Overview of Endocrine Hypertension

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ABSTRACT

Endocrine hypertension typically is referred to disorders of the adrenal gland including primary aldosteronism, glucocorticoid excess, and the pheochromocytoma-paraganglioma syndromes. Rare conditions in patients with congenital adrenal hyperplasia and glucocorticoid resistance (Chrousos syndrome) can also lead to hypertension. Nonadrenal endocrine disorders, such as growth hormone excess or deficiency, thyroid dysfunction, primary hyperparathyreoidism, testosterone deficiency, vitamin D deficiency, obesity-associated hypertension, insulin resistance and metabolic syndrome are also linked to hypertension. In this chapter, we provide an overview of endocrine hypertension including rare syndromes of mineralocorticoid excess.

INTRODUCTION

Hypertension is the most common diagnosis in USA as it affects approximately 31% of Americans (1,2) and approx. 33% of the Mozambican population using a blood pressure cutoff
of 139/89 mm Hg (3). The assignment of a diagnosis of hypertension is dependent on the appropriate measurement of blood pressure, the level of blood pressure (BP) elevation, and the duration of follow-up (4). The secondary causes of hypertension include mostly renal as well as endocrine diseases. An accurate diagnosis of endocrine hypertension offers clinicians the chance to achieve an optimal treatment with either specific pharmacologic or surgical therapy (5). Herein, the different causes of endocrine hypertension with a focus on prevalence, clinical presentation, and currently diagnostic tools.

HOW TO MEASURE BP

Manual measurement using a mercury sphygmomanometer and a stethoscope remains the Gold Standard. However due to environmental issues regarding mercury, this technique tends to be abandoned. Automatic devices have substituted them, but a standardised procedure of obtaining comparable measurements is poor and their validity in clinical practice is limited (6). The device should have an upper arm cuff and should be properly validated and calibrated. A correct cuff size that encircles 75%–100% of the arm should be used. Blood pressure assessment should be based on the mean of 2 or more properly measured seated BP readings on each of 2 or more office visits. Optimally, the measurement of the blood pressure can take place in the office, with the patient seated comfortably with legs uncrossed or in supine position for 3–5 minutes without talking or moving around. It is recommended to avoid caffeine, smoking as well as exercise before the measurement. Clothes covering the cuff location of the upper arm should be removed (7). At the first visit, BP should be recorded in both arms and the higher reading must be considered and repeated measurements after 1-2 minutes can be done. During the measurement, the patient's arm needs to be supported, and upper arm must be at the level of right atrium. Regarding auscultatory determinations, radial pulse obliteration can be palpated to estimate systolic blood pressure. Korotkoff sounds must be recorded, with readings of SBP and DBP at the onset of the first and the last audible sound, respectively (7).

CLASSIFICATION OF BP

Based on recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)(8), the classification of BP for adults aged 18 years or older has been as follows:

- Normal: Systolic lower than 120 mm Hg, diastolic lower than 80 mm Hg
- Prehypertension: Systolic 120-139 mm Hg, diastolic 80-89 mm Hg
- Stage 1: Systolic 140-159 mm Hg, diastolic 90-99 mm Hg
- Stage 2: Systolic 160 mm Hg or greater, diastolic 100 mm Hg or greater

The 2017 ACC/AHA guidelines eliminate the classification of prehypertension and divides it into two levels (9):

- Elevated blood pressure with a systolic pressure between 120- and 129-mm Hg and diastolic pressure less than 80 mm Hg
- Stage 1 hypertension, with a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 80 to 89 mm Hg

Figure 1 provides an overview of classification of BP for adults 18 years and older.

SBP [mmHg]		DBP [mmHg]	ESH/ESC 2018	AHA/ACC 2017	Position of the DHL, 2017	NICE 2016
<120	and	<80	Optimal	Normal	Optimal	Normal
120–129	and	<80	Normal	Elevated	Normal	Normal
130–139	or	80–89	Upper range of normal	Grade I hypertension	Upper range of normal	Upper range of normal
140–159	or	90–99	Grade I hypertension	Grade II hypertension	Grade I hypertension	Grade I hypertension (≥ 135/85 mmHg)*
160–179	or	100–109	Grade II hypertension	Grade II hypertension	Grade II hypertension	Grade II hypertension (≥ 150/95 mmHg)*
≥ 180	or	≥ 110	Grade III hypertension	Grade II hypertension	Grade III hypertension	Severe hypertension

Figure 1. Classification of Hypertension. AHA, American Heart Association; ACC, American College of Cardiology; ESC, European Society of Cardiology; ESH, European Society of Hypertension; DHL, German Hypertension League; NICE, National Institute for Health and Care Excellence of the United Kingdom. DBP, diastolic blood pressure; SBP, systolic blood pressure. Modified from: Jordan J, Kurschat C, Reuter H. Arterial hypertension. Dtsch Arztebl Int. 2018 Aug 20;115(33-34):557-568(10)

Prevalence of Hypertension

Several studies have previously reported prevalence of hypertension among different populations worldwide, but these data depend on different classification systems used. Hypertension affects 28.6% of adults in United States Data from the National Health and Nutrition Examination Survey 2011-2012 showed an increase in the prevalence of hypertension in all age groups compared to 1991 (11). Among adults with hypertension in that survey, 52% achieved a BP of less than 140/90 mm Hg with 76% taking antihypertensives, and with 83% being aware of their hypertension. The prevalence of hypertension increases with age and most individuals with hypertension are diagnosed with primary (essential) hypertension. Hypertension is a major risk factor for stroke, ischemic heart disease, and cardiac failure. It is the second most common reason for office visits to physicians in the United States. Analysis of the Framingham study data suggested that individuals from age 40 to 69 years have an increasing risk of stroke or coronary artery disease mortality with every 20 mm Hg increment in SBP.

Prevalence of Secondary Hypertension

In most people, hypertension is primary, but approximately 15-30% of hypertensive population has secondary hypertension (12). Among children presenting with hypertension, 50% have a secondary cause (13). Young adults (<40 years old), are reported to have a prevalence of secondary hypertension 30% (14). The secondary causes of hypertension include primarily causes such as primary renal disease, oral contraceptive use, sleep apnea syndrome, congenital or acquired cardiovascular disease (i.e. coarctation of the aorta) and excess hormonal secretion. Endocrine Hypertension was previously reported to account for approx. Recent studies suggest an overall prevalence of >5% and possibly > 10% for endocrine hypertension among the hypertensive population (15,16), but several authors have suggested that this prevalence is probably underestimated. The most common causes of endocrine hypertension are excess production of mineralocorticoids (i.e. primary hyperaldosteronism), catecholamines (pheochromocytoma), thyroid hormone, and glucocorticoids (Cushing syndrome) (17). Table 1 lists the most common causes of Secondary hypertension.

Table 1. Etiology of Secondary Hypertension	
Endocrine Causes	**Other Causes**
Adrenal-dependent causes	*Renal causes (2.5-6%)*

Pheochromocytoma and sympathetic paraganglioma	Polycystic kidney disease
Primary aldosteronism	Chronic kidney disease
Hyperdeoxycorticosteronism	Urinary tract obstruction
Congenital adrenal hyperplasia	Renin-producing tumor
11β-Hydroxylase deficiency	Liddle syndrome
17α-Hydroxylase deficiency	*Renovascular causes*
Deoxycorticosterone-producing tumor	renal artery stenosis fibromuscular dysplasia or atherosclerosis
Chrousos syndrome	*Vascular causes*
Cushing syndrome	Coarctation of aorta
Apparent mineralocorticoid excess/11β-hydroxysteroid dehydrogenase deficiency	Vasculitis
Parathyroid-dependent causes	Collagen vascular disease
Hyperparathyroidism	*Neurogenic causes*
Pituitary-dependent causes	Brain tumor
Acromegaly	Autonomic dysfunction
Cushing disease	Sleep apnea
Secondary hyperaldosteronism	Intracranial hypertension
Renovascular hypertension	*Drugs and toxins*
Thyroid-dependent causes	Alcohol
Hypothyroidism	Cocaine
Hyperthyroidism	Cyclosporine, tacrolimus
Vitamin D deficiency	NSAIDs
	Erythropoietin
	Adrenergic medications
	Decongestants containing ephedrine
	Herbal remedies containing licorice or ephedrine
	Nicotine

PREVALENCE OF RESISTANT HYPERTENSION AND TYPICAL CAUSES

The prevalence of resistant hypertension is high: 53% of patients in NHANES had a BP < 140/90 mm Hg vs. 48% in the Framingham Heart Study. In NHANES participants with chronic kidney disease, 37% had a BP < 130/80 mm Hg. In ALLHAT, 34% of patients remained uncontrolled after 5-year follow-up on at least 2 antihypertensive drugs (5).

One important question in this regard is when to screen for secondary causes. Some patients with hypertension, but without primary aldosteronism, demonstrate ACTH-dependent aldosterone hypersecretion by stress (18). The clinician should carefully screen for cardinal signs and symptoms of Cushing syndrome, hyper- or hypothyroidism, acromegaly, insulin resistance (acanthosis nigricans), or pheochromocytoma (flushing and excessive sweating). Hypertension in young patients and refractory hypertension (characterized by poorly controlled blood pressure on > 3 antihypertensive drugs) should alert the physician to screen for secondary causes (14). The importance of endocrine-mediated hypertension resides in the fact that in most cases, the cause is clear and can be traced to the actions of a hormone, often produced in excess by a tumor, such as an aldosteronoma, in a patient with hypertension due to primary aldosteronism. More importantly, once the diagnosis is made, a disease-specific targeted antihypertensive therapy can be implemented, and, in some cases, surgical intervention may result in complete cure, obviating the need for life-long antihypertensive treatment.

