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Review Article

Endocrine Hypertension: Overview of Current Understanding

Chirantan Chowdhury[1], Ruchita Aman [1], Ashrafi Siddiqua [1], Md.Abdullah Al Mamiun[1], K.M Istiak Rohan[1], Md. Mahmud Hasan [1], Ismat Rafeya [1], Marium Zaman [1], Md. Amiruzzaman [1], Farzana Haque[1], Humayun Kabir[1], Mobarak Hosen[1], Kamalesh Chandra Basu[2], Mirza Sharifuzzaman[1], Moinul Islam[1], M Saifuddin[1], Indrajit Prasad[1]

[1]Department of Endocrinology, Dhaka Medical College Hospital, Dhaka, [2]Department of Medicine, Dhaka Medical College Hospital, Dhaka

Key Words
Hypertension, Hormone. Introduction

Abstract

Hypertension is a leading cardiovascular risk factor with significant morbidity and mortality. Sometimes it remains difficult to find out the actual cause and to manage in a large segment of population. So, the ability to identify a contributing or secondary cause that is potentially curable for all patient with hypertension is of great importance and challenging. Endocrine hypertension is one of the common forms of secondary hypertension. Primary aldosteronism, pheochromocytoma, and other causes of mineralocorticoid excess are among the common causes of endocrine hypertension. Published literature were reviewed about their prevalence, clinical presentation, screening methods and specific management. Now day by day it's become more challenging for the clinicians to understand the pathophysiology, clinical spectrum of these diseases and improvement of the management protocol because of newer clinical, biochemical, and modern radiological approach.

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In the general population, although the prevalence of hypertension is increasing day by day, only in around 10 % of cases can be identified due to secondary hypertension, mainly due to renal and endocrine disorders.[1] In young adults (<40 years) the prevalence is approximately 30% due to secondary hypertension.[2] As both American college of cardiology and Endocrine society clinical practice guideline are agreed about screening should be mandatory for all newly and undiagnosed cases of hypertension.[3,9] Clinicians have an opportunity to render a surgical cure and to achieve an optimal clinical response with specific pharmacologic therapy when an accurate diagnosis of endocrine hypertension has made.[4] Herein we review the different forms of endocrine hypertension such as primary aldosteronism, pheochromocytoma, and other causes of mineralocorticoid excess and also thyroid and pituitary dependent cases with a focus of prevalence, case detection test and current standard management to reduce the risk global burden of cardiovascular risk and improve the quality of life. [Table I]

Primary aldosteronism

Primary aldosteronism (PA) is a common curable form of disorder in which inappropriate aldosterone production that leads to hypertension, cardiovascular damage, sodium retention, suppression of plasma renin, and increased potassium excretion at the distal convoluted tubule may lead to hypokalemia.[5] Early diagnosis and treatment of PA are particularly important in light of recent data suggesting that individuals with excess aldosterone are more prone to cerebrovascular disease, cardiac complications and vascular inflammation.[6,7]Clinically two most

Address of Correspondence: Prof. Indrajit Prasad, Department of Endocrinology, Dhaka Medical College Hospital, Dhaka, Bangladesh. email: drindrajit707@gmail.com

Table-I

Endocrine causes of Hypertension

Adrenal-Dependent causes
Primary aldosteronism
Pheochromocytoma
Hyperdeoxycorticosteronism
Congenital adrenal hyperplasia
11β-Hydroxylase deficiency
17α-Hydroxylase deficiency
Deoxycorticosterone-producing tumor.
Primary cortisol resistance
Cushing syndrome
AME/11βHSD Deficiency
Genetic
Type 1 AME
Type 2 AME
Acquired
Licorice or carbenoxolone ingestion(type1)
Cushing syndrome (type 2)
Thyroid-Dependent Causes
Hypothyroidism
Hyperthyroidism
Renin-Secreting Tumor
Pituitary-Dependent Causes
Acromegaly
Cushing syndrome
AME, Apparent mineralocorticoid excess
HSD, Hydroxysteroid dehydrogenase

common forms of PA are Aldosterone producing adenoma (30%) and Bilateral adrenal hyperplasia (60)% which distinguish between surgically corrected and non-surgically corrected. Accurate diagnosis has markedly better outcome when adrenalectomy done followed by adrenal venous sampling.[8]

Prevalence

Most experts previously described to be a rare cause of hypertension, accounting to less than 1%.[6] But according to American college of cardiology 2017, the overall prevalence of PA increased with the severity of hypertension, from 3.9% in stage 1 hypertension to 11.8% in stage 3 hypertension.[3] The policy to screen all, not only hypokalemic and resistant hypertensives but also the patient is already taking antihypertensive drugs because of its higher cardiovascular mortality and morbidity.[9]

Who should be screened?

The Endocrine Society Clinical Practice Guideline recommends in the following groups-[9]

1. Patients with sustained blood pressure (BP) above 150/100 mm Hg on each of three measurements obtained on different days.
2. Hypertension (BP>140/90 mm Hg) resistant to three conventional anti-hypertensive drugs (including a diuretic), or controlled BP (<140/90 mm Hg) on four or more antihypertensive drugs.
3. Hypertension and spontaneous or diuretic-induced hypokalemia.
4. Hypertension and adrenal incidentaloma.
5. Hypertension and sleep apnea.
6. Hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years); and
7. All hypertensive first-degree relatives of patients with PA.
8. Patient with newly detected Hypertension (BP>130/80 mm Hg).

Diagnostic work up

Case-detection tests

Patient preparation for screening of primary aldosteronism

1. Attempt to correct hypokalemia. A plasma [K+] of 4.0 mmol/L is the aim of supplementation.
2. Encourage patient to liberalize (rather than restrict) sodium intake.
3. Withdraw agents that markedly affect the Aldosterone-renin ratio (ARR) for at least 4 weeks: Spironolactone, eplerenone, amiloride, and triamterene and Potassium-wasting diuretics
4. If necessary to maintain hypertension control, commence other antihypertensive medications that have lesser effects on the ARR, like-
   a) Verapamil slow-release (90-120mg twice daily)
   b) Hydralazine (10-12.5 mg twice daily)
   c) Prazosin (0.5-1 mg 2-3 times daily)
   d) Doxazosin (1-2 mg once daily)
   e) Terazosin) (1-2 mg once daily)

Conditions for blood collection

Collect blood for plasma aldosterone and direct/serum renin (where PRA is not available) at 8-9 am, after the patient has been up (sitting, standing, or walking) for at least 2 hours and seated for 5–15 minutes and maintain sample at room temperature (and not on ice, as this will promote conversion of inactive to active renin) during delivery to laboratory and prior to centrifugation.[9]

Condition when Screening is positive?

