CHAPTER

43 Hypertension due to Primary Aldosteronism and Related Disorders

Emmanuel L. Bravo • Muhammed A. Rafey • Surafel F. Gebreselassie

INTRODUCTION

Distinct hypertensive syndromes related clearly to mineralocorticoid overproduction are increasingly being recognized. Primary aldosteronism (PA), first described by Conn in 1955,[1] is characterized by hypertension, hypokalemia, suppressed plasma renin activity (PRA), and increased aldosterone production. Reversal of the clinical manifestations by the surgical removal of a right adrenal adenoma established the relationship among aldosterone overproduction, hypokalemia, and hypertension for the first time.

Three heritable forms of aldosteronism are known today. FH-1 is a glucocorticoid-remediable form of aldosteronism (GRA). Two glucocorticoid-resistant forms have been described: FH-II, the familial occurrence of aldosterone-producing adenoma (APA), or bilateral adrenal hyperplasia and FH-III, the familial occurrence of massive bilateral adrenal hyperplasia.

Excessive production of deoxycorticosterone (DOC) results from (1) disorders of steroid production (congenital adrenal hyperplasia), (2) generalized glucocorticoid resistance, and (3) DOC-producing adrenocortical tumors.

A group of disorders simulating PA but with a low production of aldosterone or other mineralocorticoids has also been described. These disorders occur as a result of increased activation of mineralocorticoid receptors (MR). The list includes (1) apparent mineralocorticoid excess (AME), (2) cortisol excess, (3) gain-of-function mutation of ENaC of distal renal tubules (Liddle syndrome), and (4) hypertension exacerbated by pregnancy due to a mutation of mineralocorticoid receptors.

PRIMARY ALDOSTERONISM

PA is the most common and important cause of secondary hypertension. The urgency in identifying PA early and treating it is heightened by data from studies demonstrating that persistent elevation of aldosterone levels can result in end organ damage. In addition, findings from animal studies indicate that cardiovascular and renal injury occur independently of blood pressure levels.[2] Cross-sectional studies in humans demonstrate early subclinical end organ damage that includes an increase in carotid intima media thickness and worsening in pulse wave velocity, both gold standard measures of arterial wall stiffness. Further, these studies have shown reduced endothelial function when compared to matched controls with essential hypertension. Several studies have also demonstrated clear evidence of increased left ventricular hypertrophy, diastolic dysfunction, myocardial fibrosis, and albumin excretion rate when compared to those with primary hypertension.[3–10] It appears that these deleterious end organ effects could potentially be ameliorated with early and appropriate medical and surgical intervention.[11]

Pathophysiology of Mineralocorticoid-Induced Hypertension

Aldosterone, a major mineralocorticoid hormone, has potent effects on unidirectional transepithelial sodium transport. Inappropriately elevated aldosterone levels drive sodium and water retention, which increases circulatory volume and cardiac output; the latter, in turn, is reflexively normalized by vasoconstriction, resulting in hypertension. It is reasoned that the increase in total peripheral resistance to maintain the elevated arterial blood pressure occurs later, following vascular autoregulation.[12] However, hypervolemia is not a universal finding in patients with PA.[13] Many patients have either low or normal intravascular volume and there is no correlation between arterial blood pressure and plasma or total blood volume in either men or women with untreated PA. The potent effects of aldosterone on salt and water retention reasonably suggest that hypervolemia might have had a role in initiating the pressure rise and then may have been superseded or even partially reversed by other mechanisms. One could speculate that a secondary rise of resistance after an initial increase in cardiac output would establish new levels of equilibrium. The accumulated evidence favors the conclusion that aldosterone, by producing functional changes in the arterial wall, is responsible for the

initial vasoconstrictive response and the sustained and progressive hypertensive state that follows. Most experimental evidence from intact animal studies suggests that mineralocorticoids both increase membrane permeability to sodium and elevate intracellular sodium concentration, which in turn decreases calcium efflux.[14] By partially depolarizing the muscle cell membrane, the abnormalities of cation turnover lead to vasoconstriction and elevated vascular resistance. Such changes also increase metabolic activity and provide an early signal for vascular smooth hypertrophy, which when combined with rising blood pressure, could lead to thickening of the media and so raise the wall-to-lumen ratio. This structural adaptation implying enhanced reactivity could be crucial for both potentiating and maintaining the hypertensive process.[15] The study suggests that an increase in systemic vascular resistance leading to hypertension could occur independent of changes in intravascular volume.

Prevalence

The prevalence of PA has remained debatable as studies have been fraught with several limitations, which include bias in patient selection and reliance on tests that are not regarded as confirmatory for the diagnosis of PA.[16] A large prospective clinical trial, the PAPY (PA Prevalence in Hypertensives) Study, demonstrated that PA involves at least 11.2% of consecutive patients with newly diagnosed hypertension. Although the patients underwent a thorough workup that allowed the investigators to definitively establish the presence or absence of PA, this may still be an overestimation of PA prevalence in patients with hypertension as study participants were enrolled from specialized hypertension clinics.[17] Gordon and coworkers[18] reported the incidence of 12% of PA in 199 patients referred to their clinic for hypertension. The clue that a much lower prevalence of PA exists in patients with hypertension is provided by another study by Douma et al.[19] that evaluated patients with resistant hypertension, which showed that 11.3% of patients in this group had PA based on the confirmatory salt suppression test. Based on the prevalence of PA in patients with resistant hypertension in the general hypertensive population and the lower prevalence of PA in milder forms of hypertension, we could assume that the prevalence of PA in the general unselected hypertensive population is much lower than currently thought. Therefore, the actual prevalence of PA among unselected hypertensives is still unknown, but can be estimated from the data of Mosso et al.,[20] considering the relative proportion of the different grades of hypertension in the general population is around 4%.

Case Detection of Primary Aldosteronism

A high index of suspicion for PA must be entertained in patients who develop (1) spontaneous or unprovoked hypokalemia; (2) severe hypokalemia (<3 mEq per liter), which does not normalize even with potassium replacement or addition of potassium-sparing diuretics; (3) potassium levels that do not normalize even after discontinuation of diuretics for 4 weeks; (4) resistant hypertension with no other evidence of secondary cause; (5) hypertension with adrenal adenoma; (6) and those who have a family history of PA, early onset hypertension, or cerebrovascular accident at a young age (<40 years).

Serum Potassium

Traditionally, spontaneous hypokalemia (serum K <3.5 mEq per liter) has been regarded as the most effective screening test to diagnosis PA. But data from our studies and others have shown that a substantial number of patients with PA do not present with hypokalemia.[13] The reported prevalence of normokalemia in PA is variable. Conn reported a 7.6% prevalence of normokalemia in his series of 145 patients.[21] In the PAPY study, only 9.6% of patients with PA were found to have spontaneous hypokalemia.[17] In a study by Douma et al.,[19] 45.6% of patients with PA demonstrated hypokalemia. Others have shown a normal serum potassium concentration in 7% to 38% of reported cases.[21,22] In addition, 10% to 12% of patients with proven adrenocortical tumors may not develop hypokalemia during short-term salt loading. A normal serum potassium does not rule out PA; however, spontaneous hypokalemia associated with renal potassium wasting (UkV≥30 mEq per liter) has a high sensitivity and specificity in the diagnosis of PA.

