Nuances of Adrenal Metabolic Workup

Julie Hallanger Johnson, MD

KEYWORDS

• Adrenal nodule • Adrenal mass • Adrenal cancer • Pheochromocytoma • Hyperaldosteronism • Adrenal function evaluation

KEY POINTS

- Consider imaging characteristics in evaluation and diagnosis of adrenal nodules.
- Basic adrenal function testing is recommended in all adrenal nodules 1 cm or larger.
- Pheochromocytoma screening is mandatory before any intervention in a patient with adrenal nodule.
- Adrenal venous sampling is important in determining appropriate surgical or medical treatment of primary hyperaldosteronism.
- Adrenal steroid profiling is a tool helpful in adrenal cancer diagnosis and evaluation.

INTRODUCTION

Adrenal glands are small glands sitting just superior to the kidneys initially described anatomically in the 1500s by Bartolomeo Eustachio, though many others described fatty structures superior to the kidney prior to this.[1] It was not until Addison described symptoms of adrenal insufficiency (AI) noted in patients with tuberculosis destruction of the adrenal glands in the mid-1800s that the critical nature of adrenal function was understood.[2] In addition, Brown-Sequard demonstrated that after adrenalectomy, dogs could not survive. Later, the initial description of patients with congenital adrenal hyperplasia led to the early understanding of some components of adrenal cortical function, though the adrenal medullary epinephrine was the first hormone isolated and synthetized around 1901.[1] In the modern era, we now have access to sophisticated imaging, laboratory testing, and provocative testing which has improved our understanding of adrenal glands and the approach to diagnosis and treatment of adrenal function.

ADRENAL ENDOCRINE PHYSIOLOGY/ PATHOPHYSIOLOGY

Adrenal physiology is described in other portions of this text in detail. Briefly, the adrenal glands provide "adrenaline" or catecholamines from the adrenal medulla and cortical steroids including the mineralocorticoid aldosterone from the zona glomerulosa, the glucocorticoid cortisol from the zona fasiculata, and androgens dehydroepiandrosterone (DHEA) and dehydoepiandrosterone-sulfate (DHEA-S) from the zona reticularis. These along with their precursors and metabolites provide these substances for the body.

ADRENAL NODULE DISCOVERY AND EVALUATION

Adrenal nodules are common incidental findings on imaging studies (approximately 7%[3]) increasing with age. They include benign lesions, like adrenal adenomas, adrenal nodular hyperplasia, or medullary lesions such as pheochromocytoma. In addition, the rare adrenocortical carcinoma can be seen, or more commonly, other

Division of Endocrinology, Nutrition, and Metabolism, Department of Internal Medicine, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA
E-mail address: hallangerjohnson.julie@mayo.edu

Urol Clin N Am 52 (2025) 243–252
https://doi.org/10.1016/j.ucl.2025.01.006

Abbreviations	
ACC	adrenocortical carcinoma
ACE	angiotensin converting enzyme
ACTH	adrenocorticotropic hormone
AI	adrenal insufficiency
ARB	angiotensin receptor blocker
ARR	aldosterone-to-renin ratio
AVS	adrenal venous sampling

malignancies such as metastases, lymphoma, sarcoma. Benign lesions such as myelolipomas, adrenal cysts, hemorrhage, ganglioneuromas, or hemangiomas are also seen, sometimes mimicking other tumors by imaging features.

Once an adrenal nodule is found, 3 initial questions should be considered.

1. What are the imaging characteristics?
2. What is the size of the adrenal lesion? If previous imaging is available, has it changed?
3. What is the functionality of the adrenal gland?

The first 2 points are discussed elsewhere in this text. We will focus on functional testing of the adrenal gland. It is important to consider patient history, family history of endocrine disorders, and examination findings to determine clinical suspicion for any functional adrenal nodule. It is helpful to consider the imaging features and patient symptoms to direct the metabolic evaluation though some patients will be discovered with mild disease without attributable symptoms. It also can be helpful to consider imaging features to determine extent of work-up and treatment. Up to 40% of nodules are functional, perhaps as many as 50% to 60% of adenomas, which means that functional testing is to be done in all nodules 1 cm or larger.[4]

The basic evaluation for patients with adrenal nodules includes the following: early AM plasma renin activity, aldosterone, adrenocorticotropic hormone (ACTH), DHEA-S, cortisol, plasma metanephrines. This is then followed by a 1 mg overnight dexamethasone suppression testing for mild autonomous cortisol. All these tests and particular nuances are discussed further later. See **Table 1**.