Primary aldosteronism should be suspected if the plasma renin activity (PRA) is suppressed (e.g., <1.0 ng/mL per hour) or direct renin concentration lower border of normal threshold where PRA is not available and the Plasma Aldosteron concentration (PAC) is increased (e.g., >10 ng/dL)[5] or ARR is >63pmol/L; plus high PAC >550 pmol/L.[12]

Confirmatory test

Though a raised ARR by itself is not diagnostic of PA, confirmatory test should be performed when renin is suppressed and PAC is above 10 ng/dL.[5,6] No medication causes false-positive testing for primary aldosteronism when PAC is above 10 ng/dL.[5] But it has been reported that up to 30–50% of individuals with a positive ARR will have aldosterone levels that are suppressed normally after confirmatory testing.[6] The Endocrine Society Guideline recommends any four confirmatory tests commonly used which include fludrocortisone suppression, saline infusion, oral salt loading and captopril challenge tests.[9] [Table II]

Subtype differentiation

CT/MRI adrenals.

A high resolution computed tomography (CT) scan with fine (2–3 mm) cuts of the adrenal glands should

Table-II

Confirmatory Test

Test	Method	Interpretation
Fludrocortisone suppression test	Fludrocortisone acetate 0.1 mg every 6 h for 4 days), slow Na (30 mmol thrice daily) and sufficient dietary salt to maintain a urinary excretion rate of at least 3 mmol/kg body weight, with sufficient potassium supplementation (Given every 6 h).	Upright PA >6 ng/dl (166 pmol/l) at 10 am on day 4, confirms provided upright PRA <1.0 ng/ml/h, lower cortisol level, at 7am
Saline infusion test	IV infusion of 2 l of 0.9% sodium chloride over 4 h	Post-infusion PA >5 or >10 ng/dl (139 or 277 pmol/l)
Oral sodium load	Oral sodium chloride supplementation (300 mmol of sodium per day for 3 days) and potassium supplementation (if required) to maintain normokalemia	Urinary aldosterone on the third day >12 or >14 μg (33 or 39 nmol)/24 h, and urinary sodium >200 mmol in 24 h
Captopril suppression test	Measure ARR 2 hours after captropil oral 25-50 mg	Post-captopril ARR >12 (ng/dl)/(ng/ml/h) 40 (pmol/l)/(mU/l) and PA >12 ng/dl (330 pmol/l)

be performed when confirmatory test is positive.[6] If a solitary unilateral low noncontract CT attenuation (<10 HU) macroadenoma (>1 cm) and normal contralateral adrenal morphologic appearance is found on CT in a young patient (<35 years) with severe primary aldosteronism, may not need AVS before proceeding to unilateral adrenalectomy.[9,13] However, most patients with primary aldosteronism are over age 35 years, and in many cases, CT shows normal appearing adrenal limb thickening unilateral or bilateral microadenoma (d"1 cm), or bilateral microadenoma additional testing is required to determine the source of excess aldosterone secretion.[9,13] However imaging along is insufficient to refer to surgery because concordant results between a CT-based strategy and cosyntropin-stimulated AVS were found. Most reviewer suggest, AVS showed unilateral disease in 22% of CT negative cases, whereas CT detected a unilateral mass in 25% of the cases with bilateral or contralateral disease at AVS.[8] Thus, by relying only on CT, few patients denied curative adrenalectomy, and few others would have undergone unnecessary or inappropriate adrenalectomy.[8,9] In another study of 203 patients with PA who were evaluated with both CT and AVS, CT was accurate in only 53% of patients. Based on CT findings, 42 patients (22%) would have been incorrectly excluded as candidates for adrenalectomy, and 48 (25%) might have had unnecessary or inappropriate surgery. Therefore, AVS is essential to direct appropriate therapy in patients with PA who seek a potential surgical cure.[5]

Adrenal venous sampling (AVS)

Although it is expensive, as an indication of adrenalectomy AVS should be proposed only to patients who have unequivocal biochemical evidence of PA, are reasonable candidates for general anesthesia and surgery, wish to achieve long-term cure of PA with adrenalectomy, and do not have any surgically incurable forms of mineralocorticoid excess.[8,14] It has been reported that AVS distinguishes unilateral APA from bilateral hyperplasia with 90–100% accuracy with substantial superiority over that of adrenal CT (sensitivity 78% and specificity 75%).[6,14] Blood is obtained from both adrenal veins and from the IVC below the renal veins and assayed for aldosterone and cortisol concentrations. At Mayo Clinic, continuous cosyntropin infusion during AVS (50 ìg/hour) starting 30 minutes before sampling and continuing throughout the procedure. The venous sample from the left side typically is obtained from the common phrenic vein immediately adjacent to the entrance of the adrenal vein. Whereas the blood sample from the right adrenal vein is obtained just at the orifice of the vein. Dividing the right and left adrenal vein PAC values by their respective cortisol concentrations corrects for the dilutional effect of the inferior phrenic vein flow into the left adrenal vein; these are termed cortisol-corrected ratios. In patients with APA, the mean cortisol-corrected aldosterone ratio (i.e., the ratio of PAC/cortisol from the APA side to that from the normal side) is 18:1.[14] A cutoff point of more than 4:1 for this ratio is used to indicate unilateral aldosterone excess. In patients with IHA, the mean cortisol-corrected aldosterone ratio is 1.8:1 (high side to low side), and a ratio of less than 3:1 suggests bilateral aldosterone hypersecretion. The complication rate is 2.5% or lower experienced by AVS radiologist that are adrenal hemorrhage, symptomatic groin hematoma, dissection of * Subtype is usually determined with AVS. Unilateral disease can be caused by an aldosterone-producing adenoma (APA) or primary adrenal hyperplasia (PAH). Bilateral disease is due to idiopathic adrenal hyperplasia (IHA) adrenal vein.[9,14]

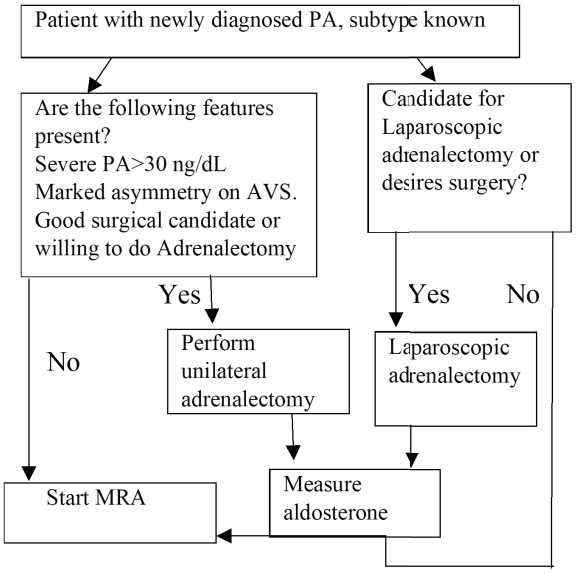

Figure 1; PA: primary aldosteronism; AVS: adrenal vein sampling; ARR: aldosterone-renin ratio; MRA: mineralocorticoid-receptor antagonist.