Plasma Aldosterone Concentration:Plasma Renin Activity Ratio (ARR)

The plasma aldosterone concentration (PAC):plasma renin activity (PRA) ratio is considered the best screening test for PA. This technique is highly sensitive but has a high false-positive rate (about 30% to 50%) because PRA, the denominator, can be very low (as low as 0.1 ng per milliliter per hour) in some laboratories. Accordingly, a minimum PRA of 0.65 ng per milliliter per hour is recommended in calculating the ratio.[23] In published studies, the screening cutoff values vary from 7.2 to 100 ng per deciliter per nanogram per milliliter per hour; consequently, there is wide variation in the sensitivity (64% to 100%) and specificity (87% to 100%) of the test.[24] Reported ratios are all laboratory dependent. In a large, multicenter, prospective trial the accuracy of ARR for pinpointing patients with aldosterone-producing adenomas (APA) was close to 80%.[25] In addition, study results demonstrated a highly significant within-patient correlation ($r=0.69$; $P< .0001$) and reproducibility (coefficient of determination: 0.47). Better diagnostic accuracy is obtained if the absolute PAC is included as a second criterion in combination with the ARR. In a retrospective study,[26] the combination of a PAC:PRA ratio >30 and a PAC value >20 ng per deciliter had a sensitivity of 90% and a specificity of 91% for APA.[26] At the Mayo Clinic, a PAC:PRA ratio of ≥20 and a PAC >15 ng per deciliter were found in more than 90% of patients with surgically confirmed APA.[27]

Several factors such as time of day, diet, posture, method of blood collection, and plasma potassium level may affect

ARR sensitivity and specificity. Other factors that may affect ARR sensitivity and specificity include age, gender, race, diabetes mellitus, and use of oral contraceptive agents. Most elderly and diabetic patients have low levels of PRA. About 40% of essential hypertensive patients have low PRA and about 27% of untreated patients with PA may have nonsuppressed PRA.[13] Pizzolo and coworkers[28] reported that oral contraceptive administration may increase ARR, contributing to the diagnostic inaccuracy in women. Only 36.9% of women with positive ARR had confirmed PA by intravenously administered salt.

Blood samples are best obtained in the morning in an ambulatory seated patient. Ideally, all antihypertensive medications should be discontinued 2 to 3 weeks before ARR testing, but in many patients, this is not feasible. Although some drugs may alter the accuracy of the PAC:PRA ratio, they are not usually an issue in patients with PA. Thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers can actually improve the diagnostic discriminatory power of the PAC:PRA ratio, whereas beta-adrenergic blockers and central alpha-2 agonists suppress PRA and may give false-positive results,[29] especially if the absolute PAC cutoff is not used. If blood pressure control is an issue, alpha-1-adrenoreceptor blockers and/or a nondihydropyridine calcium channel blocker (such as verapamil) may be used. Furthermore, specific aldosterone antagonists may stimulate plasma renin activity, giving rise to false-negative results.

Confirmatory Test(s)

The diagnosis of PA can often be established with relative ease. In the hypertensive patient receiving no treatment who demonstrates significant hypokalemia ($<$3 mEq per liter) with renal potassium wasting (24-hour urinary potassium $>$30 mEq), PRA below 1 ng per milliliter per hour, and elevated plasma or urinary aldosterone values, the diagnosis of PA is unequivocal and may not undergo salt suppression testing. Often, however, the diagnosis is not obvious because of equivocal values. In such cases, multiple measurements are needed during salt loading. Cleveland Clinic patients ingest a normal diet with additional salt added (1 tsp table salt) to food each day for 5 consecutive days. On the 5th day of increased dietary salt, 24-hour urine is collected for sodium, potassium, aldosterone, and creatinine. On the morning of the 6th day, blood is drawn for basic metabolic panel, aldosterone, and renin activity. A 24-hour urinary aldosterone $\geq$14 μg per day (mean +2 standard deviations above values obtained in essential hypertensives) is definitive evidence of a nonsuppressible aldosterone production as long as the 24-hour urinary sodium is $\geq$200 mEq. The development of hypokalemia (serum K $<$3.5 mEq per liter) with renal potassium wasting (UkV $\geq$30 mEq per liter) provides additional evidence of inappropriate aldosterone production. An aldosterone excretion greater than 14 μg per 24 hours following salt loading distinguishes most patients with PA from those with primary hypertension; only 7% of patients with PA have aldosterone excretion values that fall within the range obtained in primary hypertension.[13]

Because most classes of antihypertensive medications affect plasma aldosterone levels and PRA values, antihypertensive treatment should be modified 4 to 6 weeks before the salt loading test. Long-acting calcium channel blockers and the alpha-adrenoreceptor antagonist doxazosin may be used during this period to control blood pressure when required.

Other aldosterone suppression testing has been described.[30] These include intravenous sodium chloride loading, captopril stimulation, or fludrocortisone suppression with the measurement of PAC. The captopril stimulation test operates on the principle that ACE inhibition is without effect when PRA is suppressed and plasma aldosterone is elevated while PRA increases and plasma aldosterone decreases in patients with secondary aldosteronism. However, the specificity of the test is markedly compromised by the large number of hypertensive patients with suppressed PRA (i.e., in low renin essential hypertension, the elderly, diabetics, and African Americans).

Differentiation of Subtypes

The two major causes of PA are bilateral adrenal hyperplasia (BAH), accounting for 65% to 70% of PA patients and aldosterone-producing adenoma (APA) accounting for 30% to 35% of PA. Unilateral hyperplasia and familial hyperaldosteronism accounts for 3% to 4% of patients with PA.[31] It is important to differentiate those with APA because this is a potentially curable condition with surgical intervention.

Biochemical. Adenomas are likely to be present in a patient with spontaneous hypokalemia ($<$3 mEq per liter) and plasma 18-hydroxycorticosterone levels greater than 100 ng per deciliter. In addition, hyperaldosteronism resulting from a unilateral adrenal abnormality is exquisitely responsive to adrenocorticotropic hormone (ACTH) and not to angiotensin II infusions.[32] A plasma 18-hydroxycorticosterone level $<$100 ng per deciliter or a postural increase in plasma aldosterone, or both, are usually associated with adrenal hyperplasia but do not completely rule out the presence of an adenoma.[13] However, a postural decrease in PAC has a high positive predictive value for the diagnosis of APA because a postural decrease in PAC does not occur in hyperplasia.

Localization of Aldosterone Hypersecreting Adrenal Gland.

Adrenal Computed Tomography Scan. All patients diagnosed with PA should undergo an adrenal computed tomography (CT) scan as the initial study in subtype differentiation.[33] A high resolution CT scan with contrast with fine cuts (2.5 to 3 mm) is the imaging technique that displays the best sensitivity and specificity; it is generally more available and less costly than magnetic resonance imaging (MRI). Adrenal

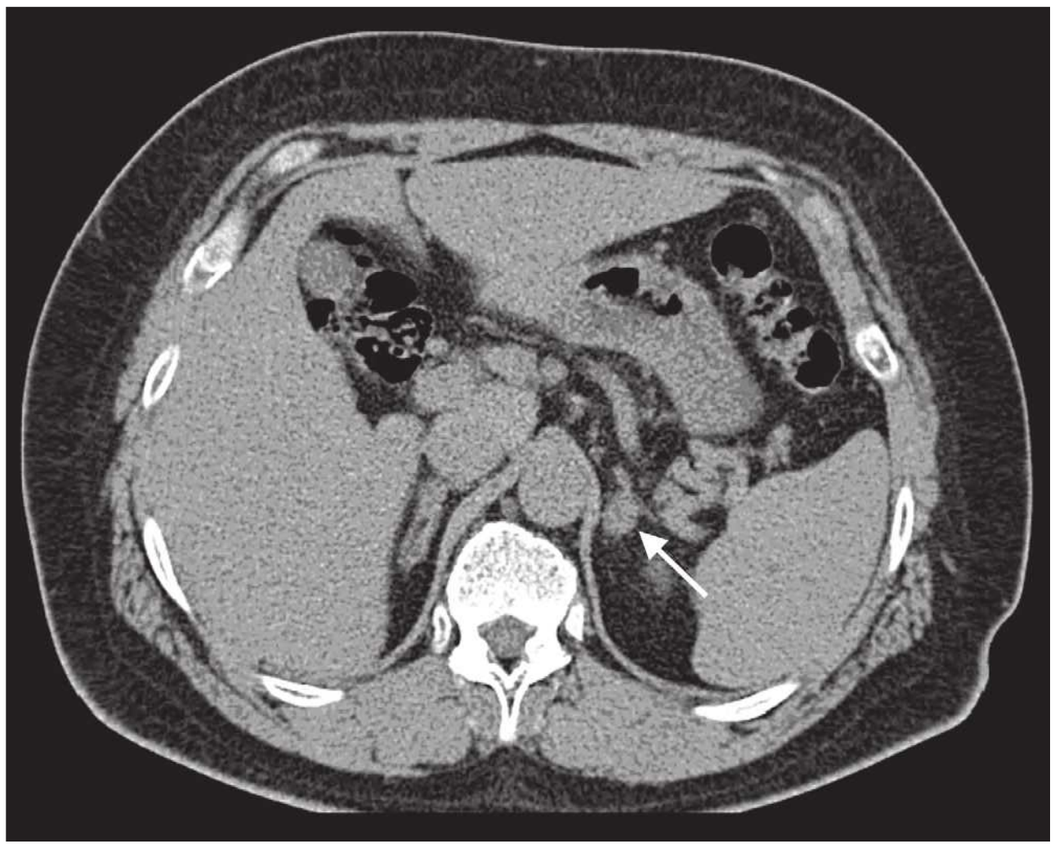

FIGURE 43.1 A 1.5 cm left adrenal adenoma (*arrow*) in the noncontrast enhanced computed tomography examination. The mass has an attenuation value <10 H and a calculated washout rate >50%. These are radiologic features consistent with an adenoma. Adrenal venous sampling (results shown in Table 43.1) provided evidence of a unilateral, left aldosterone-producing tumor.