FUNCTIONAL TUMORS

Pheochromocytoma Evaluation

Approximately 4% to 5% of adrenal nodules in a population study were consistent with pheochromocytoma (**Tables 1** and **2**).[5] Classical symptoms of pheochromocytoma include tachycardia, headache, and chest pain, with severe hypertension. These symptoms and the production of metanephrines from these tumors are proportional to the size of the tumor. Testing for pheochromocytoma should be done in adrenal nodules over 1 cm. It may not be necessary to screen if noncontrast hounsfield units (HU) less than 10 on computed tomography.[6]

Screening for pheochromocytoma should be done in all other adrenal lesions or if noncontrast imaging is unavailable. Screening testing can include plasma metanephrines or 24-hour urinary fractionated metanephrines using mass spectrometry assays.

This screening is particularly important before any intervention in setting of adrenal nodules since hypertensive crisis is a concern in undiagnosed pheochromocytomas undergoing surgical procedures or other interventions to avoid hypertensive crisis. This can occur with manipulation of the pheochromocytoma, with biopsy, or with some medications utilized in these patients. This is even true in patients with other malignancies who may have metastatic disease to the adrenal. In one case series of 33 patients with a history of cancer who had adrenalectomy, 8 of them (24%) where found to have a pheochromocytoma.[7]

Plasma metanephrines by mass spectrometry assay, given their ease of collection, are an excellent screening test. However, drawing plasma metanephrines in the seated positive can provide false-positive testing, so repeating the testing in a supine position is recommended if positive. Alternatively, a 24-hour urine fractionated metanephrine testing can be helpful to avoid these issues with positional changes. Patients should be lying supine quietly for 30 minutes (with peripheral intravenous catheter/IV in place) prior to collection to avoid false-positive testing.[8] This is due to the stimulation of norepinephrine in the upright position. Clinicians must also be aware that utilizing normal range values in a supine position draw may lead to false-negative testing. Therefore, astute clinicians should be aware of these potential downfalls to any serum testing. One approach, aside from a repeat test in the supine position, is to collect a 24-hour urinary fractionated metanephrine test after a positive plasma test.[9] The sensitivity of 24-hour urine fractionated metanephrines is 97% with 91% specificity.[10]

Assessment of both plasma and urinary catecholamines can lead to false-positive and false-negative testing. See **Table 2**. Plasma catecholamines are often falsely positive, so not always necessary, and if performed, must be done with 30 minutes of lying supine with IV in place. Some patients with succinate dehydrogenase gene (SDHx) mutations (one of the genetic predisposition syndromes for pheochromocytoma and paragangliomas) can

Table 1
Functional testing in adrenal lesions

Disease	Singe Best Test	Additional Tests	Special Considerations
Pheochromocytoma	Plasma metanephrines	24 h urine metanephrines, 24 h urine catecholamines	Interfering medications, positional changes impact normal values and lab results, clonidine suppression testing
Cortisol autonomy	1 mg overnight dexamethasone suppression test cortisol <1.8 (after confirmation of adrenocorticotropic hormone [ACTH] independence)	ACTH (normal or low) Cortisol (normal or high) DHEA-S (often low)	Dexamethasone metabolism alterations, high cortisol binding globulin, pseudo Cushing Syndrome
Aldosterone-producing adrenal lesions	Early AM plasma renin activity and aldosterone level (to calculate aldosterone/renin ratio)	Confirmatory testing with 24 h urine aldosterone with elevated 24 h urine sodium (after salt load)	Confirmatory testing could include saline suppression or salt load followed by 24 h urine collection. Understand interpretation of adrenal venous sampling procedure
Adrenal cancer	Multihormonal elevations with suspicious imaging studies	24 h urine steroid profiling	Avoid biopsy if resectable

have dopamine-producing tumors, so those patients benefit from full panel testing. Twenty-four-hour urine collections for metanephrines and catecholamines are also helpful in such cases. However, in patients with renal failure, plasma-free metanephrines are more accurate than urine testing.[11]

A 24-hour urine collection should include a 24-hour urine volume and 24-hour urine creatinine to assure it is a complete collection based upon the weight of the patient. For males, the 24-hour urine creatinine is approximately 18 to 24 mg creatinine/kg of body weight and 15 to 20 mg/kg in females though more accurate estimates have been suggested.[12]