As in other causes of hypertension, the clinician should question the patient about dietary habits (salt intake etc.), weight fluctuations, use of over the counter drugs and health supplements including teas and herbal preparations, recreational drugs, and oral contraceptives. Moreover, a detailed family history may provide valuable insights into familial forms of endocrine hypertension. The review of systems should include disease-specific questions. Many patients harboring a pheochromocytoma are symptomatic. Symptoms may include headaches, palpitations, anxiety-like attacks and profuse sweating, similar to symptoms of hyperthyroidism. The triad headache, palpitations, and sweating in a hypertensive patient was initially found to have a sensitivity of 91% and specificity of 94% for pheochromocytoma (19). More recent studies suggest that this typical triad of symptoms is found much less frequently, for instance, in only 10% of cases (20). Ten or more percent of patients with pheochromocytoma may not have any clinical symptoms and may be normotensive (19,21,22).

Patients with Cushing's syndrome often complain of weight gain, insomnia, depression, easy bruising and fatigue. Acne and hirsutism (in women) can also be observed. The challenge these days is to recognize patients with evolving Cushing's syndrome amongst the many obese and often poorly controlled diabetic individuals. An Endocrine Society Clinical Practice Guideline can assist in this task (23). Primary hyperaldosteronism is manifested by mild to severe hypertension. Hypokalemia can be present, but it is not a universal finding and there is normokalemic and normotensive primary aldosteronism (24,25). Polyuria, myopathy and cardiac dysrhythmias may occur in cases of severe hypokalemia. A thorough physical exam with attention to evidence of target organ injury and features of secondary hypertension should be conducted.

Low renin is often associated with several causes of hypertension. Figure 2 lists conditions with low renin levels.

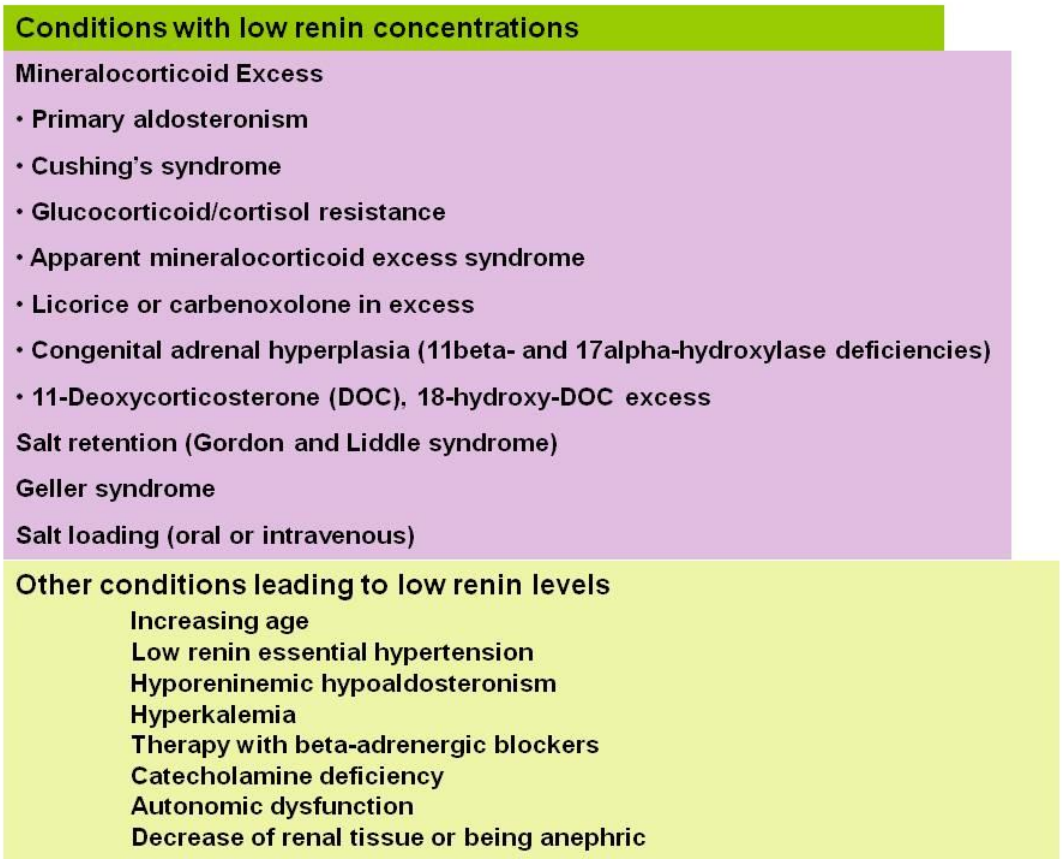

Figure 2. Low Renin Conditions

Despite the increasing understanding of the pathophysiology of hypertension, control of the disease is often difficult and far from optimal. Recent large meta-analyses and genotype studies have identified some "risk genes" for hypertension (15). Surendran and colleagues found a low frequency nonsense variant in the gene ENPEP, which codes for the enzyme aminopeptidase A that converts angiotensin II into angiotensin III and therefore being part of the regulation of the renin-angiotensin-aldosterone system (26). Liu and colleagues observed associations for the aggregation of rare and low frequency missense variants in the genes NPR1, DBH, and PTPMT1 (27). The gene DBH codes for the enzyme dopamine beta-hydroxylase, which catalyzes the conversion of dopamine into noradrenaline and, thereby, influences the autonomic nervous system. The gene PTPMT1 codes for the mitochondrial protein tyrosine phosphatase 1, which influences insulin production (27).

CLINICAL DIAGNOSIS OF ENDOCRINE HYPERTENSION

The first step when evaluating a patient with suspected endocrine-related hypertension is to exclude other causes of secondary hypertension, particularly renal disorders. A detailed medical history and review of systems should be obtained. The onset of hypertension and the response to previous anti-hypertensive treatment should be determined. Consideration of adherence to prescribed antihypertensive regimen should be given. A history of target organ damage (i.e. retinopathy, nephropathy, claudication, heart disease, abdominal or carotid artery disease) and the overall cardiovascular risk status should also be explored in detail (28).

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Table 2: Endocrine Causes of Hypertension. Clinical Presentation. Diagnostic Tools

Etiology	Clinical presentation	Diagnostic tools
Adrenal-dependent causes		
Pheochromocytoma and sympathetic paraganglioma	Headaches, palpitations, anxiety-like attacks, and profuse sweating	Free plasma or fractionated urinary metanephrines
Primary aldosteronism	Polyuria, myopathy, and cardiac dysrhythmias may occur in cases of severe hypokalemia	Increased Aldosterone/Renin Ratio. Suppressed PRA, Increased aldosterone. Low potassium.
Congenital adrenal hyperplasia		
11β-Hydroxylase deficiency	Androgen production is increased and may lead to prenatal virilization with resulting pseudohermaphroditism in females. Males may develop pseudoprecocious puberty, short stature, and sometimes prepubertal gynecomastia	Increased 17 OH PRG, DOC, 11-deoxycortisol, androstenedione, testosterone, and DHEA-S Germline mutation testing
17α-Hydroxylase deficiency	Pseudohermaphroditism in XY males, and sexual infantilism and primary amenorrhea in females	Low/low normal blood levels of androstenedione, testosterone, DHEA-S, 17-hydroxyprogesterone, aldosterone, and cortisol Germline mutation testing
Deoxycorticosterone-producing tumor	Hypertension, adrenal tumors usually large and malignant. Women may present virilization and men feminization.	Low renin and low/normal aldosterone. Increased DOC
Chrousos syndrome	Children may present with ambiguous genitalia and precocious puberty. In women, hirsutism and oligo-amenorrhea. Men may be infertile and/or oligospermic.	Hypokalemic alkalosis Increased DOC, costisol, ACTH. Increased adrenal androgen secretion.