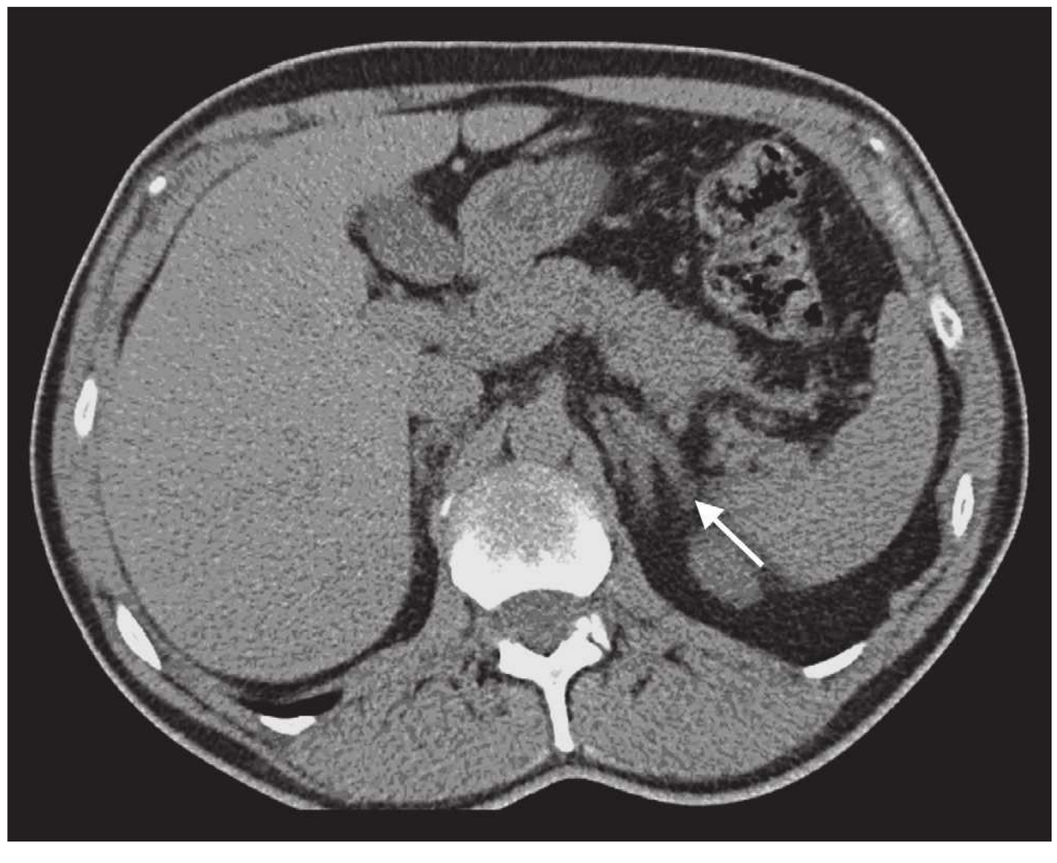

FIGURE 43.2 A noncontrast enhanced adrenal computed tomography scan of a patient with clinical characteristics suggestive of primary aldosteronism. There is marked thickening of both limbs of the left adrenal gland without discrete nodules. The right adrenal gland was reported as normal. Adrenal venous sampling (results shown in Table 43.2) showed bilateral secretion of aldosterone, indicating bilateral adrenal hyperplasia.

cortical adenomas typically have low X-ray attenuation (≤10 HU) in the noncontrast enhanced CT examination (Fig. 43.1). By adding a CT examination approximately 15 minutes after the start of the intravenous contrast enhancement, the washout rate of the iodine contrast medium from the tumor is typically faster (40%) in benign cortical adenomas compared to nonadenomas. Adenomas that are 1.5 cm or larger in diameter can accurately be detected with this procedure. Only 60% of adenomas that measure 1.0 to 1.4 cm are detected, whereas nodules that are less than 1 cm in size are more likely to be missed by a CT scan. Reported sensitivity rates of localizing adenomas by CT scans are between 75% and 80%.[34]

Adrenal Vein Sampling for Aldosterone. The Endocrine Society Guidelines[33] recommend that all patients for whom treatment is practicable and desired should undergo adrenal vein sampling (AVS). There are exceptions to this recommendation. A patient <40 years of age with spontaneous hypokalemia, PAC 15 to 20 ng per deciliter, PRA <1 ng per milliliter, with a solitary adrenocortical macroadenoma (>1 cm) that is discrete, uniform, of low attenuation (HU ≤10), has a contrast washout >40%, and a morphologically normal contralateral adrenal gland needs no further evaluation and should be referred for surgery. Older patients with PA with CT findings demonstrating bilateral morphologically normal or abnormal glands or unilateral microadenoma should be sent for AVS (Fig. 43.2). There is debate as to whether older patients with PA with adrenal CT characteristics identical to the 40-year-old patient described previously should undergo AVS for subtype characterization.

AVS is technically difficult and requires skill and expertise. Even allowing for publication bias from large centers of excellence, success rates are variable ranging from 42%[35] to 75%[36] to 98%[37] for successful bilateral cannulation. During AVS, continuous Cosyntropin is employed to increase adrenal blood flow and to augment aldosterone secretion from an APA. Blood samples are collected from the adrenal veins and the inferior vena cava (IVC) (peripheral sample) for the determination of cortisol and aldosterone concentrations. An adrenal vein:peripheral vein cortisol ratio of at least 3:1 indicates successful adrenal vein catheterization with 100% reproducibility. An aldosterone/cortisol (A/C) adrenal vein over an A/C contralateral adrenal vein of at least 4, plus an A/C contralateral adrenal vein/A/C IVC less than 1, indicates lateralization.[38] Recent data from an Italian center of excellence on a cohort of 44 cases where the diagnosis of APA was not in doubt and using an optimal lateralization ratio (as previously) demonstrated sensitivity and specificity rates of 80% and 75%, respectively (Tables 43.1 and 43.2).[38] A diagnostic approach to patients at risk for PA is shown in Figure 43.3.

11C-Metomidate Positron Emission Tomography/Computed Tomography Scan. Another imaging modality that targets the adrenal cortex is positron emission tomography (PET) using the tracer 11C-metomidate (MTO).[39] MTO binds to the 11β-hydroxylase enzyme in the adrenal cortex and is not taken up in noncortical tumors. The use of MTO-PET for imaging and the characterization of adrenocortical tumors has demonstrated high sensitivity and

43.1 Results of Adrenal Vein Sampling for Plasma Aldosterone and Cortisol Concentrations in the Patient with a Left Adrenal Nodule (Shown in Figure 43.1)

Site	Aldosterone (ng/dL)	Cortisol (μg/dL)	A/C ratio
Right	426	615	0.69
Left	15,230	545	27.94
IVC (peripheral)	65	17	3.82

Adrenal vein sampling was performed with constant infusion of Cosyntropin (50 μg/hr). The adrenal vein:IVC cortisol ratios exceed 3:1 indicating successful cannulation of both adrenal veins. Lateralization to the left is evidenced by an A/C ratio from the left that is ≥4 times greater than that from the right. Suppression of aldosterone secretion from the right adrenal gland is shown by the A/C ratio from the right/A/C ratio in IVC of <1.0 (0.18). A/C, aldosterone/cortisol; IVC, inferior vena cava.

specificity in differentiating adrenocortical from nonadrenocortical tumors.[40,41] Hennings and coworkers[41] evaluated 212 MTO-PET examinations in 173 patients in correlation with 75 histopathologic examinations in 73 patients. Sensitivity was 89% and specificity was 96% for MTO-PET in proving adrenocortical origin of the lesions. Pheochromocytomas, metastases to the adrenal gland, and nonadrenal masses were all MTO negative. A high 11C-MTO tumor uptake, quantified as the standard uptake values (SUV) 15 to 45 minutes after tracer administration, indicated an adrenocortical adenoma with hormonal overproduction. The SUV ratio between the tumor and the contralateral gland was significantly higher in all hormonally secreting adenomas. Burton and coworkers[42] tested the accuracy of 11C-MTO PET-CT scans in 15 patients with an adenoma and successful AVS study. They found that MTO qualitatively distinguished small tumors (>5 mm) from normal adrenal in all patients. They concluded that MTO offers a noninvasive technique to visualize subcentimeter adrenal adenomas and differentiate functional from nonfunctional adrenal tumors.