False-positive testing serum testing for metanephrines can occur with acetaminophen, alpha-methyldopa, tricyclic antidepressants, buspirone, phenoxybenzamine, monoamine oxidase inhibitors, levodopa, sympathomimetics and drugs like cocaine, sulphasalazine. False-positive urine testing can also occur with the afore mentioned medications as well as sotalol and labetolol.[9]

Any positive testing will require follow-up testing whether additional laboratory testing or imaging. If medications mentioned above can be held safely for 14 days, repeat testing can be done off these medications. If the plasma metanephrine and normetanephrine are both elevated, the likelihood of false positives decreases from only 1 of the 2 being elevated. If the levels are 3 fold higher than upper limit of normal, the likelihood of false-positive testing is low.[9]

Patients with unclear results will require confirmatory testing. The use of a clonidine suppression test has been recommended in cases with uncertain results to differentiate true from false positives. This test was first described in 1981 using suppression of plasma norepinephrine 3 hours after oral clonidine intake of 300 μg to rule out true pheochromocytoma.[13] Using normetanephrine instead of norepinephrine was found to provide improved accuracy. Using elevated levels of normetanephrine and lack of suppression of 50% or more of the normetanephrine levels with clonidine demonstrated a sensitivity of 96% and specificity of 100%.[14]

If pheochromocytoma or paraganglioma is proven, genetic testing is recommended as up to 40% of these patients may have genetic syndrome as a cause.[15]

Table 2
False positive and false negative adrenal nodule testing

Laboratory Test	False Positive	False Negative
Metanephrines	Seated position (plasma) Interfering medications: acetaminophen, alpha-methyldopa, tricyclic antidepressants, buspirone, phenoxybenzamine, monoamine oxidase inhibitors, levodopa, sympathomimetics and drugs like cocaine, sulphasalazine (plasma & urine) Sotalol, labetolol in urine testing[9]	Urine testing in renal failure (plasma preferred)[11]
Plasma Catecholamines	Stress of blood draw or other illness (use IV in place in supine position for more than 30 min before draw)	
Aldosterone-to-Renin Ratio	Suppressed renin and aldosterone slightly elevated	Nonsuppressed renin: diurectics, angiotensin receptor blockers (ARB), Angiotensin converting enzyme inhibitors (ACE-I), pregnancy, renovascular hypertension[23] Lower than expected aldosterone: beta-blocker use, non-steroidal anti-inflammatory drug use, central-acting antihypertensives, ACE-I, ARB, hypokalemia, salt loading
Dexamethasone suppression testing	Stress/pseudo Cushings Obesity High corticotropin-binding protein (pregnancy, oral contraceptive use)	

Cortisol-Producing Adrenal Tumors

Benign adrenal nodules and adrenocortical carcinomas can produce cortisol. The range of symptoms can include mild, even subclinical symptoms to more severe and therefore clinically evidenct disease. Mild autonomous cortisol secretion was previously called subclinical Cushing syndrome. Mild autonomous cortisol secretion is estimated to be present in 20% to 50% of adrenal nodules.[16]

Autonomous cortisol secretion, even when mild, can have negative health impacts such as increased cardiovascular risks, hypertension. When frank cortisol elevation is present, symptoms such as muscle weakness, easy bruising, weight gain, rise in glucose, rise in blood pressure, and bone loss can result.

Testing for cortisol autonomy

In autonomous adrenal nodules, it is rare to have the plasma cortisol be elevated. However, patients with mild cortisol autonomy lose the diurnal variation of cortisol secretion so the mid-day and afternoon cortisol levels are often the same as the morning levels. Therefore, patients benefit from testing for AM and PM cortisol levels. ACTH suppression either partial or complete is a helpful finding in demonstrated excess cortisol. In

addition, a DHEA-S of under 40 mcg/dL in 256 patients with autonomous cortisol-producing adrenal adenomas showed 84% specificity and an 81% positive predictive value.[17]

Cortisol-secreting adrenocortical carcinomas on the other hand, may produce multiple hormones causing elevation more than 1 hormone. Elevation of multiple abnormal adrenal hormones or adrenal hormone precursors along with a low ACTH is concerning for a malignant process. Most adrenocortical carcinomas produce multiple hormones. In addition, the presence of high ACTH, cortisol, and DHEA-S together point to a nonadrenal cause for the Cushing syndrome—ACTH-dependent Cushing syndrome— which is not discussed in this article from pituitary or ectopic sources. Certainly, ACTH can drive bilateral adrenal hyperplasia noted on imaging studies, so clinicians need to keep that possibility in mind in the evaluation of bilateral adrenal nodular disease.

