it is preferable to wait and retest.

Plasma free metanephrine levels more than three times the upper reference limit or 24-hour urinary fractionated metanephrine levels more than two times the upper reference limit are highly reliable predictors of the presence of a PPGL. In these cases, the risk of a falsely elevated test result is very low and, in such cases, clinicians can proceed with imaging studies. However, 25% of patients have levels for the above indicators that are only slightly elevated, and these patients are more difficult to analyze. For example, patients in the intensive care unit routinely have falsely elevated test results (34). Thus, biochemical testing for PPGL should be avoided in critically ill patients. Clinicians should first check for comorbidities associated with stress-mediated increased sympathetic activity in all patients who exhibit a slightly elevated level of plasma free metanephrine or 24-hour urinary fractionated metanephrine.

Another much more frequent condition associated with mildly elevated plasma metanephrine levels is sampling blood from patients in the seated position who have not had preceding rest. In such cases, clinicians should remeasure plasma metanephrine levels after patients have had 30 minutes' supine rest. If feasible, clinicians should discontinue medications known to cause false-positive test results (*e.g.*, tricyclic antidepressants) before blood or urine collection. If this is not possible, clinicians should administer tests irrespective of drug treatment, but take special care when interpreting test results.

When clinicians have excluded all obvious causes of false-positive test results, other less obvious possibilities remain. As a follow-up test, clinicians can measure both urinary fractionated metanephrine and plasma chromogranin A levels to exclude falsely elevated plasma metanephrine levels (35). A more laborious test is the

clonidine suppression test for distinguishing truly elevated (tumoral normetanephrine release) from falsely elevated (sympathetic activation) test results (36).

III. Primary Aldosteronism

In PA, aldosterone production exceeds the body's requirements and is relatively unchecked by its normal regulator, the renin-angiotensin II system (37, 38). Excessive unregulated production of aldosterone results in increased sodium reabsorption via amiloride-sensitive epithelial sodium channels within the distal nephron, leading to hypertension and renin-angiotensin II suppression. Urinary loss of potassium and hydrogen ions, exchanged for sodium at the distal nephron, may result in hypokalemia and metabolic alkalosis (37, 38).

A. Prevalence

Once thought to be a rare condition and not worth investigating in patients with hypertension unless hypokalemic, PA is now considered the most common, specifically treatable, and potentially curable form of hypertension, accounting for at least 5% to 10% of hypertensive patients, with most patients normokalemic (39, 40). In resistant hypertensive cohorts, the prevalence of PA is approximately 20% (41, 42). Most patients with PA are diagnosed during their third to sixth decades (43).

B. Clinical presentation

Hypertension occurs in most patients with PA and may be mild or severe but rarely malignant (44, 45). BP levels vary widely among patients with either aldosterone-producing adenoma or bilateral adrenal hyperplasia, and clinicians cannot use BP levels to distinguish these subtypes (46). In familial hyperaldosteronism type I, hypertension is often delayed, especially in female patients, but can be of early onset and severe enough to cause early death, usually from hemorrhagic stroke (47, 48). Family screening in familial hyperaldosteronism type I and familial hyperaldosteronism type II has revealed highly diverse phenotypes, with some patients being normotensive, which is consistent with PA evolving through a preclinical phase (47, 49–51).

Less than one-quarter of patients diagnosed with PA and less than one-half of those with aldosterone-producing adenoma are hypokalemic (39, 40, 52). In these patients, PA is indistinguishable from essential hypertension unless clinicians measure renin and aldosterone. When hypokalemia does occur, it may be associated with nocturia, polyuria, muscle weakness, cramps, paresthesias, and/or palpitations. The prevalence of obstructive sleep apnea (OSA) is increased in patients with PA and it improves with PA-specific therapy (53).

During pregnancy, hypertension and symptoms may improve or become worse. Improvement appears to be due to the antimineralocorticoid effects of high circulating levels of placental progesterone, which antagonize aldosterone action at the mineralocorticoid receptor (54, 55). Studies have reported increased luteinizing hormone choriogonadotropin-receptor expression in aldosterone-producing adenomas harboring β-catenin mutations in some pregnant women, and the increased pregnancy-related blood levels of human chorionic gonadotropin, in turn, increased the degree of hyperaldosteronism (56, 57).

C. Who should be screened?

Clinicians should consider PA screening for most patients with hypertension. In part, this is because hypertension in PA responds well to specific treatments directed against aldosterone excess. Unilateral laparoscopic adrenalectomy in patients with unilateral forms of PA cures hypertension in 50% to 60% of cases and results in significant improvements in the remainder (58–60). For nonoperated patients, medications that antagonize aldosterone action (*e.g.,* spironolactone, eplerenone, and amiloride) lead to substantial and often marked improvements in hypertension control (61, 62). Furthermore, it has become apparent that aldosterone excess in PA directly induces injury (*e.g.,* inflammation, remodeling, and fibrosis) in cardiovascular and renal tissues and induces adverse metabolic effects in ways that are at least partly independent of its effect on BP (63–66). As a result, rates of cardiovascular events (*e.g.,* arrhythmias, myocardial infarctions, strokes, and cardiovascular mortality) are higher in patients with PA than among those with essential hypertension matched for BP level (67–69). Importantly, the excess in cardiovascular morbidity is reversed after treatment (67), providing compelling support for early detection of individuals with PA.