However, the technique is complicated and the tracer is very expensive to synthesize. The 20-minute half-life of 11C-MTO makes transportation of the tracer to other centers impossible. However, given an easier, cheaper, and more stable labeling procedure, MTO-PET could be an alternative to AVS for subtype differentiation in PA.

43.2 Results of Adrenal Vein Sampling for Plasma Aldosterone and Cortisol Concentration in the Patient with Left Adrenal Gland Hyperplasia (Shown in Figure 43.2)

Site	Aldosterone (ng/dL)	Cortisol (μg/dL)	A/C ratio
Right	3,007	1,257	2.39
Left	6,814	1,253	5.44
IVC (peripheral)	55	31	1.79

Adrenal vein sampling was performed with constant infusion of Cosyntropin (50 μg/hr). The adrenal vein:IVC cortisol ratios exceed 3:1 indicating successful cannulation of both adrenal veins. The A/C ratio from the left/A/C ratio from the right is <4 (2.28) indicating no lateralization. In addition, the A/C ratio from the right/A/C ratio in peripheral vein is >1.0 (1.34), indicating nonsuppression of aldosterone secretion from the right adrenal gland. A/C, aldosterone/cortisol; IVC, inferior vena cava.

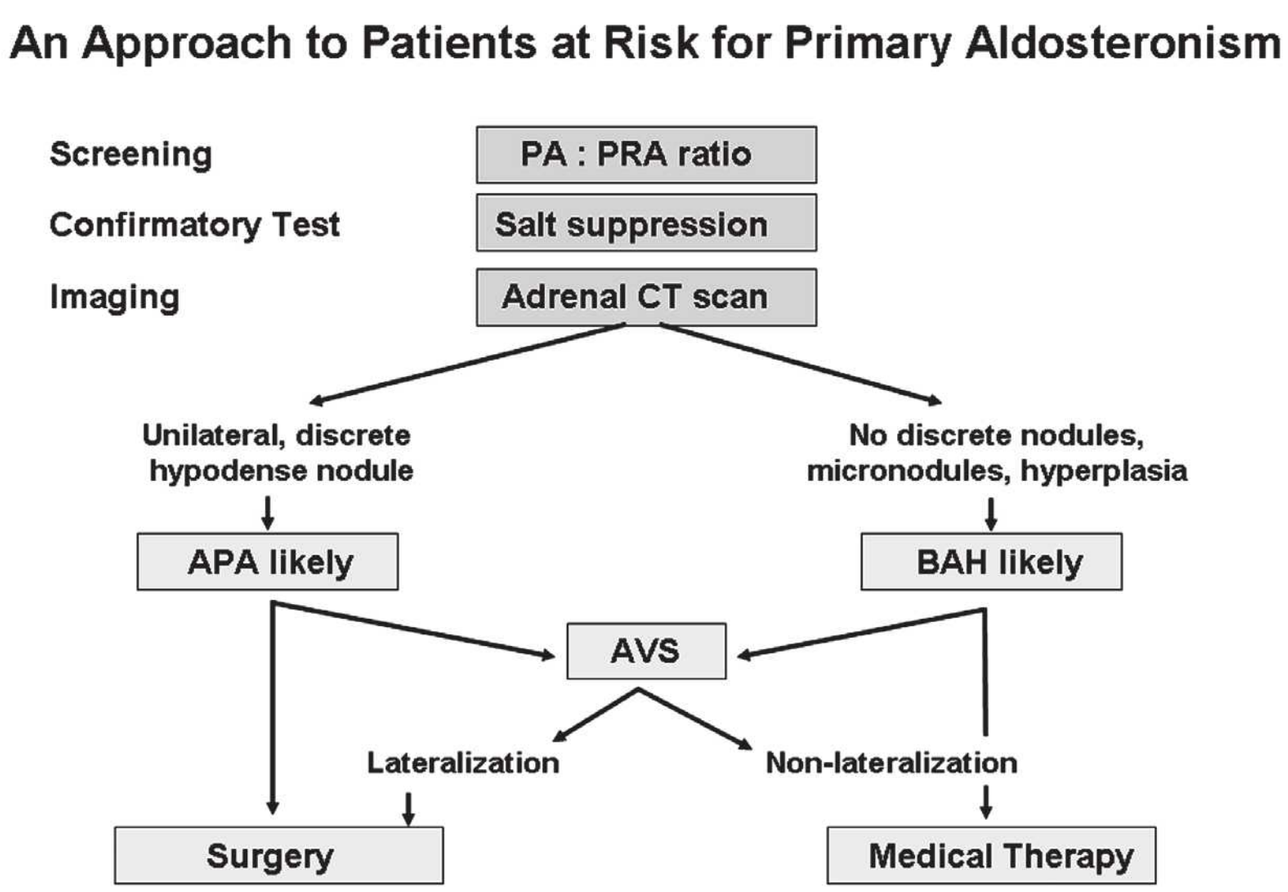

FIGURE 43.3 An approach to patients at risk for primary aldosteronism. *PA*, plasma aldosterone; *PRA*, plasma renin activity; *APA*, aldosterone-producing adenoma; *BAH*, bilateral adrenal hyperplasia; *AVS*, adrenal vein sampling.

Treatment

Medical

Medical therapy for the management of PA is directed not only at controlling blood pressure, but also at protecting end organs from the deleterious effects of excess aldosterone levels.[43] Medical therapy is indicated for those with bilateral adrenal hyperplasia or with an adenoma who are poor candidates for surgical intervention. Surgery is the treatment of choice for those with APA, although medical therapy remains an option because these tumors rarely undergo malignant transformation.[43] The hypertension associated with primary aldosteronism is dependent on excess salt and water retention and is best treated by sustained salt and water depletion (Fig. 43.4).[44] The usual doses of hydrochlorothiazide (12.5 to 50 mg per day) or furosemide (80 to 160 mg per day) in combination with an aldosterone antagonist spironolactone (100 to 200 mg per day) provides for an adequate control of blood pressure and a correction of hypokalemia within 2 to 4 weeks. Additional antihypertensive medications may be required for improved blood pressure control.[45] Among potassium sparing diuretics, spironolactone, an aldosterone antagonist, is the preferred agent because of the adverse cardiovascular effects of prolonged exposure to aldosterone. Several studies have documented a mean reduction of systolic blood pressure by 25% and diastolic blood pressure by 22% with spironolactone therapy in patients with primary hyperaldosteronism.[46,47] The most common side effects of spironolactone include dose-dependent breast and nipple tenderness and gynecomastia. Decreased libido and erectile dysfunction in men and menstrual abnormalities and breast tenderness in women have also been reported.

Eplerenone is a highly selective mineralocorticoid antagonist with efficacy similar to spironolactone.[46] It does not have androgen and progestin receptor activity and is better tolerated and a reasonable alternative in those patients who experience adverse effects with spironolactone. Parthasarathy and coworkers[47] conducted a study comparing the antihypertensive effect of eplerenone and spironolactone in patients with PA. They found a significantly greater antihypertensive effect from spironolactone than that from eplerenone. Alternatively, potassium-sparing diuretics such as triamterene or amiloride combined with hydrochlorothiazide may be used when aldosterone antagonist use is limited by its adverse effects (spironolactone) or prohibitive cost (eplerenone).