Twenty-four-hour urine-free cortisol collections are often normal in mild autonomous cortisol secretion. If a 24-hour urine is performed, a 24-hour urine volume and 24-hour urine creatinine is recommended (as in pheochromocytoma section testing). The amount of cortisol secretion is a continuous variable, from mild autonomous cortisol secretion in small autonomous adrenal adenomas to severe, such as in large functioning adrenocortical carcinomas.

False positive-testing for cortisol autonomy is possible in the following.

With high urine volumes
With stress (emotional, medical, such as sleep apnea, alcohol use disorders, psychiatric illnesses, anorexia)
Obesity
Glucocorticoid resistance or high corticotropin-binding protein (pregnancy)

In general, salivary cortisol testing at midnight is not helpful in adrenal adenomas, as it is not sensitive enough to detect mild autonomy. It may be helpful to test midnight salivary cortisone,[18] but trials to evaluate this are ongoing.

The single best test for cortisol autonomy, even mild cortisol secretion, is a 1-mg overnight dexamethasone suppression test. This involves taking 1 mg of dexamethasone at bedtime and evaluating an early AM cortisol level. Including a dexamethasone level in the early AM to assure that adequate levels of dexamethasone are achieved is recommended in circumstances where increased metabolism of dexamethasone is suspected. This is important in patients with conditions or medications that can lead to hypermetabolism of the dexamethasone. A normal result to a 1 mg overnight dexamethasone suppression test is an AM cortisol of 1.8 or less.

An 8 mg overnight dexamethasone suppression test is most helpful in patients with ACTH-dependent Cushing syndrome, rather than adrenal nodules.[19]

In bilateral adrenal nodules which have been proven to show ACTH-independent cortisol production, adrenal venous sampling (AVS) after 48 hours of dexamethasone suppression can be considered to lateralize and consider surgical approaches.[20] Utilizing a ratio of cortisol to aldosterone was initially recommended, though newer trends include use of cortisol to metanephrine or epinephrine ratios on the sampling studies.[21] The size of the lesion in some series is more helpful than the lateralization testing. In addition, with medical therapies for Cushing syndrome being more widely available, medical management of these patients is often considered as an option. The discussion of these medications is beyond the scope of this chapter.

Aldosterone-Producing Adrenal Nodules

Although adrenocortical carcinoma can produce aldosterone, primary hyperaldosteronism is most seen in in the setting of an adrenal adenoma or nodular adrenal hyperplasia. Hyperaldosteronism leads to hypertension, hypokalemia due to increased potassium excretion, and increased risk for cardiovascular disease. It is underdiagnosed and is estimated to impact at least 5% to 10% of patients with hypertension.[22]

Just as in cortisol production, the severity of primary hyperaldosteronism ranges from mild to severe. Case finding in patients with hypertension that is uncontrolled on 3 or fewer agents or controlled on 4 agents or in family members of patients with primary hyperaldosteronism is recommended.[23]

Laboratory testing in the morning is recommended, after being upright for at least 2 hours and after being seated for at least 5 minutes.[23] Screening testing includes a morning plasma renin activity as well as plasma aldosterone concentration. The aldosterone-to-renin ratio (ARR) is then calculated. Classically, the renin is fully suppressed, and aldosterone is elevated to 10 ng/dL or higher in patients with primary hyperaldosteronism. In patients with spontaneous hypokalemia, fully suppressed renin, and aldosterone greater than 20, confirmatory testing is not required.

False-negative results can occur with a higher-than-expected renin, or lower than expected aldosterone. Lack of suppression of renin can occur in

the setting of diuretic use, angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) use, sodium restriction, pregnancy, and renovascular hypertension.[23] Aldosterone can be decreased in beta-blocker use, nonsteroidal antiinflammatory drug use, central-acting antihypertensives, ACE-inhibitors and ARBs, hypokalemia, and salt loading. Mineralocorticoid receptor antagonists almost always require discontinuation for at least 4 weeks unless renin is completely suppressed while using them. If renin is suppressed while on therapy, inadequate renin suppression on medical therapy is present. If the clinical suspicion is high and the ARR is not elevated, stopping any potential medication which could cause the false-negative testing and repeating lab testing in 4 to 6 weeks is recommended. This but can be done with substitution of a noninterfering medication like verapamil—extended release, hydralazine, and prazosin, doxazosin, and terazosin.[23]

Aldosterone-to-renin ratio can be elevated if the renin is completely suppressed, and the aldosterone is within the normal range which is why the actual level of aldosterone is also important to interpret. Some centers argue for additional testing in any patient with an abnormal ARR, and other groups use aldosterone levels above 10 ng/dL.[23]

In hypertensive patients with aldosterone levels greater than 20 ng/dL, suppressed renin, and spontaneous hypokalemia, confirmatory laboratory testing is not required. Other patients will require confirmatory testing. Confirmatory testing includes a 24-hour collection after a salt load, a saline suppression test, fludrocortisone suppression testing, and captopril challenge testing.