The Endocrine Society clinical practice guideline on PA recommends the case detection of PA in patient groups with relatively high prevalence of PA (9). These include the following: patients with a sustained elevated BP [BP $\geq$150 mm Hg (systolic) and/or 100 mm Hg (diastolic)]; hypertension (BP $>$140/90 mm Hg) resistant to three conventional antihypertensive drugs, including a diuretic; controlled BP (BP $<$140/90 mm Hg) with four or more antihypertensive drugs; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension and adrenal incidentaloma; hypertension and OSA; or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age ($<$40 years old). Given the known existence of familial forms, the guideline also recommends case detection for all hypertensive first-degree relatives of patients with PA (9).

D. Case-detection tests

Plasma potassium

Because only a minority (approximately 20%) of patients with PA are hypokalemic, measurements of plasma potassium lack sensitivity as a screening test (39). However, when hypokalemia is present (especially when not provoked by the use of diuretics), plasma potassium levels serve as a valuable clue of the presence of this condition.

The aldosterone/renin ratio

The aldosterone/renin ratio (ARR) is the most reliable available screening test; it is more specific than renin measurement (levels of which are almost always suppressed in patients with PA) and more sensitive than plasma potassium or aldosterone measurements. The ratio becomes elevated before aldosterone or plasma potassium leave their normal ranges (52). However, false positives and negatives are possible and can occur for the following reasons.

- Hypokalemia may be associated with false-negative ARRs because potassium is a powerful chronic regulator of aldosterone secretion (44, 70).
- False-positive ARRs can occur in premenopausal women during the luteal phase of the menstrual cycle and also in women receiving estrogen-containing contraceptive agents, but only when clinicians measure renin as direct active renin concentration and not as plasma renin activity (71, 72).
- False-positive results may also be seen in patients with impaired renal function (renin production is reduced, whereas any associated hyperkalemia tends to elevate aldosterone) (73), in advancing age (during which production of renin falls more quickly than that of aldosterone), and in familial hyperkalemic hypertension (also known as pseudohypoaldosteronism type II and Gordon syndrome) (74, 75).
- False-negative ARRs can result when renin secretion is stimulated by the following: dietary salt restriction; concomitant malignant or renovascular hypertension (RVH); pregnancy (in which high levels of progesterone antagonize aldosterone action at the mineralocorticoid receptor); and treatment with diuretics (including spironolactone), dihydropyridine calcium channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor antagonists (70, 75–78).
- β-adrenergic blockers, α-methyldopa, clonidine, and nonsteroidal anti-inflammatory drugs can suppress renin levels and produce false-positive ARRs (70, 75, 77, 79).
- Treating with antidepressants of the selective serotonin reuptake inhibitor class lowers the ARR, but whether they can cause false-negative findings in patients with PA remains uncertain (80).

Clinicians should withdraw diuretics for at least 4 weeks and other interfering medications for at least 2 (and preferably 4) weeks before measuring ARRs. To maintain BP control, clinicians should administer other medications that have a lesser effect on results, such as verapamil slow-release (with or without hydralazine) and prazosin (70, 75, 78). In cases where clinicians cannot withdraw a potentially interfering medication, they should take into account the medication's known effects when interpreting ratios. For example, an elevated ratio in patients receiving a diuretic, ACE inhibitor, angiotensin receptor blocker, or dihydropyridine calcium blocker would make PA very likely, whereas a normal ratio in the presence of β-adrenergic blocker treatment would make the diagnosis unlikely.

Clinicians should correct hypokalemia and encourage the patient to follow a liberal sodium diet before measuring ARRs. Because of the effects of posture and time of day, collecting blood midmorning from seated patients who have been upright (*i.e.*, sitting, standing, or walking) for 2 to 4 hours maximizes the sensitivity of the ratio (70, 75, 78).

Clinicians should regard the ARR as a screening test only and should measure it more than once (serially if conditions of sampling, including medications, are being altered) before deciding whether to go on to a suppression test to definitively confirm or exclude the diagnosis (70, 75, 78). Although reference ranges and cutoffs differ depending on the laboratory, plasma aldosterone concentrations >10 ng/dL in concert with plasma renin activity <1 ng/mL/h should trigger confirmatory testing (9). Clinicians should consider referring those patients who have positive case detection of PA to an endocrinologist.

IV. Other Forms of Mineralocorticoid Excess or Effect

Table 1 lists medical disorders associated with mineralocorticoid excess resulting from deoxycorticosterone (DOC) or cortisol. Clinicians should consider these disorders if blood levels of aldosterone and renin are low in a patient with hypertension and hypokalemia (81).

A. Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by enzymatic defects in adrenal steroidogenesis that result in the deficient secretion of cortisol (82, 83). The lack of inhibitory feedback by cortisol on the hypothalamus and pituitary produces a corticotropin (ACTH)-driven buildup of cortisol precursors proximal to the enzymatic deficiency.

Approximately 90% of CAH cases are caused by 21-hydroxylase deficiency, which does not result in hypertension (84). Deficiencies of 11β-hydroxylase (CYP11B1, P450c11) or 17α-hydroxylase (CYP17, P450c17) cause hypertension and hypokalemia because of hypersecretion of the mineralocorticoid DOC. The mineralocorticoid effect of increased circulating levels of DOC also decreases renin and aldosterone secretion. These mutations are autosomal recessive in inheritance and are typically diagnosed in childhood. However, partial enzymatic defects have been shown to cause hypertension in adults.

11β-Hydroxylase deficiency

Prevalence. 11β-hydroxylase deficiency causes approximately 5% of all cases of CAH; the prevalence in whites is one in 100,000 (85). Research has described more than 40 mutations in *CYP11B1* (the gene encoding 11β-hydroxylase) (86). There is an increased prevalence among Sephardic Jews from Morocco, suggestive of a founder effect.