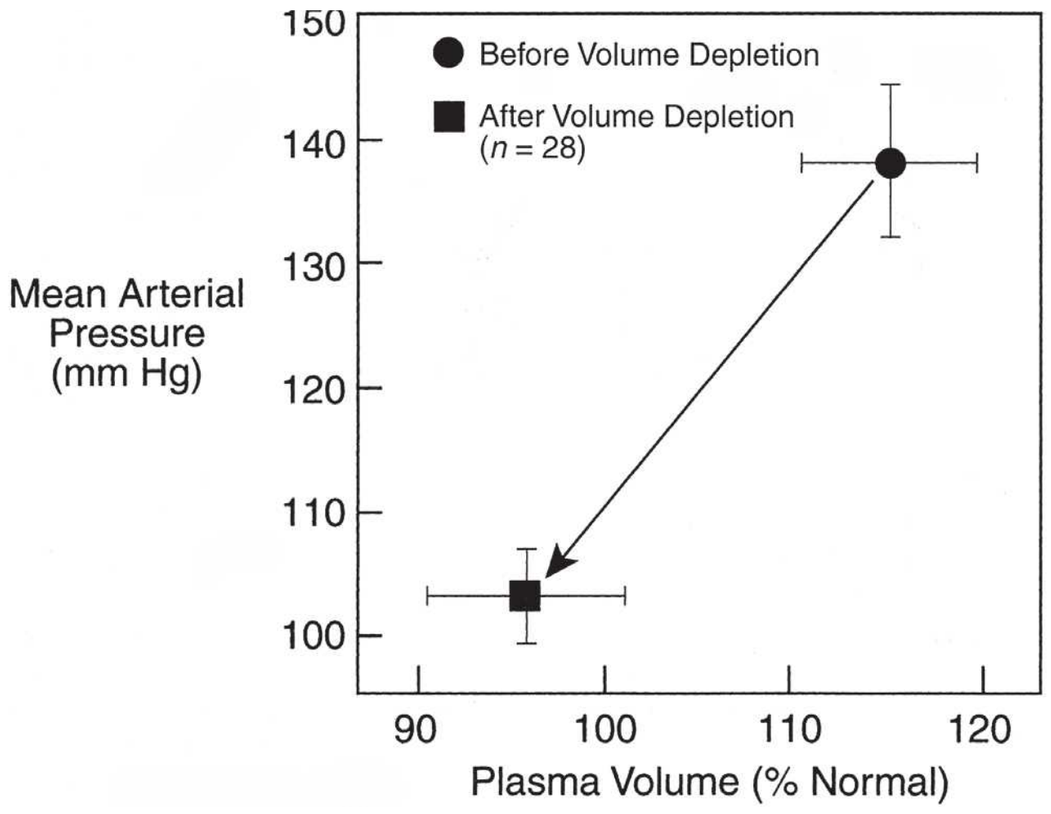

FIGURE 43.4 The effect of diuretic therapy on the blood pressure of patients with primary aldosteronism. Spironolactone (100 mg twice daily) and hydrochlorothiazide (50 to 100 mg per day) were added to current therapy. Blood pressure and plasma volume values were obtained after 8 to 12 weeks of continued therapy. Mean arterial pressure was significantly reduced in all. For the group as a whole, it fell from 138 +/− 2 to 103 +/− 9 (SEM) mm Hg ($P < .01$). Associated with reductions in mean arterial pressure were decreases in plasma volume (from 114% +/− 3% to 97% +/− 2% (SEM), $p < 0.01$. (From Bravo EL. Primary aldosteronism. Issues in diagnosis and management. *Endocrinol Metab Clin North Am*. 1994;23(2):217–282.)

Surgical

In unilateral APA, a laparoscopic adrenalectomy should be considered to minimize risk and postoperative recovery time. In those with bilateral adrenal adenomas, the surgical removal of both adrenal glands is not an option because the adverse metabolic and cardiovascular consequences of adrenal insufficiency are more difficult to treat than the hypertension caused by hyperaldosteronism. Postadrenalectomy, serum potassium levels normalize in all patients. Elevated blood pressure improves to normal levels in 35% to 50% of patients following adrenalectomy and, in those patients who remain hypertensive following surgery, there is a reduction in the number of antihypertensive medications required.[47] In a recent study that followed patients with unilateral APA, there was significant improvement in quality of life after undergoing adrenalectomy.[48] Patients undergoing surgery should receive medical therapy with an aldosterone antagonist for 8 to 10 weeks preoperatively to normalize blood pressure and serum potassium concentrations.

Clinical Outcomes. Significant lowering of blood pressure levels and the normalization of serum potassium occur with both medical[49] (spironolactone) and surgical intervention. After removal of the solitary adenoma, one-third of all cases are cured and free of all therapy, 75% of cases improved with the reduction of antihypertensive therapy, and 100% will have a reversal of hypokalemia. Factors reported to predict cure after an adrenalectomy are response to spironolactone therapy, younger age, shorter duration of hypertension, family history of hypertension in at least one first-degree relative, preoperative use of at least two antihypertensive agents, higher ARR, and 24-hour urinary aldosterone levels.[50,51] A recent study suggests that a unilateral adrenalectomy may be beneficial in carefully selected patients with BAH.[49]

OTHER HYPERTENSIVE DISORDERS ASSOCIATED WITH THE OVERPRODUCTION OF MINERALOCORTICOIDS

Glucocorticoid-Remediable Aldosteronism

Glucocorticoid-remediable aldosteronism (GRA), also known as familial hyperaldosteronism type 1 (FH-1), is an inherited autosomal disorder that mimics an APA. It is characterized by a strong family history of hypertension and moderate-to-severe hypertension often associated with early death from hemorrhagic stroke as the result of ruptured intracranial aneurysms. In a retrospective review of the International Registry of GRA, 48% of all GRA pedigrees and 18% of all GRA patients had cerebrovascular complications.[52] The frequency of intracranial aneurysms is similar to that of adult polycystic kidney disease, and it has been recommended that screening with MRI angiography should be performed in affected patients beginning at puberty, and every 5 years thereafter.

This disorder is caused by a genetic mutation that results in a chimeric gene product that fuses nucleotide sequences of the 11β-hydroxylase[53] and is regulated by ACTH (Fig. 43.5). In addition, the chimeric gene allows for the