A 24-hour urine collection for aldosterone, creatinine, and sodium after a 3-day salt load is commonly performed. However, in patients with uncontrolled hypertension, this is not always safe or feasible. These patients can also have severe hypokalemia with the salt load. Therefore, daily blood pressure monitoring and intermittent serum potassium level testing with the salt load is indicated, to maintain optimal blood pressure and potassium. A positive test confirming primary hyperaldosteronism is a 24-hour urine sodium of 200 ng/dL and 24-hour urine aldosterone of 10 mcg/24-hour urine. In one study, 24-hour urine testing for primary hyperaldosteronism showed a primary hyperaldosteronism prevalence of greater than 20%.[24]

Because of the potential challenges noted earlier, other strategies can include a saline suppression test—giving 2 L of normal saline over 4 hours to a patient in a seated position followed by aldosterone level. In normal physiology, aldosterone should suppress to less than 5 ng/dL after this salt load with saline. Between 6 and 8 ng/dL is borderline.[25] Even this amount of salt loading can lead to rise in blood pressure and drop in potassium in patients with primary hyperaldosteronism so careful monitoring is necessary.

Fludrocortisone suppression testing is done by giving fludrocortisone 0.1 mg orally every 6 hours for 4 days along with salt loading and potassium replacement and careful monitoring. Then the renin/aldosterone ratio is done at 10 AM on day 4 with aldosterone above 6 ng/dL as a positive test with suppressed renin.[26] Cortisol was also tested at 7 AM that day and if increased at 10 AM draw, it was noted that ACTH stimulation of aldosterone could have occurred, making the test not interpretable.

Captopril challenge testing can be performed by giving 25 to 50 mg of captopril after patient has been upright for 1 hour or more. Renin activity, aldosterone, cortisol are drawn before and 1 to 2 hours after the medication is given. Suppression of aldosterone of 30% or more is normal, but in patients with primary hyperaldosteronism, it does not suppress.[27] The accuracy of this test has been questioned[28] so the first 2 tests seem to be favored among many groups.

Another important consideration for testing is in young patients or patients with a strong family history of hyperaldosteronism. Genetic evaluation for familial hyperaldosteronism is recommended in these groups of patients.[23]

Adrenal Venous Sampling

Following confirmation testing, imaging of the adrenal glands with CT scanning is recommended if an incidental adrenal nodule is not already the reason for the screening testing. In young patients (under 35 year old) with solitary benign-appearing adrenal adenomas, AVS may be omitted prior to surgery.[23]

AVS is recommended for all other patients interested in surgical treatment of primary hyperaldosteronism. CT alone without AVS can both miss important micronodularity proven as a unilateral source of aldosterone on AVS and misidentify the source as unilateral when it is bilateral. Dr William Young, and colleagues, described this issue well suggesting in this 2004 series that in 194 patients with primary hyperaldosteronism, 24.7% may have had inappropriate or inadequate surgery, and 21.7% would have been treated medically when surgery was the right option if CT alone without AVS was used.[29]

Both medical and surgical treatment can treat hyperaldosteronism, but surgical treatment has

been suggested to be superior to medical therapy. Surgery improves arterial stiffness more than medical therapy.[30] Hypertension and hypokalemia improved more with surgery than with spironolactone.[31] For this reason, patients benefit from surgery for unilateral adrenal adenoma after AVS confirms appropriate side for surgical resection.

Technically the AVS procedure is challenging, particularly cannulating the right adrenal vein which is small and short and enters the inferior vena cava (IVC) at a right angle. Therefore, AVS takes training and is not available in all centers. However, in a multicenter study, centers using AVS found unilateral (therefore, surgically amenable) production of aldosterone more often than centers without AVS available.[22]