	No features of Cushing's syndrome. Hypertension.	
Liddle syndrome	Hypertension and spontaneous hypokalemia	Low potassium and low levels of aldosterone and renin
Cushing syndrome	Weight gain, insomnia, depression, easy bruising, fatigue, acne, hirsutism, hyperglycemia	24-h urinary free cortisol excretion on at least 2 occasions. Suppressed ACTH 1mg overnight dexamethasone suppression test
Apparent mineralocorticoid excess/11β-hydroxysteroid dehydrogenase deficiency	Congenital: Growth retardation/short stature, hypertension, hypokalemia, diabetes insipidus renalis, and nephrocalcinosis polyuria and polydipsia. Acquired form is attributed to licorice root ingestion and presents with hypertension and hypokalemia	Hypokalemia, metabolic alkalosis, low renin, low aldosterone, normal plasma cortisol levels Abnormal urinary cortisol-cortisone metabolite profile
Parathyroid-dependent causes		
Hyperparathyroidism	Hypercalcemia, hypercalciuria, nephrocalcinosis, cortical bone loss, proximal myopathy, weakness and easy fatigability, depression, inability to concentrate	PTH intact, increased serum calcium concentration
Pituitary-dependent causes		
Acromegaly	Enlargement of the lower lip and nose, prognathism, mild hirsutism (in women), sweating, oily skin, diabetes mellitus, acanthosis nigrigans	IGF-1
Cushing's disease	Weight gain, insomnia, depression, easy bruising, fatigue, acne, hirsutism, hyperglycemia	24-h urinary free cortisol excretion on at least 2 occasions High normal/increased plasma ACTH 1mg overnight dexamethasone suppression test MRI pituitary
Thyroid-dependent causes		
Hypothyroidism	Fatigue, weight gain, bradycardia, loss of appetite	Increased TSH Low FT3, FT4
Hyperthyroidism	Nervousness, anxiety, palpitations, hyperactivity, weight loss, tachycardia	Low TSH Increased FT3, FT4

PRIMARY ALDOSTERONISM

PREVALENCE OF PRIMARY ALDOSTERONISM

In a community-based study (Framingham Offspring) comprising 1688 nonhypertensive participants, increased plasma aldosterone concentrations within the physiologic range predisposed persons to the development of hypertension (29). Previous studies have reported a prevalence of primary aldosteronism (PA) of 1-2 %. Newer data suggest an overall prevalence of >5% and possibly > 10% among the hypertensive population (15,16). In patients with mild to moderate hypertension without hypokalemia, the prevalence of PA has been reported to be 3% (30). In patients with resistant hypertension, the prevalence ranges between 17 and 23 % (31). In a study involving 1616 patients with resistant hypertension, 21% (338 pts) had an Aldosterone/Renin Ratio of > 65 with concomitant plasma aldosterone concentrations of > 416 pmol/L (15 ng) (25). After salt suppression testing, only 11% (182 pts) of these patients had primary aldosteronism (25). In patients with adrenal incidentaloma and hypertension, the prevalence of aldosteronism is low at 2% (31). Many (up to 63%) patients with PA may not present with hypokalemia but are rather normokalemic (31,32). Low renin hypertension is not always easy to differentiate from PA (33). Born-Frontsberg and colleagues found that 56% of 553 patients with primary aldosteronism had hypokalemia and 16% had cardio-and cerebrovascular comorbidities (32). In addition to the patient group with resistant hypertension, screening for primary aldosteronism is recommended for those patients with diuretic-induced or spontaneous hypokalemia, those with hypertension and a family history of early-onset hypertension or cerebrovascular accident at young age, and those with hypertension and an adrenal incidentaloma (27,34).

Etiology of Primary Aldosteronism

PA can be a sporadic or familial condition. Many cases of sporadic PA are caused by an aldosterone-producing adrenal adenoma. However, bilateral zona glomerulosa hyperplasia is much more common in apparently sporadic primary hyperaldosteronism than previously thought and is an important differential diagnosis, since it is treated medically with aldosterone antagonists, rather than by adrenalectomy (35). Selective use of adrenal venous sampling is helpful in this setting (36,37). Very rarely, PA can be caused by an adrenal carcinoma, or unilateral adrenal cortex hyperplasia (also called primary adrenal hyperplasia) (36).

Familial aldosteronism is estimated to affect 2% of all patients with primary hyperaldosteronism and is classified as type 1, type 2, type 3, and type 4 (38–40). Patients with familial aldosteronism type 3 produce amounts of 18-OHF and 18-oxoF 10-1,000 times higher than patients with familial aldosteronism type 1 (approx. 20 times normal) or patients with familial aldosteronism type 2 or sporadic aldosteronism (41). Patients with familial aldosteronism type 3 have a paradoxical rise of aldosterone after dexamethasone, atrophy of the zona glomerulosa, diffuse hyperplasia of the zona fasciculata, and severe hypertension in early childhood (around age 7 years) that is resistant to drug therapy but curable by bilateral adrenalectomy (42).

In familial hyperaldosteronism type 1, an autosomal dominantly inherited chimeric gene defect in CYP11B1/CYPB2 (coding for 11beta-hydroxylase/aldosterone synthase) causes ectopic expression of aldosterone synthase activity in the cortisol-producing zona fasciculata, making mineralocorticoid production regulated by corticotropin (24,43). The hybrid gene has been identified on chromosome 8. Under normal conditions, aldosterone secretion is mainly stimulated by

hyperkalemia and angiotensin II. An increase of serum potassium of 0.1 mmol/L increases aldosterone by 35%. In familial hyperaldosteronism type 1 or glucocorticoid-remediable aldosteronism, urinary hybrid steroids 18-oxocortisol and 18-hydroxycortisol are approx. 20-fold higher than in sporadic aldosteronomas. Intracranial aneurysms and hemorrhagic stroke are clinical features frequently associated with familial hyperaldosteronism type 1 (35). The diagnosis is made by documenting dexamethasone suppression of serum aldosterone using the Liddle's Test (dexamethasone 0.5 mg q 6h for 48h should reduce plasma aldosterone to nearly undetectable levels (below 4 ng/dl) or by genetic testing (Southern Blot or PCR) (44). In contrast, familial hyperaldosteronism type 2 is not glucocorticoid-remediable and is caused by mutations in the inwardly rectifying chloride channel CLCN2 (42).

Familial aldosteronism type 3 is caused by heterozygous gain-of-function mutation in the potassium channel GIRK4 (encoded by KCNJ5) leading to an increase in aldosterone synthase expression and production of aldosterone (35). Familial aldosteronism type 4 results from germline mutations in the T-type calcium channel subunit gene CACNA1H (45). Germline mutations in CACNA1D (encoding a subunit of L-type voltage-gated calcium channel $Ca_V1.3$) are found in patients with primary aldosteronism sometimes associated with seizures, and neurological abnormalities (46) . Table 3 shows genetic and clinical characteristics of familial aldosteronism.

Table 3. Classification of Familial Hyperaldosteronism

Type	Gene Mutation	Treatment	Clinical manifestations
FH-1	CYP11B2/CYP11B1 Chimeric	Low-dose dexamethasone	Intracranial aneurysms and hemorrhagic stroke
FH-2	CLCN2 (R172Q, M22K, G24D, S865R, Y26N)	MRA	Primary aldosteronism
FH-3	KCNJ5 (T158A, I157S, E145Q)	Bilateral adrenalectomy	Primary aldosteronism
	KCNJ5 (G151E, Y152C)	MRA	Primary aldosteronism
FH-4	CACNA1H (M1549V, S196L, P2083L, V1951E)	MRA	Primary aldosteronism

DIAGNOSIS – SCREENING AND CONFIRMING TESTS

Primary aldosteronism is screened for by measuring plasma aldosterone (PA) and plasma renin activity (PRA) or direct renin concentration. There are various assays for measuring aldosterone, which can prove to be problematic(47,48). Measuring PRA is complicated and includes generating angiotensin from endogenous angiotensinogen. Quantification of renin's conversion of angiotensinogen to angiotensin is performed utilizing radioimmunoassays for PRA, which are not standardized among laboratories. Measuring plasma renin molecules directly by an automated chemiluminescence immnoassay as direct renin concentration also is feasible. A PA/PRA-ratio > 30 with a concomitant PA > 20 ng/dl has a sensitivity of 90% and specificity of 91% for primary aldosteronism.

Because low renin hypertension can be difficult to distinguish from PA, an upright plasma aldosterone of at least 15 ng/dl may be helpful (30).

As hypokalemia can reduce aldosterone secretion, it should be corrected before further diagnostic work-up. Also, if a patient with hypertension treated with an ACE inhibitor or ARB, calcium channel blocker, and a diuretic (all of which should increase PRA, thereby lower the PA/PRA-ratio or ARR), still has a suppressed renin and 2-digit plasma aldosterone level, primary aldosteronism is likely. False-positive ARRs may occur in premenopausal women during the luteal phase of the menstrual cycle as well as in those who are on medication with estrogen-containing contraceptive agents (14). Because of medication interference, it is commonly recommended to withdraw betablockers, ACE inhibitors, ARBs (angiotensin receptor blockers), renin inhibitors, dihydropyridine calcium channel blockers, nonsteroidal anti-inflammatory drugs, and central alpha 2-agonists approx. 2 weeks before PA/PRA-ratio or ARR testing, and to hold spironolactone, eplerenone, amiloride, and triamterene, and loop diuretics approx. 4 weeks before ARR testing. Licorice root products should also be withheld 4 weeks prior to testing (49). Confirmatory testing can be done by different techniques (31,50) [Table 4(50)]. A study including 148 hypertensive patients found that a new overnight diagnostic test using pharmaceutical renin-angiotensin-aldosterone system blockade with dexamethasone, captopril and valsartan, has low cost, is rapid, safe and easy to perform with an estimated sensitivity of 98% and specificity of 100% (51).

To clinically distinguish hyperplasia from unilateral adenoma, imaging with computed tomography and magnetic resonance imaging are helpful.