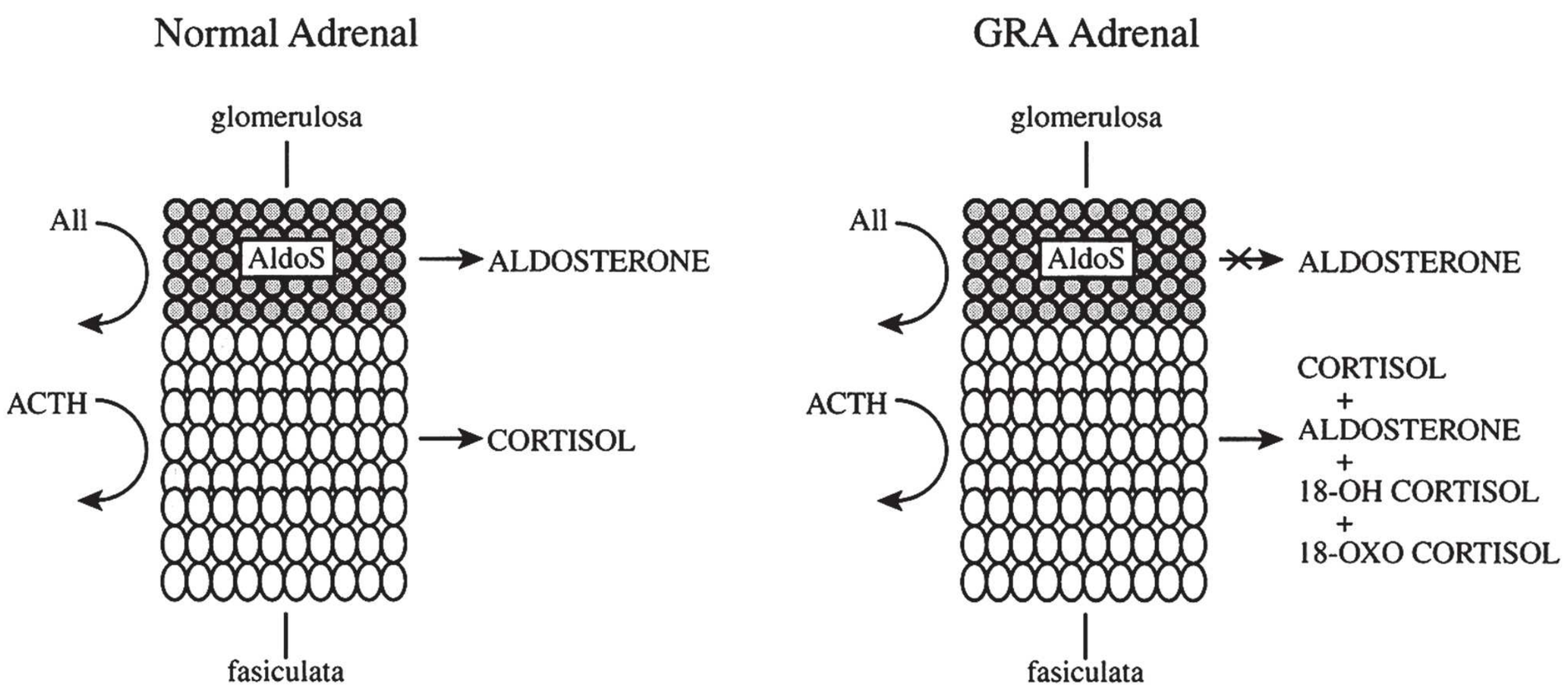

FIGURE 43.5 A model of the physiologic abnormalities in the adrenal cortex in glucocorticoid-remediable aldosteronism (GRA). In the normal adrenal gland, AldoS activity is present only in the adrenal zona glomerulosa. Aldosterone is produced in the glomerulosa layer under the regulation of angiotensin II, and cortisol is secreted from the adrenal fasciculata under the regulation of adrenocorticotropic hormone (ACTH). Steroid 11β-hydroxylase is involved in the biosynthesis of both of these hormones and is expressed in both tissues. The gene is under positive control of ACTH in fasciculata. Ectopic activity of the enzyme in fasciculata results in the metabolism of cortisol to 18-hydroxycortisol and 18-oxocortisol, as well as production of aldosterone from high levels of corticosterone present in fasciculata. These mineralocorticoids are under the control of ACTH, and can consequently be suppressed by exogenous glucocorticoids. (From Lifton RP et al., *Nature Genetics*. 1992;2:66–74.)

ectopic expression of aldosterone synthase enzyme activity in the ACTH-regulated zona fasciculata, which normally secretes only cortisol, but now also secretes aldosterone. Aldosterone secretion is positively and solely regulated by ACTH, not by potassium or angiotensin II. As a consequence, exogenous administration of low-dose glucocorticoid (which suppresses aldosterone secretion in affected individuals) reverses the clinical manifestations of the syndrome.

As in PA, PRA is suppressed, and increased aldosterone production is nonsuppressible by salt loading. Most patients with GRA are not hypokalemic; therefore, serum potassium lacks sensitivity as a screening test for this disorder. Because aldosterone secretion is solely regulated by ACTH, the dexamethasone suppression test has been employed as a diagnostic test. However, the test has a high false-positive rate. For example, Fogari and coworkers[54] reported that only one of eight of their patients with PA that tested positive with the dexamethasone suppression test had the chimeric gene for GRA. Direct genetic screening for the presence of the gene duplication in GRA is 100% sensitive and specific. It is recommended for patients with PA without a radiographic evidence of tumor, for young hypertensive individuals with suppressed PRA (especially children), and for at-risk individuals in affected families. Treatment with low-dose glucocorticoids, amiloride, and aldosterone receptor antagonists effectively controls elevated blood pressure in GRA.

Congenital Disorders of Steroid Hormone Production

P450C11β and 17α deficiencies cause hypertensive variants of congenital adrenal hyperplasia (CAH). Both enzyme deficiencies result in reduced cortisol production with subsequent overproduction of ACTH. In turn, ACTH drives the zona fasciculata to increase the production of precursor steroids with an accumulation of 11–deoxycorticosterone (DOC), a potent mineralocorticoid, leading to hypertension and hypokalemia with suppressed PRA and, unlike PA, virtual absence of aldosterone production. In both enzyme deficiency disorders, inhibiting ACTH release with glucocorticoids decreases DOC production, which results in the normalization of blood pressure and the serum potassium concentration.

In 11β-hydroxylase deficiency, there is a shunting of precursor steroids into the androgen pathway, resulting in the increased formation of androgens, which produce virilization in females or precocious puberty with advanced masculinization in males.[55] This enzyme deficiency clusters in exon 6 to 8 of the CYP11β1 gene and accounts for 15% of cases of CAH in Muslim and Jewish Middle Eastern populations.

By contrast, patients with 17α-hydroxylase deficiency present with hypogonadism in addition to hypertension, hypokalemia, suppressed PRA, and absent aldosterone production.[56] This enzyme deficiency reduces the production of all adrenal and gonadal androgens, resulting in a form of hypergonadotropic hypogonadism and abnormalities of sexual development. The hypogonadal consequence accounts for most of the clinical features of the disorder. Females with this disorder have primary amenorrhea, disproportionately long limbs relative to the trunk, and absent secondary sexual characteristics. Male patients have either ambiguous external genitalia or a female phenotype (male pseudohermaphroditism). A large number of random mutations can cause 17α-hydroxylase deficiency, making genetic diagnosis difficult.

Glucocorticoid Resistance

Cortisol synthesis is regulated through a negative feedback loop in which cortisol feeds back on the pituitary to inhibit ACTH secretion. In generalized inherited glucocorticoid resistance, cortisol remains ACTH dependent but is reset to a higher level than normal.[57] Because the peripheral tissues and pituitary are equally resistant to cortisol, affected individuals do not develop features of Cushing syndrome despite marked elevations in circulating cortisol levels. An ACTH-dependent increase in DOC and in adrenal androgens occurs. The clinical presentation is characterized by virilization and precocious puberty (due to excess adrenal androgens) and by hypertension and hypokalemia (due to excess DOC).

Two strategies are used to treat generalized glucocorticoid resistance. The first employs high amounts of glucocorticoids, such as dexamethasone, to suppress adrenal stimulation by ACTH. Alternatively, mineralocorticoid or androgen antagonists can be used.

HYPERTENSION DUE TO ACTIVATION OF MINERALOCORTICOID RECEPTORS

Syndrome of Apparent Mineralocorticoid Excess

Mineralocorticoid receptors (MR) in the distal nephron of the kidney have equal affinity for their two ligands—aldosterone and cortisol—but are protected from cortisol by the presence of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which inactivates cortisol by converting it to cortisone, preventing full MR occupancy by cortisol despite 100- to 1,000-fold plasma concentrations greater than those of aldosterone (Fig. 43.6).[58] The 11, 18 hemiacetal structure of aldosterone protects it from the action of 11β-HSD2 so that aldosterone has unimpeded access to the receptors. When this mechanism is defective, intrarenal levels of cortisol increase, causing its inappropriate access to MR.[59] The resulting antinatriuresis and kaliuresis leads to hypertension and hypokalemia. Biochemically, PRA is suppressed and aldosterone production is markedly decreased. Elevations in urinary free cortisol excretion and in the ratio of the urinary metabolites of cortisol to those of cortisone, as well as prolongation of the half-life of cortisol, are noted. Plasma cortisol concentrations usually are not elevated.