Aside from the technical challenges of the procedure itself, the biggest discussion point about AVS in the literature recently has been the use of intravenous (IV) Cortrosyn stimulation during the procedure versus completing the procedure without stimulation. Utilizing IV continuous Cortrosyn stimulation at a dose of 50 mcg/hour starting 30 minutes before the procedure is accepted and intended to reduce variability in the hormonal levels during the procedure. The ratio of adrenal venous aldosterone and cortisol are measured along with peripheral levels. If IV stimulation is utilized, the adrenal:peripheral cortisol is more than 5:1 and without stimulation 2:1. This confirms adrenal vein placement of the catheter for the ratio calculations. Then, the aldosterone:cortisol ratio is calculated for each side. Using this ratio helps correct for the dilutional effect within the left adrenal vein due to its anatomy. Then, using the high side to low side corrected aldosterone offers the determination if the production is unilateral or bilateral. A ratio of 4:1 or more confirms lateralization under Cortrosyn stimulated conditions (sensitivity 95%, specificity 100%).[29]

Certainly, the complexity of these discussions and treatments should lead to multidisciplinary team evaluation and treatment in cases where positive ARR is found.

Adrenocortical Carcinoma

Adrenocortical carcinoma (ACC) is a rare tumor occurring 1 to 2 per million patients. Most patients with ACC present with large tumors, and 60% show hormonal production. These patients come to medical attention often due to hormonal excess symptoms or compressive symptoms from a large mass. However, of incidental adrenal nodules, 0.3% will be an adrenal carcinoma. Often, these patients will be found to have multiple abnormal hormones, but this is not always discovered clinically. Urine steroid profiling (using precursor and metabolite hormones as well as typical hormone production) has been shown to have promise. DHEA-S, estrogen, and testosterone can be seen in adrenocortical tumor production, often adrenal cancers.

In this initial study of 2169 patients with newly diagnosed adrenal lesions, the combination of urine steroid profile abnormalities, noncontrast Hounsfield units of 20 or more, and a tumor size of 4 cm or more lead to a positive predictive value of 76.4% and negative predictive value of 99.7%.[32] Urine steroid profiling is a useful tool in evaluating adrenal lesions, but in small adrenal nodules, the sensitivity is less well understood since there were patients with larger nodules in the initial study.[32] Timing of finding these lesions is important and identifying the concerning masses leads to timely treatment and diagnosis as surgical treatment remains the best chance for long-term survival in ACC.

Nonfunctional Adrenal Lesions

Nonfunctional adrenal lesions are found in incidentally noted adrenal lesions 50% to 60% of the time. They can include a variety of tumor types.

Adrenal adenoma

These lesions have the same imaging characteristics as functional benign lesions with low HU on noncontrast imaging, but all the testing shows lack of function. Over time, these nodules can develop cortisol autonomy, so ongoing surveillance for cortisol autonomy is recommended. This can be accomplished with annual 1 mg dexamethasone suppression testing, particularly in patients with adrenal adenomas over 2 cm in size.[33]

Adrenal myelolipoma

These fatty lesions are benign. Rarely these can coexist with adenomas. Adrenal hyperplasia, adrenal tumors, most commonly adrenal myelolipomas are found in patients with congenital adrenal hyperplasia (CAH) due to ongoing ACTH stimulation of the adrenal tissues. These can be large and 32% of patients with myelolipomas over 6 cm have some compressive symptoms or mass effect with 14% of this size becoming hemorrhagic.[34] In those situations, surgical resection is recommended.

Adrenal hemangioma

These lesions on imaging can mimic pheochromocytoma since they are often bright on T2-weighted MR images. They often are thought to be nonfunctioning pheochromocytomas (with negative functional testing), leading to surgical excision.

Ganglioneuroma

Adrenal ganglioneuromas are rare lesions found on pathology in 1.9% of 1784 patients having adrenalectomy in one series.[35] They are often diagnosed only on pathology at resection since preoperative diagnosis is challenging. Typically, they are hormonally silent and indeterminate on imaging, even with T2 hyperenhancement on MRI like pheochromocytoma. Treatment is surgical.

Metastatic disease to the adrenal

Approximately 8% of adrenal nodules are metastatic disease.[36] Patients with bilateral adrenal nodules can present with AI. One needs to be mindful of this treatable cause for clinical decline. In addition, tumors such as lymphoma and sarcoma can involve the adrenals. Bilateral adrenal masses in patients with a history of malignancy have an elevated risk for being metastases. These do not have the appearance of bilateral adrenal adenomas with low noncontrast HU as we see in disorders like primary bilateral macronodular adrenal hyperplasia.