Clinical presentation. The impaired conversion of DOC to corticosterone results in high levels of DOC and 11-deoxycortisol; the substrate mass effect results in increased levels of adrenal androgens. Girls with CAH present in infancy or childhood with hypertension, hypokalemia, acne, hirsutism, and virilization. Boys with CAH due to 11β-hydroxylase deficiency present with hypertension, hypokalemia, and pseudoprecocious puberty. Approximately two-thirds of patients have mild to moderate hypertension.

Who should be screened? Clinicians should screen children, adolescents, and young adults who present with hypertension, spontaneous hypokalemia, and low levels of aldosterone and renin. Suspicion for this defect should be highest in girls with virilization and boys with pseudoprecocious puberty.

Case-detection tests. The initial screening tests include measuring blood levels of DOC, 11-deoxycortisol, androstenedione, testosterone, and dehydroepiandrostenedione-sulfate (DHEA-S), all of which should be increased above the upper limit of their respective reference ranges (Table 4). If levels of these hormones are above their reference ranges in patients with hypertension and hypokalemia, clinicians should pursue confirmatory testing, including germline mutation testing.

17α-Hydroxylase deficiency

Prevalence. 17α-Hydroxylase deficiency is a very rare cause of CAH. Good prevalence data are not available, but prevalence is likely less than one in 1,000,000 live births (87).

Clinical presentation. 17α-Hydroxylase is essential for the synthesis of cortisol and gonadal hormones, and deficiency results in decreased production of cortisol and sex steroids. Genetic 46,XY male patients present with either pseudohermaphroditism or phenotypically as female, and 46,XX female patients present with primary amenorrhea. Therefore, a person with this form of CAH may not come to medical attention until puberty.

Who should be screened? Clinicians should screen children, adolescents, and young adults who present with hypertension and spontaneous hypokalemia and low levels of aldosterone and renin. Suspicion for this mutation should be highest in the setting of primary amenorrhea and pseudohermaphroditism. Although very rare, there is an increased prevalence of 17α-hydroxylase deficiency among Dutch Mennonites.

Case-detection tests. The initial screening tests include measuring blood levels of androstenedione, testosterone, DHEA-S, 17-hydroxyprogesterone, aldosterone, and cortisol—all of which should be either low or at the lower quartile of their respective references ranges. The plasma concentrations of DOC and corticosterone should be above the upper limit of their respective reference ranges (Table 4). If levels of these hormones are above their reference ranges in patients with hypertension and hypokalemia, clinicians should pursue confirmatory testing, including germline mutation testing.

B. Deoxycorticosterone-producing tumor

Prevalence

Pure DOC-producing adrenal tumors are very rare and are usually large and malignant (88). Some studies have reported patients with benign DOC-producing adrenocortical adenomas (89).

Clinical presentation

Some of these adrenal neoplasms cosecrete androgens and estrogens in addition to DOC, which may cause virilization in women or feminization in men. The typical clinical presentation would be relatively rapid onset of marked hypertension associated with hypokalemia and low blood levels of aldosterone and renin. There is no specific age group that has an increased prevalence of these rare tumors.

Who should be screened?

Clinicians should screen patients who present with hypertension, spontaneous hypokalemia, and low levels of aldosterone and renin.

Table 4. Adrenal-Related Test Findings in Patients With Nonaldosterone-Mediated Mineralocorticoid Excess or Effect[a]

Disorder	24-h UFC	Urinary Cortisol: Cortisone Ratio	DOC	11-Deoxy-cortisol	Androstenedione	DHEA-S
11β-hydroxylase deficiency	↓	—	↑↑↑	↑↑↑	↑↑↑	↑↑↑
17α-hydroxylase deficiency	↓	—	↑	↑	↓	↓
DOC-producing tumor	—	—	↑↑↑	—	—	—
Primary cortisol resistance	↑↑	—	↑	↑	↑	↑
Apparent mineralocorticoid excess syndrome	↑↑↑↑[b]	↑↑↑↑	↑	—	—	—

Abbreviations: —, no change; UFC, urinary free cortisol.

[a] All of these patients have low or undetectable levels of aldosterone and renin.

[b] 24-Hour UFC excretion is markedly increased if the apparent mineralocorticoid excess is due to severe Cushing syndrome (*e.g.,* ectopic ACTH syndrome).

Case-detection tests

A high level of plasma DOC or urinary tetrahydrodeoxycorticosterone and a large adrenal tumor appearing on computed tomography (CT) confirm the diagnosis. Aldosterone secretion in these patients is typically suppressed.

C. Primary cortisol resistance

Prevalence

Patients with primary cortisol (glucocorticoid) resistance, a rare familial syndrome, can have increased cortisol secretion and plasma cortisol concentrations without evidence of Cushing syndrome (90, 91). Genetic defects in the glucocorticoid receptor and the steroid-receptor complex cause primary cortisol resistance.

Clinical presentation

The syndrome is characterized by hypokalemic alkalosis, hypertension, increased plasma concentrations of DOC, and increased adrenal androgen secretion. Hypertension and hypokalemia are due to the combined effects of excess DOC and increased cortisol access to the mineralocorticoid receptor, resulting from high rates of cortisol production that overwhelm 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2) activity.

Who should be screened?

Clinicians should screen patients (primarily children) who present with hypertension, spontaneous hypokalemia, and low levels of aldosterone and renin.