Table 4. ConfirmatoryTests (50)

Confirmation Method	Protocol	Interpretation of Results
Oral Salt Suppression Test	·Increase sodium intake for 3-4 days via supplemental tablets or dietary sodium to >200 mmol/day · Monitor blood pressure · Provide potassium supplementation to ensure normal serum levels · Measure 24h urinary aldosterone excretion and urinary sodium on 3rd or 4th day	· PA confirmed: if 24h urinary aldosterone excretion >12 mcg in setting of 24h sodium balance >200 mmol · PA unlikely: if 24h urinary aldosterone excretion <10mcg
Intravenous Saline Infusion Test	· Being infusion of 2L of normal saline after patient lies supine for 1 hour. · Infuse 2L of normal saline over 4 hours (500 mL/h) · Monitor blood pressure, heart rate, potassium · Measure plasma renin and	· PA confirmed: 4h aldosterone level > 10 ng/dL · PA unlikely: 4h aldosterone level < 5 ng/dL

	serum aldosterone at time=0h and time=4h	
Captopril Challenge Test	· Administer 25-50mg of captopril in the seated position · Measure renin and aldosterone at time=0h and again at time=2h · Monitor blood pressure	· PA confirmed: serum aldosterone high and renin suppressed* · PA unlikely: renin elevated and aldosterone suppressed* *varying interpretations without specific validated cut-offs
Fludrocortisone Suppression Test	· Administer 0.1 mg fludrocortisone q6h for 4 days · Supplement 75-100 mmol of NaCl daily to ensure a urinary sodium excretion rate of 3 mmol/kg/body weight · Monitor blood pressure · Provide potassium supplementation to ensure normal serum levels · Measure plasma renin and serum aldosterone in the morning of day 4 while seated	· PA confirmed: Seated serum aldosterone > 6 ng/dL on day 4 with PRA< 1ng/mL/h · PA unlikely: suppressed aldosterone < 6 ng/dL
Oral Salt Suppression Test	·Increase sodium intake for 3-4 days via supplemental tablets or dietary sodium to >200 mmol/day · Monitor blood pressure · Provide potassium supplementation to ensure normal serum levels · Measure 24h urinary aldosterone excretion and urinary sodium on 3rd or 4th day	· PA confirmed: if 24h urinary aldosterone excretion >12 mcg in setting of 24h sodium balance >200 mmol · PA unlikely: if 24h urinary aldosterone excretion <10mcg
Intravenous Saline Infusion Test	· Being infusion of 2L of normal saline after patient lies supine for 1 hour. · Infuse 2L of normal saline over 4 hours (500 mL/h) · Monitor blood pressure, heart rate, potassium · Measure plasma renin and serum aldosterone at time=0h and time=4h	· PA confirmed: 4h aldosterone level > 10 ng/dL · PA unlikely: 4h aldosterone level < 5 ng/dL

LOCALIZATION

Despite imaging studies, adrenal venous sampling (AVS) with cosyntropin (ACTH) infusion is often essential if the patient desires surgery in case of a unilateral adenoma: cutoff for unilateral adenoma > 4 “cortisol-corrected” aldosterone ratio (adenoma side aldosterone/cortisol: normal adrenal gland aldosterone/cortisol); cutoff for bilateral hyperplasia < 3 “cortisol-corrected” aldosterone ratio (high-side aldosterone/cortisol: low-side aldosterone/cortisol) (36,52).

MEDICAL TREATMENT

The 2016 Endocrine Society clinical practice guideline for the management of primary aldosteronism suggests that patients with hypertension, spontaneous hypokalemia, undetectable renin, and a plasma aldosterone concentration above 20 ng/dl (550 pmol/L) may not need to undergo further confirmatory testing but instead proceed with further imaging and/or adrenal vein sampling or (if unable or unwilling to undergo surgery/adrenalectomy) treatment with a mineralocorticoid antagonist (36). Bilateral adrenal hyperplasia is treated with spironolactone, eplerenone, and/or amiloride (50).

Spironolactone is a nonselective, competitive mineralocorticoid receptor antagonist and is generally considered first-line therapy for patients with BAH at doses ranging between 12.5-400 mg/d (usually 12.5-50 mg/d). It also acts as antagonist of the androgen receptor, a weak antagonist of the glucocorticoid receptor, and an agonist of the progesterone receptor. These actions are associated with adverse effects, including hyperkalemia, hyponatremia, gynecomastia, menstrual disturbances and breast tenderness and decreased libido in women, and gynecomastia in men, occuring in a dose-dependent manner.

Eplerenone, is a more expensive but selective mineralocorticoid receptor blocker with fewer antiandrogenic effects, but also with lower affinity for the mineralocorticoid receptor and less effectiveness than spironolactone with respect to BP lowering in patients with moderate hypertension (53); Generally, higher doses of eplerenone are prescribed for similar effects as spironolactone (usually 25-50 mg twice daily) (50).

Currently under investigation are aldosterone synthase inhibitors, which may not have any nongenomic/non-mineralocorticoid receptor-mediated adverse effects (54). In cases of familial hyperaldosteronism type 1, dexamethasone is effective in suppressing ACTH and, hence, aldosterone overproduction (55).

SURGICAL TREATMENT

Adrenal adenomas producing aldosterone should be removed. Nearly all patients with such endocrine hypertension have improved blood pressure control and up to 60% are cured (normotensive without antihypertensive therapy) from hypertension (56–59). This outcome is influenced by various factors including age, duration of hypertension, coexistence of renal insufficiency, use of more than 2 antihypertensive drugs preoperatively, family history of hypertension, and others. Parameters of insulin sensitivity can be restored to normal with treatment of PA (60). A cross-sectional study including 460 pts with primary aldosteronism and 1363 controls with essential hypertension found no significant difference between pre- and postoperative levels of fasting plasma glucose and serum lipids (61). This topic has been extensively reviewed from a pro and contra perspective. If a patient does not desire surgery/adrenalectomy for a unilateral aldosteronoma/hyperplasia (Figure 3), medical therapy should be initiated (54). AVS and CT/MRI of

the adrenal glands show a unilateral abnormality in 60.5% and 56%, respectively, but were congruent on the involved side in the same patient in only 37% in a recent systematic review (62). If a patient is older than age 40 years, the risk for an adrenal incidentaloma increases (62). Unilateral adrenalectomy can be helpful in some patients with primary aldosteronism and bilateral adrenal hyperplasia (56).

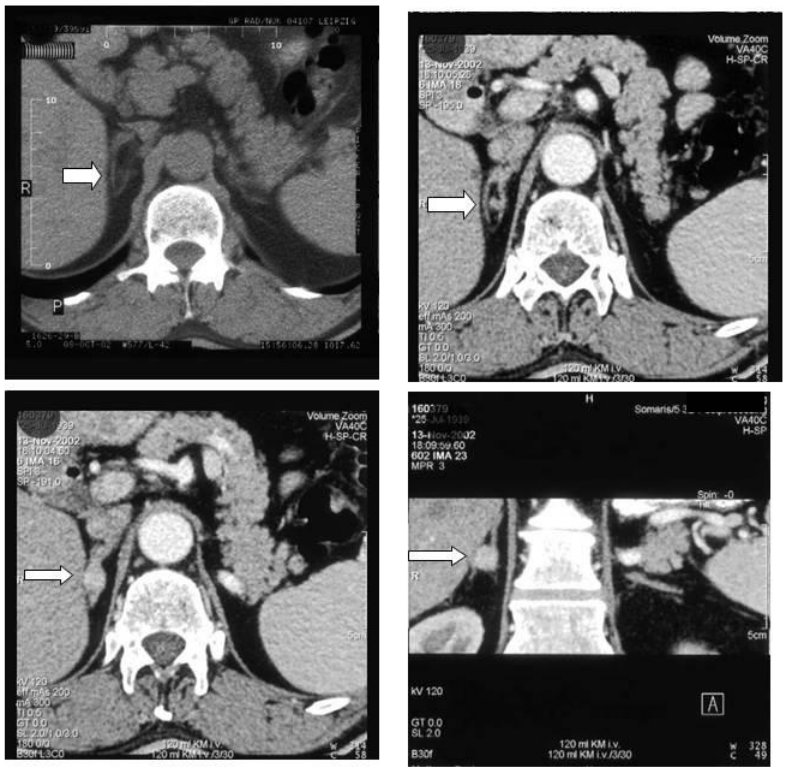

Figure 3. Conn adenoma. Appearance of a 1 cm right-sided adrenal nodule (arrow) on contrast-enhanced computed tomography in a middle-aged man with hypertension treated for 20 years, initially only with a betablocker before becoming medically refractory and hypokalemic with inappropriate kaliuresis. After laparoscopic right adrenalectomy, the patient required only one antihypertensive drug to control his blood pressure.

PHEOCHROMOCYTOMA (PPGLS)

PREVALENCE

Pheochromocytomas are rare neoplasms, with an estimated occurrance of approximately 0.2 percent of patients with hypertension. It has been reported that the annual incidence of pheochromocytoma is nearly 0.8 per 100,000 person-years (63). Pheochromocytomas may occur at any age, however they are commonly presented in the fourth to fifth decade (64) .

ETIOLOGY

Pheochromocytoma and paragangliomas (PPGLs) rare neuroendocrine tumors are composed of chromaffin tissue containing neurosecretory granules (65). Most pheochromocytomas are sporadic but as of known today, approx. 40% of patients with pheochromocytoma or paraganglioma irrespective of age at onset and family history harbor a germline mutation (66,67). At present, there are 10 currently clinically relevant syndromes known: multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, neurofibromatosis type 1, paraganglioma syndromes 1 through 5, caused by mutations of the succinate dehydrogenase genes SDHD (syndrome 1), SDHAF2 (syndrome 2), SDHC (syndrome 3), SDHB (syndrome 4), and SDHA (syndrome 5), and the hereditary pheochromocytoma syndromes resulting from germline mutations in the genes coding transmembrane protein 127 (TMEM127) and MYC-associated factor X (MAX). Further susceptibility genes include EGLN1 (PHD2), EGLN2 (PHD1), DNMT3A, IDH1, FH, MDH2, SLC25A11, KIF1B, and HIF2A (68–70). There is controversy when genetic testing should be obtained in patients with pheochromocytoma, especially considering cost effectiveness.