Adrenal Biopsy

Should be avoided unless—pheochromocytoma is ruled out, surgery is not an option to remove the lesion, and biopsy will change management. Adrenal biopsies can have both false-positive and false-negative findings and can cause hypertensive crisis in patients with undiagnosed pheochromocytoma. Biopsy can upstage adrenal cancer so it should be avoided in favor of surgical resection whenever possible.[37]

Adrenal Insufficiency

In a small percentage of patients (up to 8%), bilateral adrenal metastases can lead to primary AI[38] as can infiltrative diseases like lymphoma or infections as classically described initially by Addison in setting of tuberculosis. Adrenal hemorrhage also can lead to AI if bilateral.

AI should be suspected in the afore-mentioned settings and vague symptoms of fatigue, aching, orthostasis, nausea, and weight loss can be symptoms accompanying primary AI. In addition, the mineralocorticoid loss in primary AI can lead to hyperkalemia and hyponatremia. A high index of suspicion must be held to prevent adrenal crisis which can be fatal if untreated. Testing for AI should include early AM cortisol levels. If outpatient AM cortisol is drawn and above 10, that can be considered normal. Between 5 and 10 can be considered borderline and below 5, low. If borderline or low, a repeat level should be performed with an ACTH level. In primary AI, the ACTH is elevated. In situations where the diagnosis is unclear, a cosyntropin stimulation test is required. That test is done with a baseline cortisol and ACTH assessment, followed by a 250 mcg dose of IV cosyntropin. Testing of the cortisol at 30 minutes and 60 minutes following the cosyntropin is done. An increase of cortisol over 10 with a maximal cortisol of 18 or more indicates normal adrenal function. This test is not ideal for diagnosing secondary AI since the adrenals may still respond normally to stimulation in setting of early secondary AI.

This same vigilance for AI symptoms is also important in the setting of postoperative care of patients with cortisol autonomy or in patients treated for adrenocortical carcinoma with mitotane. These patients require careful care and management perioperatively.

To summarize, clinical evaluation for symptoms of adrenal hormone excess, imaging evaluation for concernings findings for malignancy, and hormonal laboratory testing are critical for the appropriate evaluation and treatment of patients with adrenal lesions.

CLINICS CARE POINTS

- Adrenal function testing for pheochromocytoma, hyperaldosteronism, cortisol autonomy, and additional hormonal evaluation (if worrisome nodule for malignancy) is recommended for adrenal nodules 1 cm or larger.
- Avoidance of adrenal biopsy as much as possible is recommended to avoid upstaging a possible adrenocortical carcinoma.
- AI can be seen in bilateral adrenal metastases, or bilateral adrenal infiltration by neoplasm, infection, or hemorrhage and must be identified rapidly.

DISCLOSURE

Dr J. Hallanger Johnson has no disclosures.

REFERENCES

1. Miller LW, White CP. History of adrenal research: from ancient anatomy to contemporary molecular biology. Endocr Rev 2023;44(1):70–116.
2. Addison T. On the constitutional and local effects of disease of the supra-renal capsules. Taylor and Francis; 1855.
3. Reimondo G, Castellano E, Grosso M, et al. Adrenal incidentalomas are tied to increased risk of diabetes: findings from a prospective study. The Journal of Clinical Endocrinology & Metabolism 2020; 105(4):e973–81.