Alternative strategy for subtyping

Several centers have explored noninvasive alternatives to AVS, for example, Positron emission tomography (PET) with the anesthetic-derivative C11-methomidate, which binds to aldosterone synthase, seems to be a promising approach to identifying lateralized aldosterone excess.[15]

Genetic testing

Currently, genetic testing for familial hyperaldosteronism (FH) is indicated in patients with PA diagnosed at a young age (i.e., age <30 years), particularly if they have a family history of PA and/or stroke at a young age (i.e., age <40 years) and/or if they are considered for AVS, because unilateral PA is exceptional in these cases.[8,16]

Principles of management

Normalization of blood pressure should not be the only goal but also to prevent the morbidity and fatality associated with hypertension, hypokalemia, cardiovascular damage, and nephrotoxicity.

Surgical treatment

Patients who lateralize on AVS are candidates for unilateral laparoscopic adrenalectomy with APA or unilateral hyperplasia which result in cure of hypertension 35–80%. Sometimes persistent hypertension after adrenalectomy is directly correlated with having more than one first-degree relative with hypertension, that coexist primary hypertension. Although robot assisted spare adrenalectomy is an emerging option to preserve remnant adrenal function and avoid adrenal insufficiency in patients already adrenalectomized contralaterally, However, it should be guided by superselective AVS. Superselective adrenal arterial embolization with high-concentration ethanol has also been claimed to lower blood pressure in a small uncontrolled study.[17] In all cases, demonstration of a lateralized aldosterone secretion by AVS is a "must" before undertaking surgery.

Preoperative management

Both hypertension and hypokalemia should be well controlled before patients undergo surgery.

Postoperative management

PAC should be measured 1 to 2 days after surgery to confirm a biochemical cure. Serum potassium levels should be monitored weekly for 4 weeks after surgery, and a sodium diet should be followed. Persistent hypoaldosteronism requiring mineralocorticoid replacement therapy (fludrocortisone) may occur in up to 5% of adrenalectomized patients.[10]

Medical Pharmacology

Although IHA and GRA should be treated medically but a sodium-restricted diet (<100 mEq sodium per day), maintenance of ideal body weight, tobacco avoidance, and regular aerobic

exercise contribute significantly to the success of pharmacologic treatment.

Spironolactone

The dosage is 12.5 to 25 mg per day initially and can be increased to 400 mg per day if necessary to achieve a high-normal serum potassium concentration without the aid of oral potassium chloride supplementation.[5,10] Several observational studies in patients with IAH have reported mean reductions in systolic BP of 25% and diastolic BP of 22% in response to spironolactone 50–400 mg/d for 1–96 months.[9] Serum potassium and creatinine should be monitored frequently during the first 4 to 6 weeks of therapy (especially in patients with renal insufficiency or diabetes mellitus).[10] Painful gynecomastia (one study reporting an incidence after 6 months of 6.9% at a dose <50 mg/d and 52% at a dose >150 mg/d, to avoid this use of reduced spironolactone with newer agents, such as long-acting calcium channel blockers (some of which also have mineralocorticoid antagonistic properties), beta-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Also, erectile dysfunction, and decreased libido in men, and menstrual irregularity in women.[9,10]

Eplerenone

It is steroid-based anti-mineralocorticoid that acts as a competitive and selective mineralocorticoid receptor antagonist.[5,9] It is reasonable to start with a dose of 25 mg twice daily (twice daily because of the shorter half-life of eplerenone compared with spironolactone) and titrated upward; the target is a high-normal serum potassium concentration without the aid of potassium supplements. The maximum dose

approved by the FDA for hypertension is 100 mg per day. In a multicenter trial, 141 patients were randomized to treatment with spironolactone (75 to 225 mg once daily) or eplerenone (100 to 300 mg once daily).[18] Changes from baseline in diastolic blood pressure were less on eplerenone (-5.6±1.3 SEM mmHg) than spironolactone (-12.5±1.3 SEM mmHg). Eplerenone is contraindicated in the setting of hyperkalemia (serum potassium > 5·5 mEq/l), clinically significant renal insufficiency (Serum creatinine > 2·0 mg/dl in men and > 1·8 mg/dl in women), diabetes mellitus with microalbuminuria, concomitant administration of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole), or concomitant treatment with potassium-sparing diuretics. Side effects include dizziness, headache, fatigue, diarrhea, hypertriglyceridemia, and elevated liver enzymes.[10]

Other agents

Although these are not as 1st line therapy, Amiloride, as well as triamterene an epithelial sodium channel antagonist, has been used for the treatment of PA. Although may not be as powerful as spironolactone but can correct or improve both hypertension and hypokalemia. Amiloride administered for between six weeks and six months resulted in 20–30 mm Hg fall in systolic and 10–15 mm Hg diastolic blood pressure.[5,10] Aldosterone synthase inhibitors may play a role in future. A pilot study with LCI699 showed a blood pressure lowering effect in PA patients, but a low specificity for CYP11B2 (aldosterone synthase) relative to CYP11B1 (11betahydroxylase), which has prevented its further development. CYP11B2-selective agents, which might eventually provide an effective treatment for the multitude of PA with bilateral disease, are being developed.

Pheochromocytoma and Paragangliomas

Pheochromocytomas are catecholamine producing neuro-endocrine tumors that arise from chromaffin cells of the adrenal medulla and sympathetic ganglia.6 About 15–20% of such tumors are extra-adrenalin origin and is known as paraganglioma or extra-adrenal pheochromocytoma that located in the neck and the skull, predominantly secret dopamine is rare.[4,5,6] It can be either sporadic or hereditary. Hereditary pheochromocytoma predominantly secret dopamine is rare.[4,5,6] It can be either sporadic or hereditary. Hereditary pheochromocytoma occurs with neurofibromatosis (NF), multiple endocrine neoplasia (MEN1 and 2), von Hippel–Lindau (VHL), and familial paraganglioma syndromes.[20] Both adrenergic and noradrenergic tumors are in the adrenal medulla or extra adrenal origin and usually produce epinephrine, metanephrine, norepinephrine (predominantly) and normetanephrine.[4]

Prevalence

Although pheochromocytomas are rare neoplasms, that may occur at any age most common in the third, fourth to fifth decade and are equal in both genders. The annual incidence of pheochromocytoma is approximately 0.8 per 100,000 person per years. [6,31]