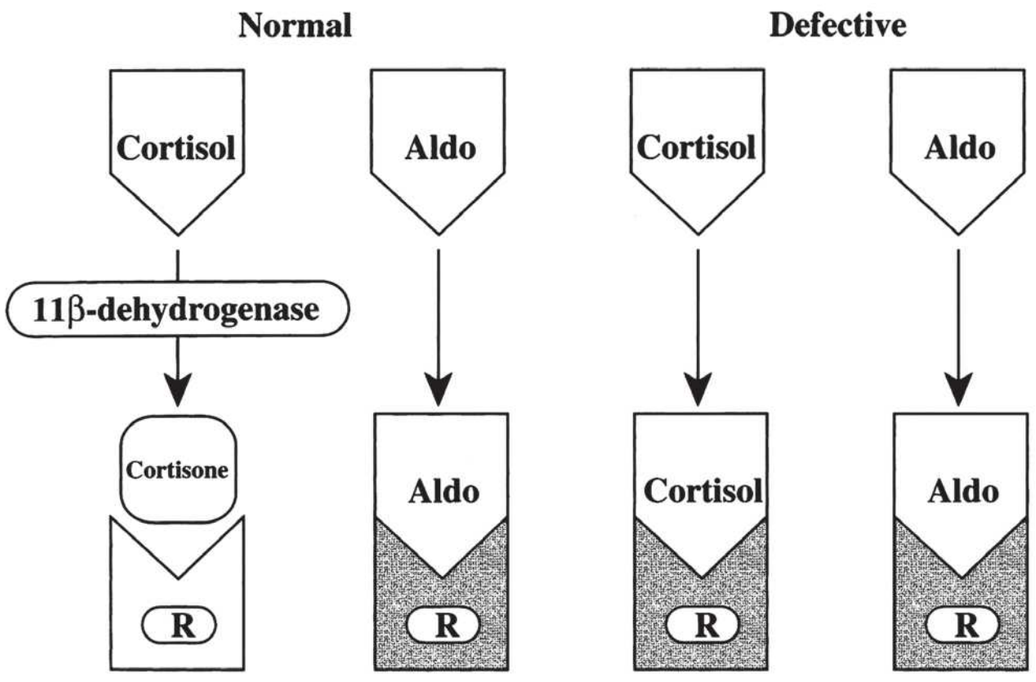

FIGURE 43.6 Enzyme-mediated receptor protection. Normal 11β-hydroxysteroid dehydrogenase converts cortisol to inactive cortisone, protecting mineralocorticoid receptors (R) from cortisol and allowing selective access for aldosterone (Aldo). When 11β-dehydrogenase is defective, cortisol gains inappropriate access to mineralocorticoid receptors with resulting antinatriuresis and kaliuresis. (From Walker BR, Edwards CR. *Endocrinol Metab North Am*. 1994;23:359–377.)

The hypertensive syndrome is reversed by spironolactone or dexamethasone and is exacerbated by the administration of physiologic doses of cortisol.

The recessively inherited apparent mineralocorticoid excess (AME) is caused by a genetic deficiency of 11β-HSD2.[60] Cortisol-mediated excessive mineralocorticoid action results in early-onset severe hypertension, failure to thrive, hypokalemia, suppressed PRA, and low aldosterone levels. The phenotype–genotype of AME may vary widely from mild to severe hypertension depending on the effect of mutation on 11β-HSD2.

Excessive licorice ingestion is known to cause an acquired form of AME. Licorice contains glycyrrhizinic acid, which is hydrolyzed to glycyrrhetinic acid, an inhibitor of 11β-HSD2. This results in an AME-phenotype, including hypertension, hypokalemia, suppressed PRA, and low plasma aldosterone levels. However, because licorice consumption does not always lead to the hypertensive syndrome, Miettinen and coworkers[61] reasoned that genes influencing licorice action may partly determine susceptibility to its side effects. In preliminary studies in human volunteers, those investigators found that a mutation of the 11β-HSD2 gene does not appear to constitute a common cause for licorice-induced hypertensive syndrome. Their studies suggest that subtle variants of the α, β, and λ subunits of the ENaC may render some individuals sensitive to licorice-induced metabolic cardiovascular alterations.

Cushing Syndrome (Resulting from Ectopic Adrenocorticotropic Hormone Excess)

The recognizable causes of Cushing syndrome include Cushing disease (72%), ectopic ACTH excess (12%), adrenal adenoma (8%), carcinoma (6%), and hyperplasia (4%). The typical clinical presentation of Cushing syndrome includes truncal obesity, moon facies, hypertension, plethora, muscle weakness and fatigue, hirsutism, emotional disturbances, and typical purple skin striae. Carbohydrate intolerance or diabetes, amenorrhea, loss of libido, easy bruising, and spontaneous fracture of ribs and vertebrae may also be encountered. Patients with ectopic ACTH excess may not have the typical manifestations of cortisol excess, but they may present with hyperpigmentation of the skin, severe hypertension, and marked hypokalemic alkalosis.

The incidence of hypokalemic alkalosis in the ectopic ACTH syndrome is greater than 90%, compared with only 10% in Cushing syndrome of other causes.[62] It is widely supposed that corticosterone or 11-DOC is responsible for mineralocorticoid excess, but poor correlation exists between the levels of these steroids and the degree of hypokalemia. A better predictor of hypokalemia is the level of cortisol.[63,64] Several studies suggest that the ratio of cortisol to cortisone metabolites is increased in all forms of Cushing syndrome. Ulick and associates[65] advanced the hypothesis that excessive circulating cortisol overwhelms the enzyme, thus escaping conversion of cortisol to cortisone and gaining inappropriate access to Mrs. Walker and coworkers[66] demonstrated a negative correlation between the extent of impairment of 11β-hydroxysteroid dehydrogenase and plasma potassium concentration in 26 patients with Cushing syndrome, 9 of whom had higher cortisol-to-cortisone ratios than the 15 patients with pituitary Cushing and the 2 patients with adrenal adenomas.

The determination of a 24-hour urinary free cortisol concentration is the best available test for documenting endogenous hypercortisolism.[67] A level of higher than 100 μg per 24 hours suggests excessive cortisol production. There are virtually no false-negative results. False-positive results may be obtained in non-Cushing hypercortisolemic states (e.g., stress, chronic strenuous exercise, psychiatric states, glucocorticoid resistance, malnutrition). If a differentiation between pituitary and ectopic sources of ACTH cannot be made based on plasma levels alone, pharmacologic manipulation of ACTH secretion should be performed. The overnight dexamethasone suppression test requires only a blood collection for serum cortisol the morning after the patient has taken a 1.0-mg dose of dexamethasone at 11 p.m. the previous evening. In physiologically normal subjects, cortisol levels at 8 a.m. will be suppressed to 5.0 μg per deciliter or less.

When the syndrome has been diagnosed by appropriate biochemical testing, the cause must be identified. A radioimmunoassay of plasma ACTH is the procedure of choice for pinpointing the basis of hypercortisolism, but this test is not available in many hospitals. In patients with ACTH-independent Cushing syndrome, ACTH levels have usually been suppressed to less than 5 pg per milliliter. In contrast, patients with the ACTH-dependent form tend to have either normal or elevated levels of ACTH, usually higher than 10 pg per milliliter. In patients with Cushing disease

43.3 Humoral Characteristics of Mineralocorticoid-Dependent Hypertension

Disorder	Aldosterone	Cortisol	Androgen
Primary aldosteronism (PA)	High	Normal	Normal
Glucocorticoid-remediable aldosteronism (GRA)	High	Normal	Normal
Excess deoxycorticosterone production			
– 11β-hydroxylase deficiency	**Low**	**Low**	**High**
– 17α-hydroxylase deficiency	**Low**	**Low**	**Low**
– Glucocorticoid resistance	**Low**	**Very high**	**High**
Apparent mineralocorticoid excess	Low	Normal	Normal
Ectopic ACTH excess	Low	Very high	Normal

ACTH, adrenocorticotropic hormone.

(i.e., basophilic pituitary microadenomas), ACTH release can be inhibited only at much higher doses of dexamethasone (2 mg every 6 hours for 2 days). The established criterion for the test is that suppression of the 24-hour urine and plasma steroids to less than 50% of baseline indicates pituitary Cushing syndrome (i.e., Cushing disease). Failure to suppress these concentrations to less than 50% of baseline is considered consistent with an ectopic source of ACTH or ACTH-independent Cushing syndrome. The best way to differentiate pituitary ACTH excess from the ectopic production of ACTH is with the inferior petrosal sinus procedure for ACTH concentration, which is invasive and carries its own risks.[68] The test has been characterized in the literature as having 100% sensitivity and 100% specificity. The criterion currently used after corticotropin-releasing hormone administration is that the ACTH gradient between the inferior petrosal sinus and the peripheral site will be greater than 2 if the patient has Cushing disease.