Case-detection tests

The initial screening tests include measuring blood levels of cortisol, DOC, 11-deoxycortisol, androstenedione, testosterone, and DHEA-S—all of which are usually above the upper limit of their respective reference ranges (Table 4). In addition, 24-hour urinary cortisol excretion is above the upper limit of the reference range and serum ACTH is not suppressed. Confirmatory testing includes germline mutation testing.

D. Apparent mineralocorticoid excess syndrome

Apparent mineralocorticoid excess is the result of impaired activity of the microsomal enzyme HSD11B2, which normally inactivates cortisol in the kidney by converting it to cortisone (an inactive 11-keto compound) (92). Cortisol can be a potent mineralocorticoid, and when HSD11B2 is genetically deficient or its activity is blocked, high levels of cortisol are present in the kidney.

Prevalence

Decreased HSD11B2 activity may be hereditary or it may be secondary to the pharmacologic inhibition of enzyme activity by glycyrrhizic acid [the active principle of licorice root (*Glycyrrhiza glabra*)] (93). The congenital forms are rare autosomal recessive disorders; researchers have identified fewer than 50 of these cases worldwide (94).

Clinical presentation

Congenital apparent mineralocorticoid excess typically presents in childhood with hypertension, hypokalemia, low birth weight, failure to thrive, hypertension, polyuria and polydipsia, and poor growth (86). Acquired apparent mineralocorticoid excess due to licorice root ingestion presents with hypertension and hypokalemia; the cause is revealed by the patient's medical history. When massive cortisol hypersecretion associated with Cushing syndrome due to ectopic ACTH syndrome overwhelms HSD11B2, hypokalemic hypertension may be one of the outcomes (95).

Who should be screened?

Clinicians should screen patients with apparent mineralocorticoid excess due to congenital deficiency or HSD11B2 inhibition; these patients can have hypertension, hypokalemia, metabolic alkalosis, and low renin, low aldosterone, and normal plasma cortisol levels.

Case-detection tests

Clinicians can confirm a diagnosis of apparent mineralocorticoid excess by demonstrating an abnormally high

ratio of cortisol to cortisone in a 24-hour urine collection. The characteristic abnormal urinary cortisol-cortisone metabolite profile reflects decreased HSD11B2 activity; the ratio of cortisol to cortisone is typically increased 10-fold above the normal value (92). The mineralocorticoid excess state caused by ectopic ACTH secretion is related to the high rates of cortisol production that overwhelm HSD11B2 activity. DOC levels may also be increased in severe ACTH-dependent Cushing syndrome and contribute to hypertension and hypokalemia in this disorder.

E. Liddle syndrome: abnormal renal tubular ionic transport

In 1963, Grant Liddle described an autosomal dominant renal disorder with a presentation similar to PA that includes hypertension, hypokalemia, and inappropriate kaliuresis (96). However, blood levels of aldosterone and renin were very low, so researchers termed the disorder pseudoaldosteronism.

Prevalence

Autosomal dominant mutations in the β or γ subunit of the amiloride-sensitive epithelial sodium channel cause Liddle syndrome (86). It is extremely rare, with fewer than 30 families reported worldwide (97).

Clinical presentation

This mutation results in enhanced activity of the epithelial sodium channel, and patients present with increased renal sodium reabsorption, potassium wasting, hypertension, and hypokalemia. However, as mentioned, blood levels of aldosterone and renin are low.

Who should be screened?

Clinicians should screen children and adults who present with hypertension, spontaneous hypokalemia, and low levels of aldosterone and renin. A family history of hypertension associated with hypokalemia makes Liddle syndrome more likely.

Case-detection tests

A clinician who discovers low aldosterone and renin levels in a hypokalemic hypertensive patient should consider Liddle syndrome. Once the clinician excludes the other causes of this presentation (Table 4), they should consider treating the patient with amiloride or triamterene. The clinician can easily distinguish Liddle syndrome from apparent mineralocorticoid excess based on a marked improvement in hypertension when amiloride or triamterene are combined with a sodium-restricted diet. Other ways to distinguish Liddle syndrome from apparent mineralocorticoid excess include a lack of efficacy of spironolactone and dexamethasone, and a normal 24-hour urine cortisone/cortisol ratio. Clinical genetic testing is available.

V. Secondary Aldosteronism and Renovascular Hypertension

A. Definition and prevalence

Seminal studies more than 80 years ago established that reduced blood flow to the kidneys could initiate a rise in systemic BP, defined as RVH. Over the years, there has been extensive research regarding the renin-angiotensin-aldosterone system (RAAS) as a primary hormonal axis underlying this process, and renovascular disease has become one of the most widely studied "angiotensin-dependent" models of hypertension and vascular disease.

Secondary hyperaldosteronism reflects pathologically elevated aldosterone levels due to activation of the renin-angiotensin axis; RVH is one such instance. Other situations associated with secondary aldosterone excess include renal infarction, volume depletion with or without administration of diuretics, renal hypoperfusion related to cardiac or hepatic failure, or (rarely) primary overproduction of renin from a juxtaglomerular tumor. Secondary hyperaldosteronism associated with volume depletion or cardiac or hepatic failure is not typically associated with hypertension.

Most studies addressing the prevalence of renovascular disease focus on the frequency of identifying renal artery stenosis rather than establishing the actual occurrence of hypertension. This distinction is important because the kidney tolerates some degree of vascular occlusion without clinical manifestations. The prevalence of actual RVH is substantially less than that for renal artery stenosis. Some argue that establishing a diagnosis of RVH depends on reducing BP after technically successful revascularization or removal of the affected kidney.