Clinical presentation

Approximately 50 percent of patients with pheochromocytoma when present, they are typically paroxysmal and varies from no symptoms to minor discrete symptoms.[4,23,31] The classic triad of pounding headache, profuse sweating, and palpitations occurs in spells that occur multiple times or as infrequently as once monthly and lasts for 15 to 20 minutes. Spells may be either spontaneous or precipitated by postural change, anxiety, medications (e.g., â-adrenergic antagonists, metoclopramide, anesthetic agents, tricyclic antidepressant, glucocorticoids), or any condition that increase intra-abdominal pressure.[32] Other less common orthostatic hypotension and dilated and hypertrophic cardiomyopathy (also takotsubo) and congestive heart failure, myocardial infarction, stroke are the symptomatic presentations caused by pheochromocytoma.[23,26]. Pheochromocytoma is also associated with some co-secreted hormones that dominate clinical symptoms include ACTH (Cushing's syndrome), parathyroid hormone-related peptide (hypercalcemia), vasopressin (SIADH), vasoactive intestinal peptide (watery diarrhea), and growth hormone–releasing hormone (acromegaly), calcitonin (MEN2). Fasting hyperglycemia and diabetes mellitus are caused in part by the á-adrenergic inhibition of insulin release.[6]

Who should be screened?

Though routine biochemical screening of all hypertensive patients is not recommended but not cost effective. If there is any paroxysmal signs or symptoms, incidentally, discovered adrenal mass, fatal consequences, even family member of newly diagnosed pheochromocytoma should prompt biochemical testing, irrespective of BP level.[4]

When to consider:

1. Hyperadrenergic spells (e.g., self-limited episodes of non-exertional forceful palpitations, diaphoresis, headache, tremor, or pallor)
2. Resistant hypertension
3. A familial syndrome that predisposes to catecholamine-secreting tumors (e.g., MEN2, NF1, VHL)
4. A family history of pheochromocytoma
5. An incidentally discovered adrenal mass with imaging characteristics consistent with pheochromocytoma.
6. Pressor response during anesthesia, surgery, or angiography
7. Onset of hypertension at a young age (<20 years)
8. Idiopathic dilated cardiomyopathy
9. Cyanotic congenital heart disease

Diagnostic work-up

The biochemical diagnosis must be confirmed by the presence of increased concentrations of fractionated metanephrines and catecholamines in urine or plasma.[27] If there is a low index of suspicion, such as Resistant hypertension, hyperadrenergic spells (palpitations, diaphoresis, headache, tremor, or pallor) then 24-hour urinary fractionated catecholamines and metanephrines should be done. And if there is a high index of suspicion such as resistant hypertension, positive family history, a genetic predisposition (e.g., MEN2), a history of resected pheochromocytoma and present, history of recurrent hypertension or spells with associated pallor, and an incidental adrenal mass that has imaging characteristics consistent with pheochromocytoma, it suggest plasma fractionated metanephrines is a first-line test.[28,31] In addition, it has also done for children because obtaining a complete 24-hour urine collection is difficult in pediatric patients.[6]

Most laboratories now measure fractionated catecholamines (dopamine, norepinephrine, and epinephrine) and fractionated metanephrines (metanephrine and normetanephrine) by high performance liquid chromatography (HPLC) with electrochemical detection or tandem mass spectroscopy.[29]

24-hour urine collection are determined by some laboratories was kept refrigerated during the collection, while some laboratories (eg, Mayo Medical Laboratories) standardized their assays for urine kept at room temperature.[29,30]

Positive case-detection test

A positive test for a catecholamine-secreting tumor includes one or more of the following findings: 24-hour urine fractionated metanephrines and catecholamines:

1. Normetanephrine >900 mcg/24 hours or metanephrine >400 mcg/24 hours
2. Norepinephrine >170 mcg/24 hours
3. Epinephrine >35 mcg/24 hours
4. Dopamine >700 mcg/24 hours

Plasma fractionated metanephrines: The diagnostic cutoffs to exclude pheochromocytoma are metanephrine <0.3 nmol/L and/or normetanephrine <0.66 nmol/L.[31]

Indeterminate case-detection test

For patients with indeterminate test results (above the upper limit of the reference interval for the laboratory but below the threshold for positive case detection), additional testing is based upon high and low index of suspicion that the patient has a pheochromocytoma.

Localization

Localization should be performed with either CT or MRI. Approximately 85% of catecholamine-secreting tumors are found in the adrenal glands, and 95% are found in the abdomen and pelvis.[20] MRI is preferred for children and pregnant or lactating women.[5] If the diagnosis is still considered likely, Gallium Ga-68 DOTATATE PET) is proving to be more sensitive was approved by the US Food and Drug Administration (FDA)

in June 2016 and Gallium Ga-68 DOTATOC (DOTA-0-Phe1-Tyr3-octreotide) was approved in 2019 and appears to have comparable diagnostic accuracy to Ga-68 DOTATATE. Hence, newer compounds such a Fludeoxyglucose-positron emission tomography (FDG-PET) is more sensitive than Iobenguane I-123 and CT/MRI for detection of metastatic diseases.[30]

Genetic testing

Genetic testing should be considered if a patient has one or more of the following: (1) paraganglioma, (2) bilateral adrenal pheochromocytoma, (3) unilateral adrenal pheochromocytoma and a family history of pheochromocytoma/paraganglioma, (4) unilateral adrenal pheochromocytoma with onset at a young age (<45 years), or (5) other clinical findings suggestive of one of the previously discussed syndromic disorder. Genetic testing is usually performed postoperatively after a pathologic diagnosis has been confirmed.[6]

Management

A multidisciplinary approach team is required as most common complication are intraoperative blood pressure lability and postoperative hypotension.

Preoperative management

The most common á-adrenergic antagonist utilized for blood pressure control and arrhythmia prevention 7 to 10 days preoperatively is phenoxybenzamine. Monitor blood pressure in seated and standing position twice daily and keep target is low normal (<120/80 mm hg). For long term treatment (metastatic) and some condition where more favorable adverse profile selective á1-