CLINICAL FEATURES

The clinical presentation of patients with PPGLs shows a wide variety from no or minor symptoms, to dramatic life-threatening manifestations. Asymptomatic patients present mostly incidentally discovered adrenal masses. Normotensive patients may also have sporadic pheochromocytomas (71). It appears that approx. 15% of patients with pheochromocytoma are normotensive (19,21). The classic triad of pounding headache, profuse sweating, and palpitations occurs sporadically with a duration from several minutes to 1 hour. Paroxysmal hypertension occurs commonly in 35-50% of patients. The patients show a complete relief of symptoms between episodes. The high BP surges and the other symptoms are associated with the underlying tumoral catecholamine release, which is the major cause for the high prevalence of cardiovascular emergencies, such as myocardial infarction, stroke, and heart failure. Pheochromocytoma (PHEO) and PPGLs may be the prevalent cause of acute Takotsubo-like catecholamine cardiomyopathy (TLC) (72–75). This association has been reported in in up to 3% of patients with secreting PPGL. The real prevalence of PPGL in TTC remains to be determined. The biochemical profile of pheochromocytomas associated with the a forementioned hereditary syndromes varies (76). Patients with MEN 2 and VHL syndrome may have clinically “silent” pheochromocytomas. Blood pressure does not correlate with circulating catecholamines in patients with pheochromocytoma. Sipple syndrome for multiple endocrine neoplasia type 2 first described by Max Schottelius and Felix Fraenkel in 1886 (77).

DIAGNOSIS – SCREENING

The diagnosis can be established by measuring free plasma or fractionated urinary metanephrines (metanephrine and normetanephrine) (22). When plasma free metanephrines cannot be measured by HPLC with electrochemical detection or high-throughput automated liquid–chromatography-tandem mass spectrometry (LC-MS/MS), measuring plasma free metanephrines by RIA or measuring plasma chromogranin A may represent good markers for pheochromocytoma. In rare circumstances, pheochromocytomas release large *O*-methylated dopamine metabolite methoxytyramine, which can be elevated in extra-adrenal tumor location (in particular, neck and skull-base paragangliomas) and the presence of metastatic disease (78). In patients with renal failure, plasma concentrations of free metanephrines can be increased several folds (79). For optimal diagnostic accuracy, established reference values for plasma free and 24-hour urinary fractionated metanephrines should be btained, according to age and sex. The upper cutoff level of plasma free normetanephrine, but not for metanephrine or methoxytyramine is higher in older patients (80).

Several medications can cause false-positive biochemical testing**.** Thus, plasma normetanephrine levels may increase in patients treated with tricyclic antidepressants, antipsychotics, buspirone, MAO inhibitors, sympathomimetics, cocaine, levodopa, phenoxybenzamine, acetaminophen, *alpha*-methyldopa, and sulphasalazine. Plasma metanephrine levels may increase in patients treated with buspirone, MAO inhibitors, sympathomimetics, cocaine, and levodopa. Urine normetanephrine levels may be higher in patients receiving all the above-mentioned substances, as well as labetalol and sotalol. Urine normetanephrine levels may be increased by buspirone, MAO inhibitors, sympathomimetics, cocaine, levodopa, labetalol and sotalol (14). People who eat biogenic amines may have false-positive urinary metanephrine results. However, for measuring plasma free metanephrines and the *O*-methylated dopamine metabolite

methoxytyramine, no specific dietary requirements are needed, but fasting state (14,81).

The 2014 Endocrine Society clinical practice guideline recommends that all patients with pheochromocytoma-paraganglioma should be engaged in shared decision making for genetic testing (22). All patients with paraganglioma should undergo testing for succinate dehydrogenase (SDH) mutations and those patients with metastatic disease should be tested for SDHB mutations. Recognizing the distinct genotype-phenotype presentations of patients with hereditary tumors, the guideline recommends a personalized approach to patient management. Of note is that SDHD and SDHAF2 are maternally imprinted and therefore one or more generations can be skipped. During the first 2 decades of life (before the age of 20 years), the most common hereditary pheochromocytoma-paraganglioma syndromes found are related to von Hippel Lindau disease, paraganglioma syndrome type 4 (SDHB), and neurofibromatosis type 1. Pheochromocytomas related to multiple endocrine neoplasia type 2 occur most frequently between the third and fifth decade of life and should first be considered in a patient presenting with bilateral pheochromocytomas. The mean penetrance of pheochromocytoma or paraganglioma in individuals carrying a RET germline mutation is 50% by the age of 44 years (82).

Approximately 35% of extra-adrenal pheochromocytomas are considered “malignant” (metastasizing) as opposed to approximately 10% of those arising in the adrenal gland. The 2017 WHO classification of endocrine tumors replaced the term “malignant” with “metastatic”. The risk for metastases increases when the tumor exceeds 5 cm in size and when there is a germline mutation in the SDHB gene (83,84).

LOCALIZATION

CT or MR imaging can localize the tumor in approx. 95 % of cases. For metastatic pheochromocytomas, 18F-Fluorodopamine and 18F-FDG PET appears to be more helfpul than 123I-MIBG or 131I-MIBG scintigraphy (85,86). In fact, MIBG scintigraphy should nowadays only been used in selected patients (85,87). Many medications can interfere with 123I-MIBG or 131I-MIBG uptake (for instance, calcium channel blockers, antipsychotics) and should be discontinued before the scan/imaging. The 2014 Endocrine Society guideline recommends the use of 123I-MIBG in patients with metastatic pheochromocytoma-paraganglioma when radiotherapy with 131I-MIBG is planned and occasionally in some patients with an increased risk for metastatic disease (large tumor size, extra-adrenal tumor, multifocal or recurrent disease) (22). For patients with head and neck paragangliomas, 111In-octreotide has a very good sensitivity (88). Newer functional imaging techniques such as 68Ga-labeled 1,4,7,10-tetraazacylododecane-1,4,7,10-tetraacetic acid-octreotate (DOTATATE) of 18F-labeled L-dihydroxyphenylalanine (L-DOPA) have excellent resolution in detecting pheochromocytomas and paragangliomas.

MEDICAL TREATMENT

The Endocrine Society, the American Association for Clinical Chemistry, and the European Society of Endocrinology have released clinical practice guidelines recommended preoperative blockade of hormonally functional PPGL to prevent cardiovascular complications, along with medication for normalization of blood pressure as well as heart rate. Alpha-adrenergic blockade (i.e., doxazosin, prazosin or terazosin) followed by a β-adrenergic blockade (i.e., propranolol, atenolol) is recommended for preoperative preparation (89). It is also suggested to administer high-sodium diet and fluid intake to prevent

low blood pressure after surgery. Approx. 50% of patients with metastatic pheochromocytomas respond to 131I-MIBG therapy by partial remission or at least stable disease. Selective alpha1 blocking agents, such as prazosin (Minipress), terazosin (Hytrin), and doxazosin (Cardura), have more favorable adverse effect profiles and are used when long-term therapy is required (metastatic pheochromocytoma). Newer therapy options of metastatic pheochromocytoma-paraganglioma include 90Y-DOTATATE and 177Lu-DOTATATE. Chemotherapy is usually administered according to the so-called Averbuch protocol from 1988. New therapies may include tyrosine kinase inhibitors in selected patients (90).

SURGICAL TREATMENT

For tumors exceeding 5 cm in size, open adrenalectomy has long been considered the suggested procedure for tumor removal rather than laparoscopic or retroperitoneoscopic minimally invasive tumor removal, to ensure complete tumor resection, prevent tumor (capsule) rupture, and avoid local recurrence (22) (Figure 4 and 5)

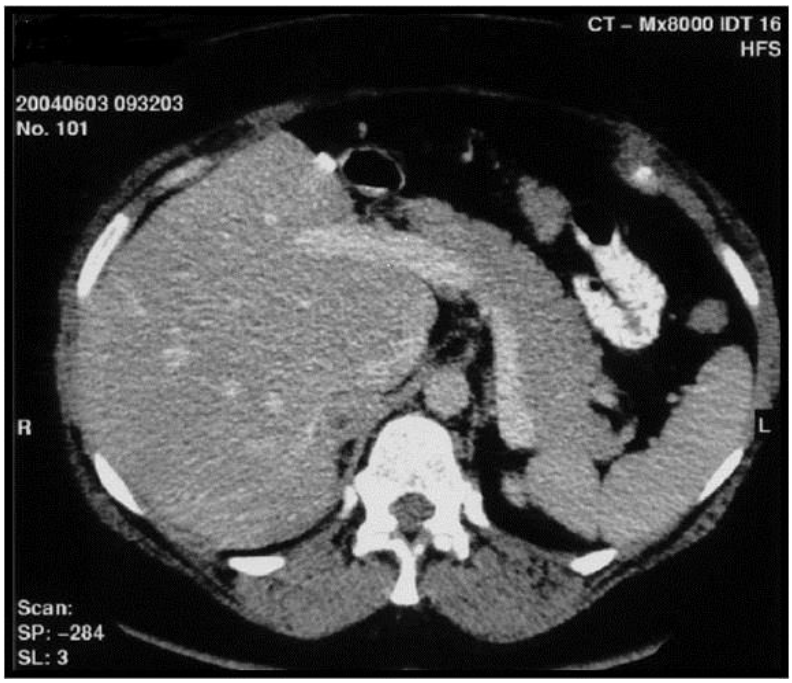

Figure 4. Computed tomography showing recurrence of a right adrenal pheochromocytoma. unpublished observation in a patient with MEN2-related bilateral pheochromocytomas and unilateral tumor recurrence 11 years after bilateral adrenalectomy, photo: courtesy of Prof. Andrea Tannapfel).