Most renal artery stenosis in the United States is caused by atherosclerotic disease (≈85%) or some form of fibromuscular dysplasia (≈15%). The prevalence of atherosclerotic renal artery stenosis increases with age and other atherosclerotic manifestations. Population-based studies indicate that 6.8% of individuals older than 65 years have renal artery stenosis with more than 60% lumen occlusion.

Studies of image-based screening in patients undergoing angiography for other atherosclerotic diseases showed that 14% to 33% of these patients have renal artery stenosis, depending upon the extent of disease. Similarly, studies of image-based screening in potential kidney donors showed that 3% to 5% of normal subjects have some degree of fibromuscular dysplasia.

How often these lesions produce RVH and the true prevalence of RVH remain unclear, but estimates from referral hypertension centers suggest that 1% to 5% of hypertensive subjects may have a component of RVH.

B. Clinical presentations

Renovascular occlusive disease leading to RAAS activation can produce a spectrum of manifestations including RVH, accelerated/malignant phase hypertension, impaired cardiac function, circulatory congestion ("flash pulmonary edema"), and, ultimately, parenchymal kidney injury with irreversible loss of kidney function. Recognizing these manifestations and establishing the likelihood of improving BP control and cardiac and kidney function remain major challenges for clinicians. Table 5 details the clinical scenarios that warrant screening and diagnostic studies for RVH.

C. Who should be screened?

The utility of screening and diagnostic testing for RVH and other causes of secondary aldosteronism partly depends upon the commitment to act upon the results. The pressure to identify renal artery stenosis has diminished in recent years. One reason for this is that medical therapy is remarkably effective at blocking the RAAS, without the need for either endovascular or surgical revascularization. Several recent prospective randomized controlled trials (RCTs) have failed to identify major additional benefits from stent revascularization for atherosclerotic renal artery stenosis (98). Thus, it may be argued that clinicians should limit screening for these disorders to cases where medical therapy is failing or the risks of circulatory or renal failure truly warrant restoring the circulation, as identified in Table 5. Because these RCTs failed to enroll or excluded many high-risk subjects, clinicians must individualize treatment of many patients, particularly those with rapidly declining kidney function, accelerated hypertension, or episodes of pulmonary edema.

D. Case-detection tests

Imaging studies

Renal artery duplex ultrasound measurements of peak systolic velocity along the vessel path have a sensitivity above 85% and specificity of 92% for atherosclerotic disease with more than 60% lumen occlusion (99, 100). Renal artery duplex is relatively inexpensive and available; rarely has false-positive results in experienced laboratories; and provides information on kidney size, resistive index, and perfusion. However, it commonly has operator-dependent false-negative results and technical failures (101).

CT angiography has a sensitivity above 90% and specificity of 97%, similar to catheter angiography and high-resolution magnetic resonance angiography. CT angiography provides detailed imaging of the cortex and medulla with high-resolution of vessels. However, it is relatively expensive and has the potential for iodinated-contrast toxicity.

Magnetic resonance angiography provides detailed imaging and functional testing of oxygenation imaging. However, it is also relatively expensive and has the potential for gadolinium toxicity.

Radionuclide scintigraphy, with or without ACE inhibition (captopril renogram), rarely produces false-negative findings and provides limited information about large-vessel disease. However, it commonly has false-positive findings with impaired renal function.

Table 5. Clinical Scenarios Associated With Renovascular Disease

Clinical Scenario
Onset hypertension before age 30 years
Accelerated, resistant, malignant hypertension
Deterioration of renal function (rise in creatinine more than 30% of pretreatment levels) in response to ACE inhibitors or angiotensin-receptor blockers
New onset of hypertension after age 50 years (suggestive of atherosclerotic renal artery stenosis)
Asymmetric kidneys with more than 1.5-cm difference in size and otherwise unexplained loss of kidney function
Sudden unexplained pulmonary edema ("flash pulmonary edema")

Endocrine testing studies

Clinicians use peripheral plasma renin activity, direct renin mass measurements, and plasma aldosterone concentrations to define secondary aldosterone excess. However, these measurements are nonspecific and highly subject to conditions of testing, including sodium balance and drug therapy. Measuring plasma renin activity after administrating an ACE inhibitor (*i.e.*, captopril)—a measurement referred to as "enhanced plasma renin activity"—is nonspecific and has limited sensitivity and poor predictive value.

Clinicians commonly used renal vein renin measurements for diagnostic testing related to surgical revascularization. Although moderately invasive, these measurements have substantial validity for predicting BP response to either revascularization or nephrectomy (102) and allow localization of renin production in specific disorders (*e.g.*, juxtaglomerular cell tumors, renal infarction). However, they are subject to testing conditions (as are all hormonal measurements of the RAAS). Clinicians use these measurements less often in the endovascular stent era, in part because BP is less commonly the primary motivation for diagnostic testing (vs salvaging kidney function or treating recurrent pulmonary edema).

VI. Other Endocrine Disorders Associated With Hypertension

A. Cushing syndrome

Prevalence

Iatrogenic Cushing syndrome is relatively common. However, endogenous Cushing syndrome is rare, with an

incidence of less than one per 1 million people per year (103). Excess ACTH secretion by a pituitary tumor is the cause of endogenous Cushing syndrome in 85% of patients and is termed "Cushing disease." Cushing disease occurs five times more frequently in women than in men, with the peak incidence occurring between 20 and 50 years of age. Ectopic ACTH-secreting neoplasms and the ACTH-independent forms of Cushing syndrome (*e.g.*, adrenal adenoma, adrenal carcinomas, and adrenal nodular hyperplasias) are responsible for 15% of the endogenous cases. Hypertension occurs in 75% to 80% of patients with Cushing syndrome (104, 105). The mechanisms of hypertension include increased production of DOC, enhanced pressor sensitivity to endogenous vasoconstrictors (*e.g.*, epinephrine, angiotensin II), increased cardiac output, activation of the RAAS by increased hepatic production of angiotensinogen, and cortisol activation of the mineralocorticoid receptor.