4. Bancos I, Prete A. Approach to the patient with adrenal incidentaloma. J Clin Endocrinol Metab 2021; 106(11):3331–53.
5. Mantero F, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. J Clin Endocrinol Metab 2000;85(2):637–44.
6. Gruber ML, Strajina V, Bancos I, et al. Not all adrenal incidentalomas require biochemical testing to exclude pheochromocytoma: Mayo clinic experience and a meta- analysis. Gland Surg 2020;9(2):362–71.
7. Adler JT, Mack E, Chen H. Isolated adrenal mass in patients with a history of cancer: remember pheochromocytoma. Ann Surg Oncol 2007;14(8): 2358–62.
8. Lenders JW, Willemsen JJ, Eisenhofer G, et al. Is supine rest necessary before blood sampling for plasma metanephrines? Clin Chem 2007;53(2): 352–4.
9. Lenders MWJ, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metabol 2014;99(6):1915–42.
10. Perry GC, Sawka AM, Singh R, et al. The diagnostic efficacy of urinary fractionated metanephrines measured by tandem mass spectrometry in detection of pheochromocytoma. Clin Endocrinol 2007; 66(5):703–8.
11. Eisenhofer G, Huysmans F, Pacak K, et al. Plasma metanephrines in renal failure. Kidney Int 2005; 67(2):668–77.
12. Kestenbaum B, Ix JH, Gansevoort R, et al. Population-based limits of urine creatinine excretion. Kidney International Reports 2022;7(11):2474–83.
13. Bravo LE, Tarazi RC, Fouad FM, et al. Clonidine-suppression test. N Engl J Med 1981;305(11):623–6.
14. Eisenhofer G, Goldstein DS, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. The Journal of Clinical Endocrinology & Metabolism 2003;88(6):2656–66.
15. Dahia PLM. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. Nat Rev Cancer 2014;14(2):108–19.
16. Fassnacht M, Tsagarakis S, Terzolo M, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 2023;189(1):G1–42.
17. Carafone EL, Zhang CD, Li D, et al. Diagnostic accuracy of dehydroepiandrosterone sulfate and corticotropin in autonomous cortisol secretion. Biomedicines 2021;9(7):741.
18. Debono M, Harrison RF, Whitaker MJ, et al. Salivary cortisone reflects cortisol exposure under physiological conditions and after hydrocortisone. The Journal of Clinical Endocrinology & Metabolism 2016;101(4): 1469–77.
19. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol 2021; 9(12):847–75.
20. Papakokkinou E, Jakobsson H, Sakinis A, et al. Adrenal venous sampling in patients with ACTH-independent hypercortisolism. Endocrine 2019; 66(2):338–48.
21. Acharya R, Dhir M, Bandi R, et al. Outcomes of adrenal venous sampling in patients with bilateral adrenal masses and ACTH-Independent Cushing's Syndrome. World J Surg 2019;43(2):527–33.
22. Rossi GP, Bernini G, Caliumi C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol 2006; 48(11):2293–300.
23. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016;101(5):1889–916.
24. Brown JM, Siddiqui M, Calhoun DA, et al. The unrecognized prevalence of primary aldosteronism. Ann Intern Med 2020;173(1):10–20.
25. Dogra P, Bancos I, Young WF Jr. Primary aldosteronism: a pragmatic approach to diagnosis and management. Mayo Clin Proc 2023;98(8):1207–15.
26. Stowasser M, Gordon RD, Gunasekera TG, et al. High rate of detection of primary aldosteronism, including surgically treatable forms, after 'non-selective' screening of hypertensive patients. J Hypertens 2003;21(11):2149–57.
27. Agharazii M, Douville P, Grose JH, et al. Captopril suppression versus salt loading in confirming primary aldosteronism. Hypertension 2001;37(6): 1440–3.
28. Mulatero P, Bertello C, Garrone C, et al. Captopril test can give misleading results in patients with suspect primary aldosteronism. Hypertension 2007; 50(2):e26–7.
29. Young WF, Stanson AW, Thompson GB, et al. Role for adrenal venous sampling in primary aldosteronism. Surgery 2004;136(6):1227–35.
30. Štrauch B, Petrák O, Zelinka T, et al. Adrenalectomy improves arterial stiffness in primary aldosteronism. Am J Hypertens 2008;21(10):1086–92.
31. Miyake Y, Tanaka K, Nishikawa T, et al. Prognosis of primary aldosteronism in Japan: results from a nationwide epidemiological study. Endocr J 2014; 61(1):35–40.
32. Bancos I, Taylor AE, Chortis V, et al. Urine steroid metabolomics for the differential diagnosis of adrenal incidentalomas in the EURINE-ACT study: a prospective test validation study. Lancet Diabetes Endocrinol 2020;8(9):773–81.

33. He X, Peter PR, Auchus RJ. Approach to the patient with an incidental adrenal mass. Med Clin North Am 2021;105(6):1047–63.
34. Hamidi O, Raman R, Lazik N, et al. Clinical course of adrenal myelolipoma: a long-term longitudinal follow-up study. Clin Endocrinol 2020;93(1):11–8.
35. Lee J-H, Chai YJ, Kim TH, et al. Clinicopathological features of ganglioneuroma originating from the adrenal glands. World J Surg 2016;40(12):1.
36. Ebbehoj A, Li D, Kaur RJ, et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. Lancet Diabetes Endocrinol 2020;8(11):894–902.
37. Naffouje SA, Sabesan A, Hallanger-Johnson J, et al. Adrenal biopsy, as a diagnostic method, is associated with decreased overall survival in patients with T1/T2 adrenocortical carcinoma: a propensity score-matched analysis. J Surg Oncol 2021; 124(8):1261–71.
38. Tallis PH, Rushworth RL, Torpy DJ, et al. Adrenal insufficiency due to bilateral adrenal metastases - a systematic review and meta-analysis. Heliyon 2019;5(5):e01783.