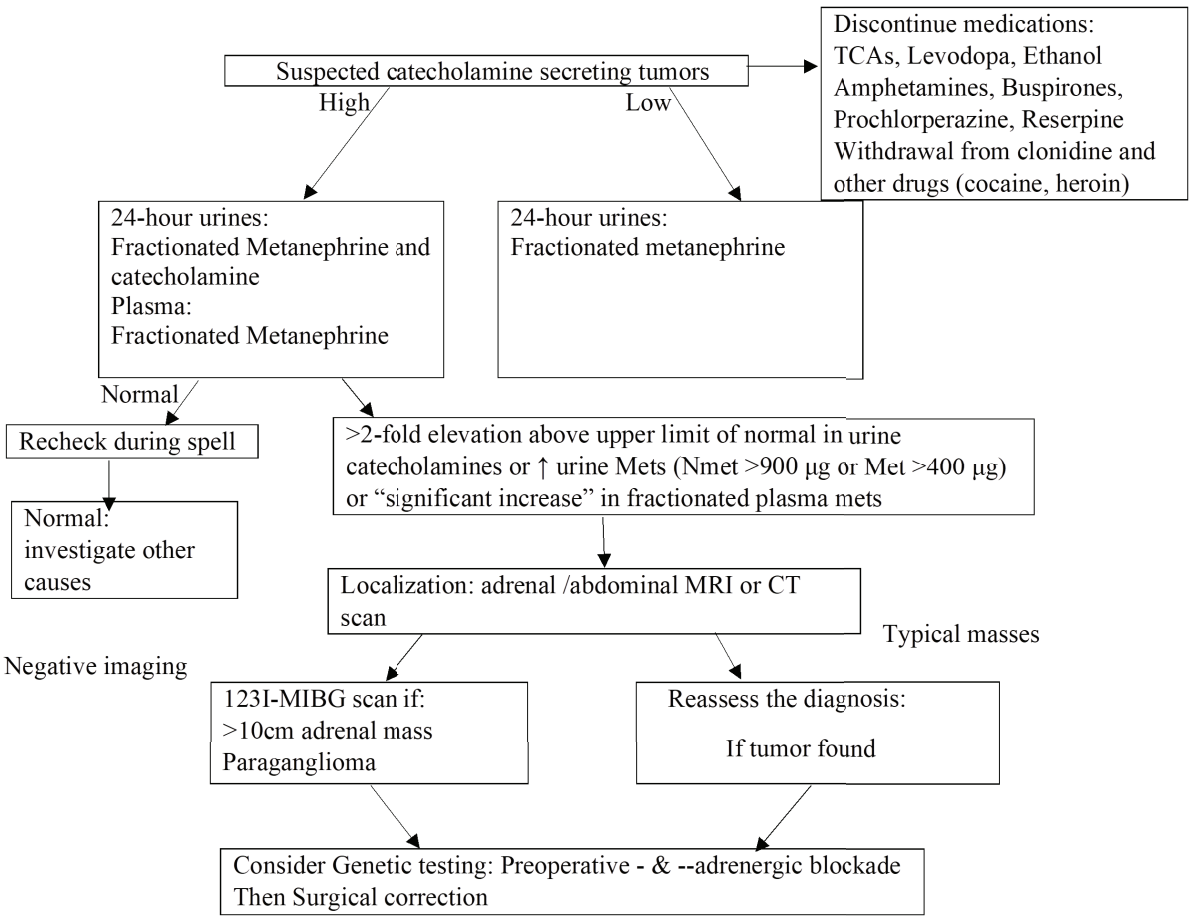

Fig.-2: *Evaluation and treatment of catecholamine-secreting tumors. Nmet; normetanephrine, Met; Metanephrine*

adrenergic blocking agents (e.g., prazosin, terazosin, doxazosin) are preferable.[6,20,31] On the second or third day of alpha-adrenergic blockade, patients are encouraged to start a diet high in sodium content (>5000 mg daily) except in congestive heart failure. â-adrenergic antagonist (propranolol) should be administered only after á-adrenergic blockade is effective to control tachycardia associated with circulating catecholamines and the á-adrenergic blockade. Calcium channel blockers, Nicardipine is the most used (30 mg twice daily) given orally to control blood pressure preoperatively and if needed is given as an intravenous infusion intraoperatively.

Metyrosine have been ineffective or in patients in whom tumor manipulation or destruction (e.g., radiofrequency ablation of metastatic sites) will be marked but with caution in long term therapy sedation, depression, diarrhea, anxiety, nightmares, crystalluria and urolithiasis, galactorrhea, and extrapyramidal signs.[33]

Table-II

Intravenously administered drugs for pheochromocytoma.

Anti hypertensive agents	Dosage
Phentolamine	1-mg followed by 2-mg to 5-mg, IV boluses or continuous.
Nitroprusside	2 ìg/kg of body weight per minute
Nicardipine	Initiate at 5 mg/hr.; then increased by 2.5 mg/hr daily 15 min up to 15 mg/hr
Esmolol	Initial IV loading 0.5mg/kg over 1 minute, followed by maintenance 0.05mg /Kg per minute for next 4 minutes

Surgery, intraoperative monitoring, and management

Laparoscopic Adrenalectomy for patients with solitary adrenal pheochromocytomas smaller than 8 cm in diameter remains the primary treatment to achieve cure.[34] An anterior midline abdominal surgical approach is indicated for abdominal paragangliomas and of the neck, chest, and urinary bladder require specialized approaches. To avoid post operative hypotension and adrenal crisis, adequate preoperative á-adrenergic blockade and volume expansion and adequate fluid (5%DA) is necessary.[31]

Long term Postoperative follow-up

A 24-hour urinary fractionated catecholamines and metanephrines should be measured 1 to 2 weeks after surgery. If bilateral adrenalectomy was performed, lifelong glucocorticoid and mineralocorticoid replacement therapy is prescribed. The risk for recurrent disease is higher in patients with familial disease, large tumor size (>5 cm) and approximately 15% on long term follow-up.[35,36] Genetic testing should be considered for patients younger than 45 years of age or those with family history or any sign suggesting genetic cause one or more of the following: a family history of pheochromocytoma; paraganglioma; and any sign that suggests a genetic cause, should have biochemical testing for all first-degree relatives of a patient with pheochromocytoma or paraganglioma.[6,31]Other forms of Mineralocorticoid excess of effects

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by enzymatic defects in adrenal steroidogenesis that result in deficient secretion of cortisol. Though 90% of CAH cases are caused by 21-hydroxylase deficiency, but deficiencies of 11â-hydroxylase (CYP11B1, P450 11B1) or 17á-hydroxylase (CYP17A1, P450 17A1) cause hypertension and hypokalemia because of hypersecretion of the mineralocorticoid DOC.[5] These mutations are typically diagnosed in childhood. However, partial enzymatic defects have been shown to cause hypertension in adults.[4,6,37]

β-Hydroxylase Deficiency

Prevalence

Approximately, affects 1 in 100,000 live births up to 5% of all cases of CAH are caused by 11â-hydroxylase deficiency. [40] Research has described more than 40 mutations in CYP11B1 (the gene encoding 11b-hydroxylase). [38]

Clinical presentation

The impaired conversion of DOC to corticosterone results in high levels of DOC and 11-deoxycortisol; Consequently, the two characteristic clinical features are hypertension with hypokalemia, as found in any other form of mineralocorticoid excess, and androgen excess. Girls present in infancy or childhood with hypertension, hypokalemia, acne, hirsutism, and virilization. Boys present with hypertension, hypokalemia, and precocious pseudo puberty. Biochemical features include high serum concentrations of 11-deoxycortisol, DOC, DHEA and DHEAS, androstenedione, and testosterone, with low cortisol and corticosterone.