Clinical presentation

Typical signs and symptoms of Cushing syndrome include the following: weight gain with central obesity (thin extremities), facial rounding and plethora, supraclavicular fat pads, dorsocervical fat pads, easy bruising ("spontaneous"), fine "cigarette paper skin" and decreased skin-fold thickness, poor wound healing, purple striae (usually >1 cm in width), proximal muscle weakness, emotional and cognitive changes (*e.g.,* irritability, crying, depression, restlessness), hirsutism, hyperandrogenism (*e.g.,* acne), hypertension, osteopenia and osteoporosis, glucose intolerance and diabetes mellitus, polyuria, hyperlipidemia, opportunistic and fungal infections (*e.g.,* mucocutaneous candidiasis, tinea versicolor, pityriasis), menstrual dysfunction and altered reproductive function, and renal lithiasis. These clinical features may occur slowly over time. Therefore, comparing the patient's current appearance with old photographs is invaluable. Many of these signs and symptoms are common and not distinguishing features (*e.g.,* obesity, hypertension, abnormal glucose tolerance, and menstrual dysfunction).

Who should be screened?

Clinicians should screen any patient with hypertension who presents with signs or symptoms consistent with the clinical presentation of Cushing syndrome (as outlined in the previous paragraph).

Case-detection tests

Standard laboratory studies may reveal fasting hyperglycemia, hyperlipidemia, hypokalemia, and leukocytosis with relative lymphopenia. Mineralocorticoid production is usually normal in endogenous Cushing syndrome; aldosterone and renin levels are usually normal or suppressed, and DOC levels are normal or mildly increased. Aldosterone, DOC, and sex steroids may be elevated in adrenal carcinomas (106).

The case-detection tests for endogenous cortisol excess include a 1-mg overnight dexamethasone-suppression test and measuring midnight salivary cortisol and free cortisol in a 24-hour urine collection. When results of case-detection tests for Cushing syndrome are abnormal, clinicians should pursue confirmatory testing. The Endocrine Society's clinical practice guideline on Cushing syndrome further details tests that confirm Cushing syndrome and determine the cause of cortisol excess (95).

B. Thyroid dysfunction

Hyperthyroidism

Prevalence. Hyperthyroidism is more common in women, with a prevalence between 0.5% and 1.0% (107–109). In the National Health and Nutrition Examination Survey III, two of 1,000 subjects who were not taking thyroid medication and not reporting histories of thyroid disease had "clinically significant" hyperthyroidism (110). Prevalence in the elderly population ranges between 0.4% and 2.0% (111–113). The most common causes include Graves' disease, toxic multinodular goiter, toxic adenoma, and thyroiditis. There are no data on the prevalence of hyperthyroidism in patients who present with hypertension.

Clinical presentation. When excessive amounts of circulating thyroid hormones interact with thyroid hormone receptors on peripheral tissues, both metabolic activity and sensitivity to circulating catecholamines increase. Thyrotoxic patients usually have tachycardia, high cardiac output, increased stroke volume, decreased peripheral vascular resistance, and increased systolic BP (114). Clinical presentation may be dominated by weight loss (despite an increased appetite), heat intolerance, muscle weakness, and hyperhidrosis. In addition, in those patients with Graves' disease, symptoms related to thyroid ophthalmopathy may dominate the presentation.

Who should be screened? Clinicians should screen all patients with hypertension suspected of also having hyperthyroidism based on the clinical presentation.

Case-detection tests. Case-detection testing includes measuring blood concentrations of thyroid-stimulating hormone and free thyroxine. In addition, these patients should undergo a comprehensive history and physical examination that includes measuring pulse rate, BP, respiratory rate, body weight, and thyroid gland palpation. After establishing clinical and biochemical

hyperthyroidism, clinicians often also perform imaging tests and assess thyroid autoantibodies; both these tests can be useful in identifying the underlying cause of hyperthyroidism. Initial management in patients with hypertension and hyperthyroidism includes using a β-adrenergic blocker to treat hypertension, tachycardia, and tremor. The definitive treatment of hyperthyroidism is cause specific (115).

Hypothyroidism

Prevalence. The prevalence of subclinical hypothyroidism ranges between 4.3% and 8.5%, and the prevalence of overt hypothyroidism ranges between 0.3% and 0.4% (110, 116). The frequency of hypertension (usually diastolic) is increased threefold in patients with hypothyroidism and may account for as many as 1% of cases of diastolic hypertension in the general population (117, 118). The mechanisms for BP elevation include increased systemic vascular resistance and extracellular volume expansion. There are no data on the prevalence of hypothyroidism in patients who present with hypertension.

Clinical presentation. The clinical presentation of hypothyroidism depends on the degree of thyroid hormone deficiency and the rapidity of the loss of the thyroid hormones thyroxine and triiodothyronine. Patients may be lethargic and exhibit slow cerebration, slow speech patterns, cold intolerance, constipation, and bradycardia. These patients typically have dry, brittle hair and edema of the face and eyelids (periorbital edema), which is associated with the subcutaneous accumulation of glycosaminoglycans. The tongue may be thickened and the voice deep and coarse. Patients with hypothyroidism generally have a slow pulse and diastolic hypertension. Cardiac output is decreased, and patients may experience dyspnea from exertion.