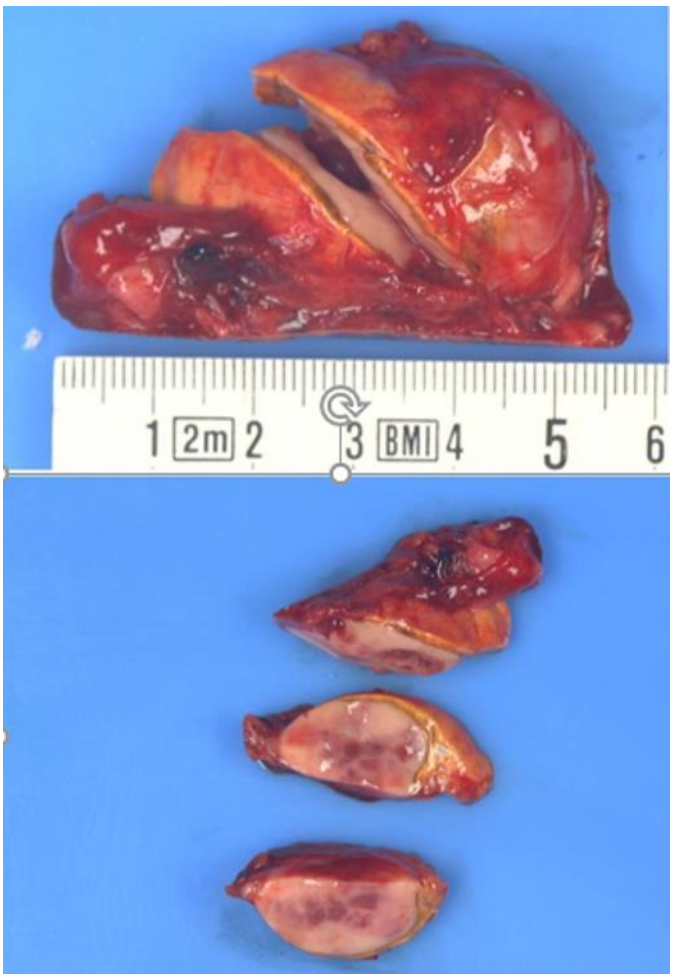

Figure 5. Macroscopic photo of a right adrenal pheochromocytoma removed from the above patient with multiple endocrine neoplasia type 2.

For pheochromocytomas less than 6 cm, a recent cohort study from a multicenter consortium-based registry for 625 patients treated for bilateral pheochromocytomas between 1950 and 2018 compared patients undergoing total vs. cortical-sparing adrenalectomy and found that patients undergoing cortical-sparing adrenalectomy did not demonstrate decreased survival, despite development of recurrent pheochromocytoma in 13%. The authors recommend cortical-sparing adrenalectomy should be considered in all patients with hereditary pheochromocytoma (91). A retrospective, multicenter, international study in patients carrying the Met918Thr RET variant with no age restrictions who were followed from 1970 to 2016 based on registry data from 48 centers globally, found that adrenal-sparing surgery in multiple endocrine neoplasia type 2B can preserve normal adrenal function. In that study, three (10%) of the 31 patients in whom adrenal-sparing surgery had been performed, developed long-term recurrence, while normal adrenal function was mantained in 16 (62%) of patients (92). Apparently one third of one functioning adrenal gland is sufficient for normal glucocorticoid and mineralocorticoid secretion (93).

CUSHING'S SYNDROME

Hypercortisolemia is associated with hypertension in approximately 80% of adult cases and half of children (94,95). A workshop consensus paper attempted to rationalize the treatment of hypertension in patients with Cushing's syndrome (95). In patients with Cushing's disease, night-time blood pressure decline is significantly lower than that in patients with essential hypertension (96). After cure of Cushing's syndrome, approximately 30% of patients have persistent hypertension (97). In children and adolescents, blood pressure normalization occurs in most patients within a year and seems to be dependent on the degree and duration of presurgical hypercortisolemia (94). In patients with Cushing's disease, renin and DOC levels are usually normal, whereas in ectopic corticotropin syndrome, hypokalemia is common and related to an increased mineralocorticoid activity with suppressed renin and elevated DOC levels (98).

There are several mechanisms of blood pressure elevation in Cushing's syndrome: increased hepatic production of angiotensinogen and cardiac output by glucocorticoids, reduced production of prostaglandins via inhibition of phospholipase A, increased insulin resistance, and oversaturation of 11beta-Hydroxysteroid dehydrogenase activity with increased mineralocorticoid effect through stimulation of the mineralocorticoid receptor (99). Screening studies for Cushing's syndrome include measuring 24-h urinary free cortisol excretion on at least 2 occasions, performing a 1 mg dexamethasone suppression test, checking a midnight salivary cortisol and diurnal rhythm of cortisol secretion, and others listed in the recent Endocrine Society Clinical Practice Guideline (100). Therapy should be directed at removing glucocorticoid excess (101). Hypokalemia (especially in patients with ectopic ACTH production) can be treated with mineralocorticoid receptor antagonists such as spironolactone or eplerenone. Thiazide diuretics may also be helpful.

Given the increasing improvement in imaging and laboratory (assays etc.) techniques/modalities, one can expect an increasing number of incidentally discovered tumors and nodules in various organs including the adrenal glands. The future challenge will be when and to which extent to test individuals for disease conditions (102,103). For those individuals with adrenal incidentalomas but clearly lack of clinical features of Cushing's syndrome, subclinical hypercortisolism may be detected biochemically depending upon which cutoff values and assays will be used (104). For the latter population, the American Association of Clinical Endocrinologists recommend using a cutoff for (8 AM) serum cortisol of 5 mcg/dl after 1 mg overnight (11 PM) dexamethasone which reveals approx. 58% sensitivity at a 100% specificity (105). A lower cutoff for serum cortisol suppression, i.e. 1.8 mcg/dl, usually rules out Cushing's syndrome (102). A prospective, randomized study including 45 patients with subclinical hypercortisolism and adrenal incidentalomas was divided into 23 pts who underwent adrenalectomy and 22 pts under surveillance. Monitoring included glycemic control, blood pressure, lipid profile, obesity, and bone mineral density. In the surgical group, diabetes mellitus improved in 62% and hypertension in 67% of pts, whereas the conservative group showed worsening of glycemic control, blood pressure and lipid profiles (37).

To better understand the sequelae of disturbed adrenal hormone synthesis, please refer to Figure 6 and related Endotext chapters (106,107).

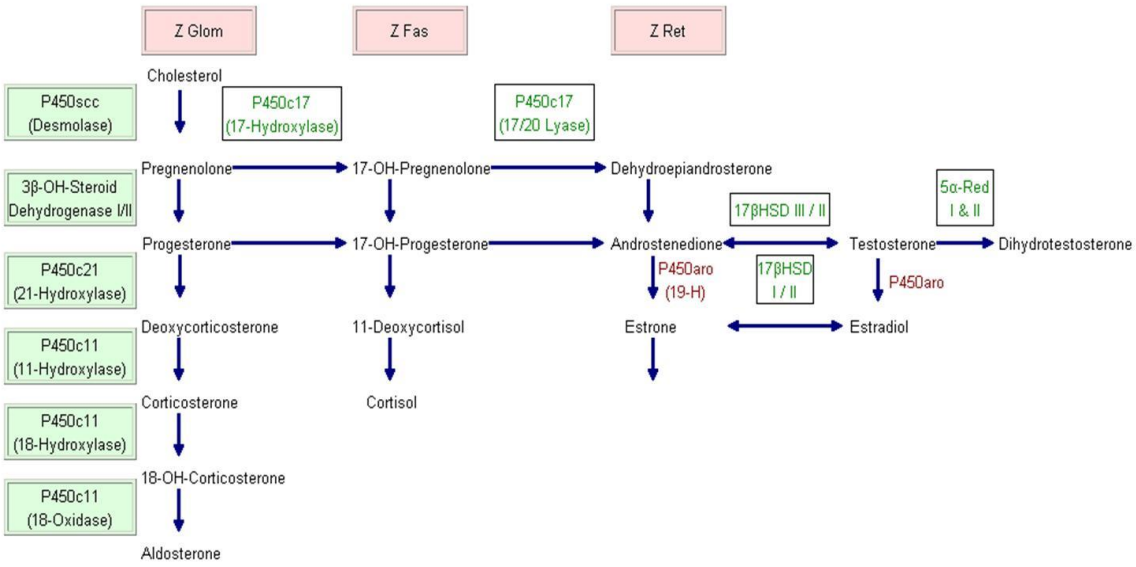

Figure 6. Adrenal Steroid Synthesis. Z Glom = zona glomerulosa; Z Fas = zona fasciculata; Z Ret = zona reticularis; 19-H = 19-Hydroxylase; HSD = Hydroxysteroid dehydrogenase; P450aro = aromatase; 5alpha-Red = 5alpha-Reductase. The 3 adrenal cortex zones Z Glom, Z Fas, and Z Ret stand above the "column" of hormones that are produced in the respective zone. The steroidogenic enzymes on the left starting with P450scc (Desmolase) are listed in order for "vertical and horizontal reading", i.e. Desmolase converts cholesterol to pregnenolone, 3beta-OH-Steroid Dehydrogenase I/II convert pregnenolone to progesterone, 17-OH-Pregnenolone to 17-OH-Progesterone, and P450c11 converts deoxycorticosterone to 18-OH-Corticosterone and 11-Deoxycortisol to cortisol, etc. (modified from ref. 35: Koch CA. Encyclopedia of Endocrine Disease, 2004)