Treatment approach

The goals of therapy in children with 11OHD are to reduce mineralocorticoid and adrenal androgen precursor synthesis sufficiently to ameliorate the hypertension, hypokalemia, and androgen excess. Children are generally treated with glucocorticoids only, typically hydrocortisone (10 to 25 mg/m2), spironolactone is sometimes added to antagonize both androgens and mineralocorticoids, allowing reduced glucocorticoid dosing, particularly in adults woman. In adult males, at a minimum, replacement dose Spironolactone can cause gynecomastia and sexual dysfunction in males, whereas eplerenone and the potassium-sparing diuretics triamterene and amiloride are alternatives. es of hydrocortisone should be administered to avoid the development of adrenal rest tumors. [40]

17α-Hydroxylase deficiency

Prevalence

17α-Hydroxylase deficiency is a very rare cause of CAH; good prevalence data are not available, but the prevalence is likely less than 1 in 1 million live births.

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 males present with either genital ambiguity or as phenotypic females, and 46, XX females present with primary amenorrhea. Biochemical tests include measurement of blood levels of androstenedione, testosterone, DHEAS, 17 hydroxyprogesterone, aldosterone, and cortisol—all of which should be either low or at the lower quartile of the respective reference ranges. The plasma concentrations of DOC and corticosterone should be above the upper limit of the respective reference ranges. Confirmatory testing includes germline mutation testing. [4,40]

Treatment

The goals of treatment in classic 17OHD are to mitigate the effects of mineralocorticoid excess, prevent glucocorticoid deficiency, and restore desired secondary sexual characteristics with attendant benefits such as improved bone mineral density (BMD). For patients reared as female, spironolactone is the drug of choice to block the mineralocorticoid receptor.

Deoxycorticosterone-producing tumor.

Prevalence

Pure DOC-producing adrenal tumors are exceedingly rare and are usually large and malignant. [41]

Clinical presentation

The typical clinical presentation would be relatively rapid onset of marked hypertension associated with hypokalemia and low blood levels of aldosterone and renin. Some of these adrenal neoplasms produces androgens and estrogens in addition to DOC, which may cause virilization in women or feminization in men.[4,6]

Who should be screened?

Clinician should screen if patient present with hypertension, spontaneous hypokalemia and low blood level for renin and aldosterone.[4,6]

Case-detection tests

A high level of plasma DOC or urinary tetra-hydro deoxycorticosterone and a large adrenal tumor appearing on computed tomography (CT) confirm the diagnosis. Aldosterone secretion in these patients is typically suppressed.[4,6]

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. [42,43]

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 11beta-hydroxysteroid dehydrogenase type (HSD11B2) activity.

Who should be screened?

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

Case-detection tests

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. 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 genetic testing.

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. Cortisol can be a potent mineralocorticoid, and when HSD11B2 is genetically deficient or its activity is blocked, elevated 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)] .[44] The congenital forms are rare autosomal recessive disorders; researchers have identified fewer than 50 of these cases worldwide. [45]

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.[38] Acquired apparent mineralocorticoid excess due to licorice root ingestion presents with hypertension and hypokalemia; the cause is revealed by the patient's medical history.

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.[37] 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.

Liddle syndrome: abnormal renal tubular ionic transport

In 1963, Grant Liddle described an autosomal dominant renal disorder with a presentation like PA that includes hypertension, hypokalemia, and inappropriate kaliuresis.[39] However, blood levels of aldosterone and renin were very low, so researchers termed the disorder pseudo aldosteronism.

Prevalence

Autosomal dominant mutations in the beta or gamma subunit of the amiloride-sensitive epithelial sodium channel cause Liddle syndrome.[38]

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

Low aldosterone and renin levels in a hypokalemic hypertensive patient should consider Liddle syndrome. Once the clinician excludes the other causes of this presentation they should consider treating the patient with amiloride or triamterene. 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 and include a lack of efficacy of spironolactone and dexamethasone, and a normal 24-hour urine cortisone/cortisol ratio. Clinical genetic testing is available.

Other endocrine disorder related to Hypertension.

Pituitary related disorder

Cushing syndrome

Though Iatrogenic Cushing syndrome is relatively common, Endogenous Cushing's syndrome also can be caused by excessive secretion of ACTH in 85% of cases called Cushing's disease. Other Ectopic ACTH-secreting neoplasms and the ACTH-independent forms of Cushing syndrome are responsible for 15% of the endogenous cases.[4,6]

Prevalence

The prevalence of endogenous Cushing's syndrome has been reported to be between 2 and 5 per million people.[6]

Who should be screened?

According to the Endocrine Society Clinical Practice Guideline recommends testing for Cushing's syndrome in the following group: [46]

- Patients with unusual features for age (e.g., hypertension, osteoporosis)
- Patients with progressive features of Cushing's syndrome
- Children with low height percentile and increasing weight
- Patients with adrenal incidentaloma compatible with adenoma

Case detection test

Standard laboratory studies include a 1-mg overnight dexamethasone-suppression test and measuring midnight salivary cortisol (at least 2 measurement) and free cortisol in a 24-hour urine collection (at least 2 measurement). When results are abnormal, confirmatory testing should be done. The Endocrine Society's clinical practice guideline on Cushing syndrome further details tests that confirm Cushing syndrome and determine the cause of cortisol excess. [46]

Management

The first line treatment is pituitary surgery via a transsphenoidal approach, remission barely reaches 80%.[47] And, with microadenoma are between 65 and 90%. Medical treatment with ketoconazole, Metyrapone, Mitotane, Pasireotide, and Dopamine agonist. Medical treatment is indicated in the following groups:1) Patients who failed surgical therapy, 2) In patients receiving radiotherapy (while waiting for its effects), 3) Prior to surgery to reduce anesthetic risk. Ketoconazole in a dose between 400 and 1200 mg daily induces an average remission rate of 70% (25–93%). Metyrapone has been shown to induce short-term control in 75% of patients and long-term control in 83% following radiotherapy. [48]

Acromegaly

Prevalence

Acromegaly is a rare disorder, with a prevalence of 40 to 70 cases per 1 million people. [49]

Clinical Presentation

The effects of chronic excess growth hormone include acral and soft tissue overgrowth, progressive dental malocclusion, chondral and synovial tissue overgrowth within joints related to degenerative arthritis, low-pitched voice, excessive sweating, and perineural hypertrophy leading to nerve entrapment (e.g., carpal tunnel syndrome), cardiac dysfunction, and hypertension that occurs in 20% to 40% of the patients. [5,6]

Who should be screened?
Patients with hypertension with incidentally discovered pituitary tumors and patients with typical clinical manifestations of acromegaly, associated with several conditions (e.g., sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension).