Who should be screened? Clinicians should screen all patients for hypothyroidism who have hypertension with any of the features listed in the previous paragraph.

Case-detection tests. Measuring serum thyrotropin and free thyroxine are the key case-detection tests. In primary hypothyroidism, the serum thyrotropin concentration is above the reference range and the blood concentration of free thyroxine is usually below the lower limit of the reference range. In central hypothyroidism due to hypothalamic or pituitary dysfunction, the serum thyrotropin concentration is inappropriately low for the low levels of free thyroxine. Treating thyroid hormone deficiency decreases BP in two-thirds of patients with hypertension and normalizes BP in the remainder. Synthetic levothyroxine is the treatment of choice for hypothyroidism (119).

C. Hypercalcemia and primary hyperparathyroidism

Prevalence

The most common cause of hypercalcemia is primary hyperparathyroidism. The prevalence of primary hyperparathyroidism is 0.20% in women and 0.09% in men, and the incidence increases with advancing age (120). Hypercalcemia is associated with an increased frequency of hypertension (121). The frequency of hypertension in patients with primary hyperparathyroidism varies from 10% to 60% (121). There are no data on the prevalence of primary hyperparathyroidism in patients who present with hypertension.

Clinical presentation

Most patients with primary hyperparathyroidism are asymptomatic. Others may present with symptoms related to chronic hypercalcemia, such as polyuria and polydipsia, constipation, osteoporosis, renal lithiasis, peptic ulcer disease, and hypertension. The mechanisms of hypertension are unclear because there is no direct correlation with the elevated parathyroid hormone or calcium levels. The hypertension associated with hyperparathyroidism can also occur as a complication of hypercalcemia-induced renal impairment.

Who should be screened?

Clinicians should screen all patients with hypertension and hypercalcemia for hyperparathyroidism.

Case-detection tests

Clinicians can confirm hyperparathyroidism as the cause of hypercalcemia by measuring serum parathyroid hormone and 24-hour urinary calcium excretion. Clinicians use urine calcium measurements to exclude familial hypocalciuric hypercalcemia (122). Clinicians should consider referral to a specialist when hypercalcemia is present. The treatment of hyperparathyroidism is surgery; hypertension may or may not remit after successful parathyroidectomy (123, 124).

D. Acromegaly

Prevalence

Acromegaly is a rare disorder, with a prevalence of 40 to 70 cases per 1 million people (125, 126).

Clinical presentation

Chronic growth hormone excess from a growth-hormone–producing pituitary tumor results in the clinical syndrome of acromegaly. The effects of chronic excess growth hormone include acral and soft tissue overgrowth, progressive dental malocclusion, degenerative arthritis related to chondral and synovial tissue overgrowth within joints, low-pitched sonorous voice,

excessive sweating and oily skin, perineural hypertrophy leading to nerve entrapment (*e.g.,* carpal tunnel syndrome), cardiac dysfunction, and hypertension (127). Hypertension occurs in 20% to 40% of the patients and is associated with sodium retention and extracellular volume expansion (128, 129). There are no data on the prevalence of acromegaly in patients who present with hypertension.

Who should be screened?

Patients with hypertension who should be screened for acromegaly include patients with incidentally discovered pituitary tumors and patients with typical clinical manifestations of acromegaly, especially those with acral and facial features or who have several associated conditions (*e.g.,* sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension).

Case-detection tests

Measuring serum insulin-like growth factor 1 is the case-detection test of choice (130). Clinicians should consider referring patients to an endocrine subspecialist when insulin-like growth factor 1 is above the upper limit of the age- and sex-adjusted reference range. Pituitary surgery is the treatment of choice; if necessary, clinicians also prescribe medical therapy or irradiation or both (130). Hypertension associated with acromegaly is treated most effectively by reducing excess growth hormone (129). If a surgical cure is not possible, the hypertension usually responds well to diuretic therapy.

E. Obstructive sleep apnea

OSA is repeated partial (hypopnea) or complete (apnea) airway closure during sleep. It is characterized by sleep disruption, intermittent hypoxemia and hypercapnea, and changes in intrathoracic pressure. The physiological effects of OSA, including those on endocrine pathways, are multiple and complex. Experimental and clinical studies indicate that OSA induces multiple adverse effects, including endothelial dysfunction, inflammation, oxidative stress, vascular stiffness, RAAS stimulation, metabolic abnormalities, cardiac structure and function alterations, and sympathetic nervous system activation (131).

OSA is strongly associated with hypertension; this is particularly true with resistant or difficult-to-treat hypertension (132–140). Several, but not all, observational studies have reported a positive correlation between aldosterone levels and the severity of OSA in patients with resistant hypertension (141–146). Studies suggest that intensifying diuretic therapy (including mineralocorticoid receptor antagonists) can reduce the severity of OSA in patients with resistant hypertension (147–150).

Prevalence

Approximately 20% of adults have at least mild sleep apnea (apnea-hypopnea index, 5 to 14 events per hour), and an estimated one in 15 has moderate to severe OSA (apnea-hypopnea index, $\geq$15 events per hour) (134). OSA is two to three times more common in men than women (151, 152), although the prevalence of OSA seemingly increases in women after menopause (153). OSA is strongly associated with being overweight or obese, with a prevalence of 60% to 80% in obese individuals (154, 155). OSA is also associated with type 2 diabetes (156). The prevalence of OSA increases with age, being two to three times more common in older persons (>65 years) compared with younger individuals (30 to 64 years) and having an estimated prevalence of 65% in a community-based sampling of persons >65 years of age (157–159). OSA appears to be more common in African Americans than whites, particularly children and adolescents, and studies of adults suggest that African Americans tend to have more severe OSA than whites (160–163).