GLUCOCORTICOID RESISTANCE (CHROUSOS SYNDROME)

This autosomal recessive or dominant inherited disorder is rare and caused by inactivating mutations of the glucocorticoid receptor gene (108,109). Cortisol and ACTH are elevated but there are no clinical features of Cushing syndrome. Permanent elevation of ACTH can lead to stimulation of adrenal compounds with mineralocorticoid activity (corticosterone, DOC), along with elevated cortisol secretion may lead to stimulation of the mineralocorticoid receptor, resulting in hypertension. In women, hirsutism and oligo-amenorrhea may develop through stimulation of androgens (androstendione, DHEA, 5-androstendiol). Clinically, children may present with ambiguous genitalia and precocious puberty. Men may be infertile and/or oligospermic. Women may have acne, excessive hair, menstrual irregularities with oligo-anovulation, as well as infertility (108–110).

Treatment entails suppression of ACTH secretion with high doses of dexamethasone (1-3 mg/day). Mineralocorticoid receptor-dependent hypertension may be treated with blockade of the receptor, with spironolactone or eplerenone.

CONGENITAL ADRENAL HYPERPLASIA

11BETA-HYDROXYLASE DEFICIENCY

The most common cause of congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency. Hypertension per se has not been regarded as a

component of this syndrome. Recent data have suggested that hypertension may be more prevalent in this patient population than previously thought (111–113).

Approx. 5% of all cases of CAH care caused by 11beta-hydroxylase deficiency. 11beta-hydroxylase is responsible for the conversion of deoxycorticosterone (DOC) to corticosterone (precursor of aldosterone) and 11-deoxycortisol to cortisol. In approximately 2/3 of individuals affected by a deficiency of this enzyme, monogenic low renin hypertension with low aldosterone levels occurs caused by accumulation of 11-deoxycortisol and DOC (114,115). The earliest age of onset of hypertension was reported at birth (116). The inheritance mode is autosomal recessive. The responsible gene CYP11B1 is located on chromosome 8 and is mutated (40,117,118). Since corticotropin (ACTH) is chronically elevated and precursors such as 17-OH progesterone and androstendione accumulate, androgen production is increased and may lead to prenatal virilization with resulting pseudohermaphroditism in females. Males may develop pseudoprecocious puberty, short stature, and sometimes prepubertal gynecomastia (119,120). Usually, glucocorticoid replacement reduces hypertension in these patients. In selected patients, bilateral adrenalectomy may be safe and effective in managing high blood pressure (121).

17ALPHA-HYDROXYLASE DEFICIENCY

This enzyme deficiency is rare and leads to diminished production of cortisol and sex steroids. Chronic elevation of ACTH causes an increased production of DOC and corticosterone with subsequent hypertension, hypokalemia, low aldosterone concentrations with suppressed renin as well as pseudohermaphroditism in XY males (122), and sexual infantilism and primary amenorrhea in females (123,124). Diagnosis may be delayed until puberty. Plasma adrenal androgen levels are low as are cortisol, aldosterone, plasma renin activity, and 17alpha-hydroxyprogesterone. DOC, corticosterone, and 18-hydroxycorticosterone are elevated. Blood pressure is reduced by glucocorticoid replacement. The responsible gene for cytochrome P450C17 is located on chromosome 10q24.

DEOXYCORTICOSTERONE-PRODUCING TUMOR

Deoxycorticosterone-producing tumors are rare adrenal tumors presented mostly large and malignant (125). Along with deoxycortisone, androgens and estrogens may be cosecreted. Women may present virilization and men feminization. Hypertension and hypokalemia may manifestate with rapid onset. Renin and aldosterone are often low.

APPARENT MINERALOCORTICOID EXCESS

Low-renin hypertension (undetectable aldosterone, hypokalemia) can present in various forms, one of them is apparent mineralocorticoid excess (AME), an autosomal recessive disorder caused by deficiency of the 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2) enzyme (49,126,127). This enzyme converts cortisol to the inactive cortisone in renal tubular cells.

In 1977, New et al. (128) first described this syndrome and in 1995 Wilson et al. (129) first reported that mutations in the 11beta-HSD2 gene located on chromosome 16q22 cause AME. The 11beta-HSD2 enzyme is co-expressed with the mineralocorticoid receptor in renal tubular cells and leads to conversion of cortisol to cortisone (130,131). Cortisone does not bind to the mineralocorticoid receptor. Cortisol and aldosterone bind with equal affinity to the mineralocorticoid receptor, but normal circulating concentrations of cortisol are 100 to 1000 fold higher than those of aldosterone (132). If 11beta-HSD2 is oversaturated or defective, more cortisol will be available to bind to the mineralocorticoid receptor

(133). Diminished 11beta-HSD2 activity may be hereditary or acquired. Acquired deficiency of this enzyme may result from inhibition by glycyrrhhetinic acid which may occur with use of licorice, chewing tobacco, and carbenoloxone. In childhood, AME often causes growth retardation/short stature, hypertension, hypokalemia, diabetes insipidus renalis, and nephrocalcinosis. Diminished 11beta-HSD2 activity may play a role in the pathogenesis of preeclampsia (134). The diagnosis of AME can be established by measuring free unconjugated steroids in urine (free cortisol/free cortisone ratio), and/or steroid metabolites (tetrahydrocortisol + allotetrahydrocortisol/tetrahydrocortisone) (135). Affected individuals have low renin and aldosterone levels, normal plasma cortisol levels, and hypokalemia. Treatment of AME consists of spironolactone, eplerenone, triamterene, or amiloride. Renal transplant is an option for patients with advanced renal insufficiency.

CONSTITUTIVE ACTIVATION OF THE MINERALOCORTICOID RECEPTOR (GELLER SYNDROME)

The Mineralocorticoid (MC) receptor can be mutated leading to the onset of hypertension before age 20 (136). In vitro experiments demonstrate that progesterone and spironolactone, usually antagonists of the (MC) receptor, become agonists in Geller syndrome, suggesting “gain of function” mutations in the MC gene on chromosome 4q31. The inheritance pattern is autosomal-dominant.

LIDDLE SYNDROME

In 1963, Liddle (137) described patients with severe hypertension, hypokalemia, and metabolic alkalosis, who had low plasma aldosterone levels and plasma renin activity. An improvement of the hypertension occurred after salt restriction and triamterene therapy. Spironolactone is ineffective in this autosomal-dominant inherited syndrome. So-called “gain of function” mutations in the genes coding for the beta- or gamma-subunit of the renal epithelial sodium channel, located at chromosome 16p13, lead to constitutive activation of renal sodium reabsorption and subsequent volume expansion. The 24-h urine cortisone/cortisol ratio is normal.

PSEUDOHYPALDOSTERONISM TYPE 2

Pseudohypoaldosteronism type 2 or Gordon’s syndrome (138) is a rare Mendelian disorder, transmitted in an autosomal dominant fashion, and can cause low renin hypertension (139). It has an unknown prevalence, since many patients remain undiagnosed. Published families with this condition (hypertension, hyperkalemia, metabolic acidosis, normal renal function, low/normal aldosterone levels) are predominantly from Australia or the United States (138). Hypertension in these patients may develop as a consequence of increased renal salt reabsorption, and hyperkalemia ensues as a result of reduced renal K excretion despite normal glomerular filtration and aldosterone secretion (140). The reduced renal secretion of potassium makes this condition look like an aldosterone-deficient state, thus the term “pseudohypoaldosteronism”.

These features are chloride dependent. Infusion of sodium chloride instead of sodium bicarbonate corrects the abnormalities, as does the administration of thiazide diuretics, which inhibit salt reabsorption in the distal nephron. Gordon and coworkers found that all features could be reversed by very strict dietary salt restriction (138). Gordon syndrome is an autosomal, dominantly inherited disorder with genes mapping to chromosomes 1, 12, and 17 (141,142). Mutations have been identified in WNK kinases WNK1 and WNK4 on chromosomes 12 and 17, respectively (141,143). Abnormalities such as activating mutations in the amiloride-sensitive sodium channel of the distal renal tubule are responsible for the clinical phenotype

(144,145). Severe dietary salt restriction, antihypertensives, with preferably use of thiazide diuretics, can control the hypertension in this syndrome. Interestingly, common variants in WNK1 contribute to blood pressure variation in the general population (146).