Case detection test
Measuring serum insulin-like growth factor 1 by a Glucose tolerance test is the case-detection test of choice. [5,6] MRI of pituitary is also helpful.

Management

Trans-sphenoidal surgery is the treatment of choice and medical by Octreotide and Pasereotide for better outcome when inoperable or surgery is incomplete with residual diseases. Pegvisomant is also used.

Thyroid related disorder

Hyperthyroidism

Prevalence
Hyperthyroidism is more common in women, with a prevalence between 0.5% and 1.0%. [50]

Clinical presentation
Thyrotoxic patients usually have tachycardia, high cardiac output, increased stroke volume, decreased peripheral vascular resistance and increased systolic BP, weight loss (despite an increased appetite), heat intolerance, muscle weakness, and hyperhidrosis.

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

Case-detection tests
Measuring blood concentrations of thyroid-stimulating hormone and Functional T4, Functional T3. 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.

Management
Treatment is given according to cause of hyperthyroidism.

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%. [51]

Clinical Presentation
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.

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

Case-detection tests
Measuring serum thyrotropin and free thyroxine are the key case-detection tests. In central causes, the serum thyrotropin concentration is inappropriately low for the low levels of free thyroxine.

Management
Treatment is given according to cause of hypothyroidism.

Secondary Aldosteronism and Renovascular Hypertension

Prevalence
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. [6]

Clinical presentations
Renovascular occlusive disease leading to RAAS activation can produce a spectrum of manifestations including RVH, accelerated/malignant phase hypertension, impaired cardiac function, flash pulmonary edema, and, ultimately, parenchymal kidney injury with irreversible loss of kidney function.

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.

Case-detection tests

Imaging studies of renal artery duplex ultrasound measurements of peak systolic velocity along the vessel paths have a sensitivity above 85% and specificity of 92% for atherosclerotic disease with more than 60% lumen occlusion. CT angiography has a sensitivity above 90% and specificity of 97%, like catheter angiography and high-resolution magnetic resonance angiography. Magnetic resonance angiography, Radionuclide scintigraphy also done. [6]

Management

Revascularization and medical management are the choice of renovascular diseases.

Conflict of Interest - None.

References:

1. Pappachan JM, Buch HN. Endocrine Hypertension: A Practical Approach. Adv Exp Med Biol. 2017; 956: 215-237. doi:10.1007/5584_2016_26
2. Camelli S, Bobrie G, Postel-Vinay N, Azizi M, Plouin PF, Amar L. LB01.11. Journal of Hypertension. 2015;33(Supplement 1). doi:10.1097/01.hjh.0000467473.21331.70
3. Whelton PK, Carey RM, Mancia G, Kreutz R, Bundy JD, Williams B. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/hypertension guidelines. European Heart Journal. 2022;43(35):3302-3311. doi:10.1093/eurheartj/ehac432
4. Young WF, Calhoun DA, Lenders JWM, Stowasser M, Textor SC. Screening for endocrine hypertension: An endocrine society scientific statement. Endocrine Reviews. 2017;38(2):103-122. doi:10.1210/er.2017-00054
5. Badiu C MD, PhD. WILLIAMS TEXTBOOK OF ENDOCRINOLOGY. Acta Endocrinol (Buchar). 2019;15(3):416. doi:10.4183/aeb.2019.416
6. Sukor N. Endocrine hypertension—current understanding and comprehensive management review. Eur J Intern Med. 2011;22(5):433-440. doi:10.1016/j.ejim.2011.05.004
7. Käyser SC, Dekkers T, Groenewoud HJ, et al. Study Heterogeneity and Estimation of Prevalence of Primary Aldosteronism: A Systematic Review and Meta-Regression Analysis. J Clin Endocrinol Metab. 2016;101(7):2826-2835. doi:10.1210/jc.2016-1472
8. Rossi GP. Primary Aldosteronism: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;74(22):2799-2811. doi:10.1016/j.jacc.2019.09.057
9. 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):1889-1916. doi:10.1210/jc.2015-4061
10. Young WF. Primary aldosteronism: renaissance of a syndrome. Clin Endocrinol (Oxf). 2007;66(5):607-618. doi:10.1111/j.1365-2265.2007.02775.x
11. Young. Jr WF. Treatment of primary aldosteronism. UpToDate. https://www.uptodate.com/contents/treatment-of-primary-aldosteronism. Published August 15, 2022. Accessed March 11, 2023.
12. Letavernier E, Peyrard S, Amar L, Zinzindohoué F, Fiquet B, Plouin PF. Blood pressure outcome of adrenalectomy in patients with primary hyperaldosteronism with or without unilateral adenoma. J Hypertens. 2008;26(9):1816-1823. doi:10.1097/HJH.0b013e3283060f0c
13. Lim V, Guo Q, Grant CS, et al. Accuracy of adrenal imaging and adrenal venous sampling in predicting surgical cure of primary aldosteronism. J Clin Endocrinol Metab. 2014;99(8):2712-2719. doi:10.1210/jc.2013-4146
14. Young WF, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA. Role for adrenal venous sampling in primary aldosteronism. Surgery. 2004;136(6):1227-1235. doi:10.1016/j.surg.2004.06.051
15. Burton TJ, Mackenzie IS, Balan K, et al. Evaluation of the sensitivity and specificity of11C-metomidate positron emission tomography (PET)-CT for lateralizing aldosterone secretion by Conn's adenomas. The Journal of Clinical Endocrinology & Metabolism. 2012;97(1):100-109. doi:10.1210/jc.2011-1537
16. Lenzini L, Prisco S, Caroccia B, Rossi GP. Saga of Familial Hyperaldosteronism: Yet a New Channel. Hypertension. 2018;71(6):1010-1014. doi:10.1161/HYPERTENSIONAHA.118.11150
17. Hokotate H, Inoue H, Baba Y, Tsuchimochi S, Nakajo M. Aldosteronomas: experience with superselective adrenal arterial embolization in 33 cases. Radiology. 2003;227(2):401-406. doi:10.1148/radiol.2272011798
18. Parthasarathy HK, Ménard J, White WB, et al. A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens. 2011;29(5):980-990. doi:10.1097/HJH.0b013e3283455ca5
19. Amar L, Azizi M, Menard J, Peyrard S, Watson C, Plouin PF. Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism.