OSA and hypertension commonly coexist. Approximately 50% of individuals with OSA are hypertensive, and an estimated 30% to 40% of patients with hypertension have OSA (131, 136–138). OSA is particularly prevalent in persons with resistant hypertension, with a prevalence of 70% to 90% (140–142, 146). However, continuous positive airway pressure (CPAP) therapy in patients with OSA and resistant hypertension, although beneficial, has not resulted in dramatic improvements in BP. For example, an RCT that blindly assessed outcomes of 117 patients with moderate to severe OSA who were randomly assigned to 6-month CPAP treatment or no therapy reported no significant difference in any BP change between CPAP and control groups (164). In an open-label, multicenter RCT of parallel groups of patients with OSA and resistant hypertension, CPAP treatment of 12 weeks compared with control groups resulted in a decrease in 24-hour mean BP and diastolic BP and an improvement in the nocturnal BP pattern (165).

Clinical presentation

Individuals with OSA often complain of a history of snoring (particularly loud snoring that is bothersome to others), episodes of witnessed apneas or chaotic breathing, and/or daytime sleepiness that is often severe. Other complaints include fragmented sleep with frequent arousals, snore arousals with a choking or gasping sensation, nocturia, dry mouth and/or headaches in the morning, daytime fatigue, cognitive dysfunction including memory impairment and/or difficulty concentrating, and symptoms of gastroesophageal reflux disease. Associated disease processes that are increased in

the setting of OSA include hypertension, heart disease, atrial fibrillation, prior stroke, gastroesophageal reflux disease, and sexual dysfunction.

The physical examination can be unremarkable, but OSA is more likely in persons who are obese (body mass index >30 kg/m^2), older (>65 years), have an enlarged neck circumference (men, >43 cm; women, >37 cm), a small upper airway, and/or retrognathia or micrognathia.

Who should be screened?

Clinicians should screen all hypertensive individuals for OSA based on a history of relevant signs and symptoms. Although the decision to pursue definitive testing must be individualized, a history of loud snoring, witnessed apnea, and/or complaints of otherwise unexplained daytime sleepiness likely warrants further testing. Although resistant hypertension by itself is not yet sufficient reason alone to order definitive testing for OSA, clinicians should have a low threshold for ordering such testing, given the extraordinarily high prevalence of OSA in persons with resistant hypertension.

Case-detection tests

Polysomnography. The definitive diagnosis of OSA requires evaluation by polysomnography. Historically, sleep technicians monitor patients in a sleep laboratory. This allows for continuous recording of multiple parameters, including sleep staging using an electroencephalogram; eye movements, using an electrooculogram; body position, using video; limb movements, using an electromyogram; respiration (*i.e.*, flow, effort, oxygen saturation); and snoring. Recently, however, there is growing use of home sleep monitoring systems for diagnosing OSA. Such home-based systems are less expensive and more convenient for the individual being tested, but generally measure fewer parameters (often forgoing electroencephalogram and electrooculogram assessments). If a clinician suspects OSA in a hypertensive person, the clinician should refer the patient to a certified sleep specialist for evaluation and appropriate polysomnographic evaluation, whether via monitored or home testing.

VII. Summary of Overall Approach to Considering and Detecting Endocrine Hypertension

Clinical context is important. For example, case detection for endocrine hypertension may not be clinically important in an older patient with multiple life-limiting comorbidities. However, screening for endocrine hypertension may be key to enhancing and prolonging life in most patients with hypertension, especially younger patients.

A. Case in point

A 36-year-old woman presents with new-onset hypertension with repeated measurements of a systolic BP of 150 to 170 mm Hg and a diastolic BP of 95 to 110 mm Hg. Except for occasional headaches and palpitations, she is asymptomatic. She has been healthy and active. She does not use tobacco or alcohol. She has gained 5 kg over the past 1 year, and she has a history of recurrent renal lithiasis. Her husband said that she snores at night, but he has not observed periods of apnea. On questioning, she said that she does not feel rested in the morning. When she was in her 30s, she was told that she had a goiter. Her first menstrual period was at age 11 years and she has three biologic children. She does not eat confectionary licorice. Her family history is positive for hypertension in her father, hyperthyroidism in her maternal grandmother, and hypothyroidism in her mother. There is no family history of endocrine disorders or adrenal tumors.

The degree of hypertension in this 36-year-old woman merits an investigation for secondary causes. Because of the history of headaches and palpitations, case-detection testing for pheochromocytoma is indicated. We should check serum calcium and phosphorus levels because of her history of renal lithiasis. The weight gain over the past year could be a clue to Cushing syndrome and we should exclude this diagnosis. Her history of snoring and not feeling rested in the morning should prompt testing for OSA. We should exclude thyroid dysfunction based on her history of a goiter and family history of autoimmune thyroid disease. Because there are usually no symptoms or signs of PA, we should exclude this diagnosis in all patients with marked hypertension. In addition, she is in the age group in which we should consider fibromuscular dysplasia of the renal arteries. Depending on the degree of hypertension and urgency, we can perform case-detection testing for the potential diagnoses listed here either sequentially or simultaneously.

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