INSULIN RESISTANCE

The metabolic syndrome is characterized by hypertension, abdominal/visceral obesity, dyslipidemia, and insulin resistance (147). At least 24% of adults in the United States meet the criteria for the diagnosis of metabolic syndrome, and this number may even be higher for individuals over the age of 50 years (148). Insulin resistance is significantly associated with hypertension in Hispanics and can cause vascular dysfunction (16,149). Patients with essential hypertension often are insulin resistant (150). Interestingly, not all insulin resistant patients are obese. Excess weight gain, however, accounts for as much as 70% of the risk for essential hypertension and also increases the risk for end stage renal disease (16). In insulin-sensitive tissues, insulin can directly stimulate the calcium pump leading to calcium loss from the cell (151). In an adipocyte, elevated cytosolic calcium concentrations can induce insulin resistance. In a cell resistant to insulin, the insulin-induced calcium loss from cells would be decreased. With the subsequent increase in intracellular calcium, vascular smooth muscle cells respond more eagerly to vasoconstrictors and thus lead to rising blood pressure. Other mechanisms possibly explaining the association of insulin resistance and hypertension are increased sodium retention and increased activity of the adrenergic nervous system. In obesity, increased production of most adipokines (bioactive peptides secreted by adipose tissue) impacts on multiple functions including insulin sensitivity, blood pressure, lipid metabolism, and others (152,153).

PRIMARY HYPERPARATHYROIDISM

Parathyroid hormone levels in hypertensive patients usually are in the normal range and appropriate for the serum calcium concentration. However, patients with essential hypertension excrete more calcium compared to normotensive people, suggesting an enhanced parathyroid gland function (154). When infused, PTH is a vasodilator, although chronic infusion of PTH raises blood pressure in healthy subjects (155,156). High-calcium intake may lower blood pressure (157,158). However, hypercalcemia is associated with an increased incidence of hypertension (1). In patients with primary hyperparathyroidism, hypertension is observed in approximately 40% of cases. The mechanisms of these observations/associations are unclear. Hypertension is usually not cured or better controlled after parathyroidectomy (159). In patients with asymptomatic primary hyperparathyroidism, surgery/parathyroidectomy did not show any benefit regarding blood pressure or quality of life when compared to medical management (160). On the other hand, severe hypertension may improve in patients with primary hyperparathyroidism who undergo parathyroidectomy. Arterial stiffness measured in the radial artery seems to be increased in patients with mild primary hyperparathyroidism (161). Patients with primary hyperparathyroidism have carotid vascular abnormalities (162). In normotensive patients with primary hyperparathyroidism, SBP variability is increased and is reduced by parathyroidectomy (163,164). Furthermore, parathyroidectomy in patients with primary hyperparathyroidism may decrease risk of cardiovascular diseases by lowering total cholesterol levels, although ambulatory diastolic BP increases in response to surgery (165). Another contributory factor to hypertension in patients with primary HPT may be endothelial dysfunction (166). In MEN syndromes, hypertension in patients with hyperparathyroidism may be related to an underlying pheochromocytoma or primary aldosteronism. Criteria

for parathyroidectomy have recently been revisited at the Fourth International Workshop on the management of asymptomatic primary hyperparathyroidism, including now skeletal and/or renal involvement (nephrocalcinosis on imaging) (167).

HYPERTHYROIDISM

Hyperthyroidism increases systolic blood pressure by increasing heart rate, decreasing systemic vascular resistance, and raising cardiac output (168–171). In thyrotoxicosis, patients usually are tachycardic and have high cardiac output with an increased stroke volume and elevated systolic blood pressure (172,173). Approx. one third of patients with hyperthyroidism have hypertension which often resolves after achieving euthyroidism (174). Subclinical hyperthyroidism may contribute to left ventricular hypertrophy and thereby lead to hypertension , although it has not yet been found to be associated with hypertension (174).

HYPOTHYROIDISM

Hypothyroid patients have impaired endothelial function, increased systemic vascular resistance, extracellular volume expansion, and an increased diastolic blood pressure (89,171,175). Hypothyroid patients have higher mean 24-h systolic blood pressure and BP variability on 24-h ambulatory BP monitoring (176). In 32% of hypertensive hypothyroid patients, replacement therapy with thyroxine leads to a fall in diastolic blood pressure to 90 mm Hg or less (177). There is a positive association between serum TSH and blood pressure within the normal serum TSH range, statistically significant for diastolic hypertension (177). Subclinical hypothyroidism may or may not to be associated with hypertension. Hypothyroidism can lead to volume-dependent blood pressure elevation with low plasma renin concentrations (178–180).

ACROMEGALY

The prevalence of hypertension in patients with growth hormone excess is approximately 46% and more frequent than in the general population (181,182). Growth hormone has antinatriuretic actions and may lead to sodium retention and volume expansion (181,182). Increased systolic output and high heart rate as manifestations of a hyperkinetic syndrome may lead to congestive heart failure (181,183). Blood pressure values are increased in patients with acromegaly associated with reduced glucose tolerance or diabetes compared to those with normal glucose tolerance (181). The RAAS system appears to be implicated in the pathogenesis of hypertension in patients with growth hormone excess (181,183–185). Comorbidities in acromegalics, such as hypertension, hyperlipidemia, diabetes mellitus, and cardiomyopathy, all may improve even with partial biochemical control of growth hormone excess (184,186). However, in some patients, hypertension and diabetes mellitus may persist after attempting biochemical cure/remission (187).

OTHER POTENTIAL ENDOCRINE CONDITIONS CAUSING ENDOCRINE HYPERTENSION

There is accumulating evidence that vitamin D deficiency may be linked to an increased cardiovascular risk and hypertension (188). Potential mechanisms in this setting are concurrent insulin resistance and direct vitamin D action through the renin-angiotensin-aldosterone system (Figure 7).

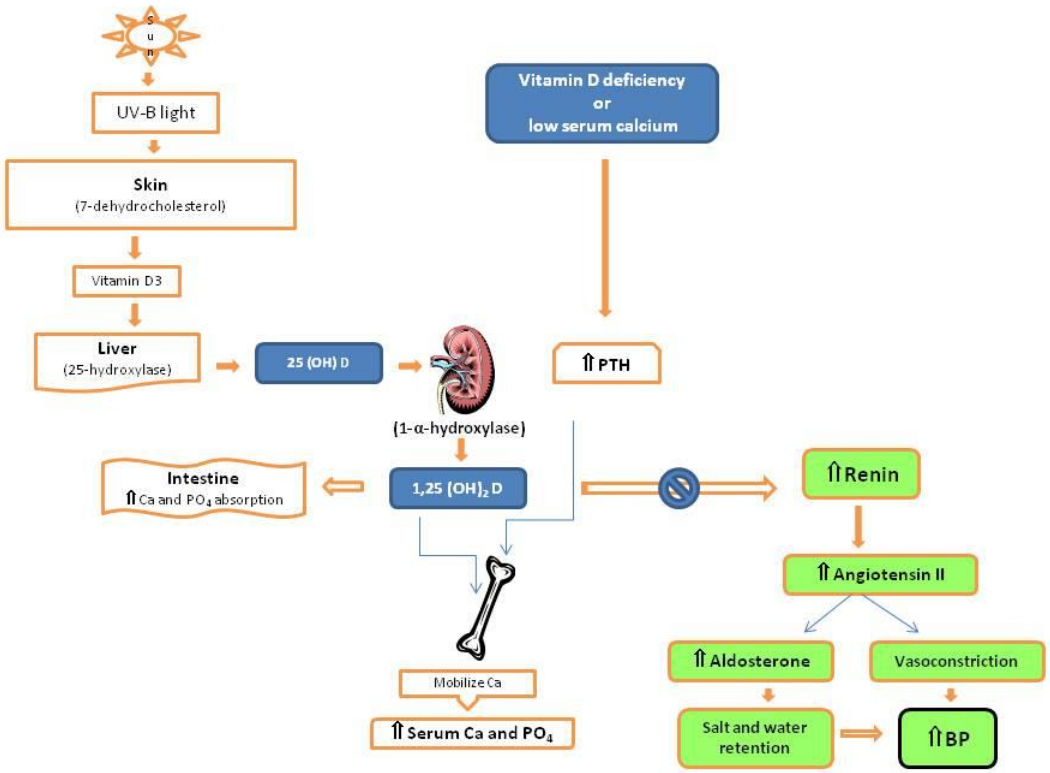

Figure 7. Pathway of vitamin D metabolism and its relationship with PTH and the renin-angiotensin-aldosterone system (modified from Ullah et al., 2009)(188)

Testosterone deficiency is frequently identified in obese individuals and those with diabetes mellitus and/or metabolic syndrome including hypertension. Replacement therapy in selected patients may be beneficial not only related to their symptomatology of androgen deficiency such as low libido, poor erections, fatigue, and others, but also in regards to their metabolic profile and blood pressure (189,190).

Similarly, individuals with growth hormone deficiency may be at risk for developing hypertension, mostly because of their body composition being more “fat” and “inflamed” when compared to subjects with growth hormone sufficiency, as assessed by serum IFG-1 levels matched to gender and age. The key in such patients will be to replace them with growth hormone individually to an IGF-1 level at which no features of growth hormone excess develop and to increase physical activity. In obese subjects who are willing to take on major lifestyle changes with the goal to lose weight, eat and live healthier, temporary medication assistance (phentermine, topiramate, liraglutide, lorcaserin, orlistat, naltrexone-bupropion) including administration of growth hormone may be acceptable (191–193).

Individual tissue-dependent sensitivity of the glucocorticoid receptor and actions of endogenous

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