Hypertension. 2010;56(5):831-838. doi:10.1161/HYPERTENSIONAHA.110.157271

20. Tsirlin A, Oo Y, Sharma R, Kansara A, Gliwa A, Banerji MA. Pheochromocytoma: a review. Maturitas. 2014;77(3):229-238. doi:10.1016/j.maturitas.2013.12.009
21. Adler JT, Meyer-Rochow GY, Chen H, et al. Pheochromocytoma: current approaches and future directions. Oncologist. 2008;13(7):779-793. doi:10.1634/theoncologist.2008-0043
22. Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab. 2007;92(11):4069-4079. doi:10.1210/jc.2007-1720
23. Bravo EL, Tagle R. Pheochromocytoma: State-of-the-art and future prospects. Endocrine Reviews. 2003;24(4):539-553. doi:10.1210/er.2002-0013
24. Stolk RF, Bakx C, Mulder J, Timmers HJ, Lenders JW. Is the excess cardiovascular morbidity in pheochromocytoma related to blood pressure or to catecholamines?. J Clin Endocrinol Metab. 2013;98(3):1100-1106. doi:10.1210/jc.2012-3669
25. Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. N Engl J Med. 2019;381(6):552-565. doi:10.1056/NEJMra1806651
26. Zhang R, Gupta D, Albert SG. Pheochromocytoma as a reversible cause of cardiomyopathy: Analysis and review of the literature. Int J Cardiol. 2017;249:319-323. doi:10.1016/j.ijcard.2017.07.014
27. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline [published correction appears in J Clin Endocrinol Metab. 2023 Feb 08;:]. J Clin Endocrinol Metab. 2014;99(6):1915-1942. doi:10.1210/jc.2014-1498
28. Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. N Engl J Med. 2007;356(6):601-610. doi:10.1056/NEJMcp065470
29. Vanderveen KA, Thompson SM, Callstrom MR, et al. Biopsy of pheochromocytomas and paragangliomas: Potential for disaster. Surgery. 2009;146(6):1158-1166. doi:10.1016/j.surg.2009.09.013
30. Young. Jr WF. Pheochromocytoma and paraganglioma in children. UpToDate. https://www.uptodate.com/contents/pheochromocytoma-in-children. Published May 9, 2022. Accessed March 11, 2023.
31. Young, Jr, WF, Kebebew E. Treatment of pheochromocytoma in adults. UpToDate. https://www.uptodate.com/contents/treatment-of-pheochromocytoma-in-adults. Published February 21, 2021. Accessed March 11, 2023.s
32. Young WF Jr, Maddox DE. Spells: in search of a cause. Mayo Clin Proc. 1995;70(8):757-765. doi:10.4065/70.8.757
33. McBride JF, Atwell TD, Charboneau WJ, Young WF Jr, Wass TC, Callstrom MR. Minimally invasive treatment of metastatic pheochromocytoma and paraganglioma: efficacy and safety of radiofrequency ablation and cryoablation therapy. J Vasc Interv Radiol. 2011;22(9):1263-1270. doi:10.1016/j.jvir.2011.06.016
34. Bittner JG 4th, Gershuni VM, Matthews BD, Moley JF, Brunt LM. Risk factors affecting operative approach, conversion, and morbidity for adrenalectomy: a single-institution series of 402 patients. Surg Endosc. 2013;27(7):2342-2350. doi:10.1007/s00464-013-2789-7
35. Press D, Akyuz M, Dural C, et al. Predictors of recurrence in pheochromocytoma. Surgery. 2014;156(6):1523-1528. doi:10.1016/j.surg.2014.08.044
36. Amar L, Fassnacht M, Gimenez-Roqueplo AP, et al. Long-term postoperative follow-up in patients with apparently benign pheochromocytoma and paraganglioma. Horm Metab Res. 2012;44(5):385-389. doi:10.1055/s-0031-1301339
37. Auchus RJ, Arlt W. Approach to the patient: the adult with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2013;98(7):2645-2655. doi:10.1210/jc.2013-1440
38. New MI, Geller DS, Fallo F, Wilson RC. Monogenic Low Renin hypertension. Trends in Endocrinology & Metabolism. 2005;16(3):92-97. doi:10.1016/j.tem.2005.02.011
39. Liddle GW. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. Trans Assoc Am Physicians. 1963;76:199–213.
40. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet. 2005;365(9477):2125-2136. doi:10.1016/S0140-6736(05)66736-0
41. Müssig K, Wehrmann M, Horger M, Maser-Gluth C, Häring HU, Overkamp D. Adrenocortical carcinoma producing 11-deoxycorticosterone: a rare cause of mineralocorticoid hypertension. J Endocrinol Invest. 2005;28(1):61-65. doi:10.1007/BF03345531
42. Nicolaides NC, Roberts ML, Kino T, et al. A novel point mutation of the human glucocorticoid receptor gene causes primary generalized glucocorticoid resistance through impaired interaction with the LXXLL motif of the P160 coactivators: Dissociation of the transactivating and transreppressive activities. The Journal of Clinical Endocrinology & Metabolism. 2014;99(5). doi:10.1210/jc.2013-3005
43. Charmandari E, Kino T, Chrousos GP. Primary generalized familial and sporadic glucocorticoid resistance (Chrousos syndrome) and hypersensitivity. Hormone Resistance and Hypersensitivity. 2013:67-85. doi:10.1159/000342505
44. Flores-Robles BJ, Sandoval AR, Dardon JD, Blas CA. Lethal liquorice lollies (liquorice abuse causing pseudohyperaldosteronism). BMJ Case Rep. 2013;2013:bcr2013201007. Published 2013 Sep 19. doi:10.1136/bcr-2013-201007
45. Stewart PM, Krozowski ZS, Gupta A, et al. Hypertension in the syndrome of apparent mineralocorticoid excess due to mutation of the 11 beta-hydroxysteroid dehydrogenase

type 2 gene. Lancet. 1996;347(8994):88-91. doi:10.1016/s0140-6736(96)90211-1

46. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93(5):1526-1540. doi:10.1210/jc.2008-0125
47. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Müller OA, Fahlbusch R. Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. J Neurosurg. 2008;108(1):9-18. doi:10.3171/JNS/2008/108/01/0009
48. Verhelst JA, Trainer PJ, Howlett TA, et al. Short and long-term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. Clin Endocrinol (Oxf). 1991;35(2):169-178. doi:10.1111/j.1365-2265.1991.tb03517.x
49. Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. Pituitary. 1999;2(1):29-41. doi:10.1023/a:1009965803750
50. Knudsen N, Jorgensen T, Rasmussen S, Christiansen E, Perrild H. The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. Clin Endocrinol (Oxf). 1999;51(3):361-367. doi:10.1046/j.1365-2265.1999.00816.x
51. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160(4):526-534. doi:10.1001/archinte.160.4.526