Table 43.3 shows the humoral characteristics of mineralocorticoid-dependent hypertension.

Liddle Syndrome

Liddle syndrome is a rare autosomal dominant disorder with variable penetrance. Patients with Liddle syndrome clinically present with hypertension, hypokalemia, and metabolic alkalosis at a relatively young age. However, some patients with Liddle syndrome are not hypokalemic[69] at presentation. Sporadic cases of Liddle syndrome have also been described.[70] Thus, the absence of hypokalemia at presentation and/or the absence of a family history do not preclude the diagnosis. In the absence of hypokalemia, a positive family history of hypertension at a young age, with some members being hypokalemic, should lead to the suspicion of the genetic disorder.

The defect in Liddle syndrome results from the constitutive activation of amiloride-sensitive epithelial sodium channels (ENaC) on distal renal tubules, which causes excessive sodium reabsorption. This channel is composed of at least three subunits and is normally regulated by aldosterone. The mutations causing Liddle syndrome have been localized to genes on chromosome 16p12 that encodes the β and λ subunits of ENaC.[71] Deletions or substitutions in a short proline-rich segment of the intracytoplasmic C-terminus result in the inability of these subunits to bind with an intracellular protein ligase (Nedd4) that normally removes the luminal sodium channel from the cell surface in response to decreased circulating aldosterone.[72] Failure to remove sodium channels results in an increased number of ENaC at the renal distal apical cell surface. These mutations in "gain-of-function" result in excessive sodium reabsorption (leading to hypertension and suppressed PRA) and increased potassium secretion (producing hypokalemia and metabolic alkalosis). Aldosterone levels are undetectable, and antagonism of MR with specific aldosterone receptor antagonists have no effect on either blood pressure or serum potassium. Hypertension and hypokalemia are effectively treated with sodium deprivation or potassium-sparing agents that block the collecting tubule sodium channels (amiloride or triamterene).[73] Genetic testing is the most reliable method of establishing the diagnosis of Liddle syndrome.[74]

Activating Mutations of Mineralocorticoid receptors

In 2000, Geller and coworkers[75] described a group of women with early onset hypertension (<20 years of age), which was markedly exacerbated by pregnancy. Hypertension in these patients could be very severe and unresponsive to antihypertensive therapy. There were no proteinuria, edema, or neurologic changes, excluding preeclampsia. Hypertension was often accompanied by hypokalemia (with renal potassium-wasting), and suppressed PRA and aldosterone levels, which normally increase 10-fold in pregnancy, were undetectable.

These investigators found a mutation in the MR, S810L, which results in constitutive MR activity and alters specificity, with progesterone and other steroids, lacking 21-hydroxyl groups that are normally MR antagonists, becoming potent agonists of MR L80. Similarly, spironolactone, another MR antagonist commonly used in the treatment of patients with hypertension and hypokalemia, is also a potent agonist of MR L810 and is contraindicated in MR L810 carriers. The hypertension is promptly reversed by delivery.

REFERENCES

1. Conn JW. Presidential address. I. Painting background. II. Primary aldosteronism, a new clinical syndrome. J Lab Clin Med. 1955;45(1):3–17.

2. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation. 1991;83(6):1849–1865.

3. Rossi GP, Bernini G, Desideri G, et al. Renal damage in primary aldosteronism: results of the PAPY Study. Hypertension. 2006;48(2):232–238.
http://www.ncbi.nlm.nih.gov/pubmed/16801482

4. Bernini G, Galetta F, Franzoni F, et al. Arterial stiffness, intima-media thickness and carotid artery f brosis in patients with primary aldosteronism. J Hypertens. 2008;26(12):2399–2405.
http://www.ncbi.nlm.nih.gov/pubmed/19008719

5. Milliez P, Girerd X, Plouin PF, et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol. 2005;45(8):1243–1248.

6. Tsuchiya K, Yoshimoto T, Hirata Y. Endothelial dysfunction is related to aldosterone excess and raised blood pressure. Endocr J. 2009;56(4):553–559.
http://www.ncbi.nlm.nih.gov/pubmed/19352049

7. Stowasser M, Sharman J, Leano R, et al. Evidence for abnormal left ventricular structure and function in normotensive individuals with familial hyperaldosteronism type I. J Clin Endocrinol Metab. 2005;90(9):5070–5076.
http://www.ncbi.nlm.nih.gov/pubmed/15941863

8. Ribstein J, Du Cailar G, Fesler P, et al. Relative glomerular hyperf ltration in primary aldosteronism. J Am Soc Nephrol. 2005;16(5):1320–1325.
http://www.ncbi.nlm.nih.gov/pubmed/15800124

9. Sechi LA, Novello M, Lapenna R, et al. Long-term renal outcomes in patients with primary aldosteronism. JAMA. 2006;295(22):2638–2645.

10. Shigematsu Y, Hamada M, Okayama H, et al. Left ventricular hypertrophy precedes other target-organ damage in primary aldosteronism. Hypertension. 1997;29(3):723–727.

11. Strauch B, Petrák O, Zelinka T, et al. Adrenalectomy improves arterial stiffness in primary aldosteronism. Am J Hypertens. 2008;21(10):1086–1092.
http://www.ncbi.nlm.nih.gov/pubmed/18654122

12. Guyton AC, Coleman TG, Bower JD, et al. Circulatory control in hypertension. Circ Res. 1970;27(Suppl 2):135.
http://www.ncbi.nlm.nih.gov/pubmed/5506139

13. Bravo EL, Tarazi RC, Dustan HP, et al. The changing clinical spectrum of primary aldosteronism. Am J Med. 1983;74(4):641–651.

14. Moreland RS, Lamb FS, Webb RC, et al. Functional evidence for increased sodium permeability in aortas from DOCA hypertensive rats. Hypertension. 1984;6(2 Pt 2):I88–I94.

15. Folkow B, Oberg B. The effect of functionally induced changes of wall/lumen ratio on the vasoconstrictor response to standard amounts of vasoactive agents. Acta Physiol Scand. 1959;47:131–135.
http://www.ncbi.nlm.nih.gov/pubmed/13823750

16. Rossi GP, Bernini G, Caliumi C, et al. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol. 2006;48(11):2293–2300.
http://www.ncbi.nlm.nih.gov/pubmed/17161262

17. Rossi GP, Belf ore A, Bernini G, et al. Prospective evaluation of the saline infusion test for excluding primary aldosteronism due to aldosterone-producing adenoma. J Hypertens. 2007;25(7):1433–1442.
http://www.ncbi.nlm.nih.gov/pubmed/17563566

18. Gordon RD, Stowasser M, Tunny TJ, et al. High incidence of primary aldosteronism in 199 patients referred with hypertension. Clin Exp Pharmacol Physiol. 1994;21(4):315–318.
http://www.ncbi.nlm.nih.gov/pubmed/7923898

19. Douma S, Petidis K, Doumas M, et al. Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study. Lancet. 2008;371(9628):1921–1926.

20. Mosso L, Carvajal C, González A, et al. Primary aldosteronism and hypertensive disease. Hypertension. 2003;42(2):161–165.
http://www.ncbi.nlm.nih.gov/pubmed/12796282

21. Conn JW, Knopf RF, Nesbit RM. Clinical characteristics of primary aldosteronism from an analysis of 145 cases. Am J Surg. 1964;107:159–172.
http://www.ncbi.nlm.nih.gov/pubmed/14099489

22. Ferriss JB, Beevers DG, Brown JJ, et al. Clinical, biochemical and pathological features of low-renin ("primary") hyperaldosteronism. Am Heart J. 1978;95(3):375–388.
http://www.ncbi.nlm.nih.gov/pubmed/622981

23. Olivieri O, Ciacciarelli A, Signorelli D, et al. Aldosterone to renin ratio in a primary care setting: the Bussolengo study. J Clin Endocrinol Metab. 2004;89(9):4221–4226.
http://www.ncbi.nlm.nih.gov/pubmed/15356010

24. Montori VM, Young WF Jr. Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism. A systematic review of the literature. Endocrinol Metab Clin North Am. 2002;31(3):619–632.
http://www.ncbi.nlm.nih.gov/pubmed/12227124

25. Rossi GP, Seccia TM, Palumbo G, et al. Within-patient reproducibility of the aldosterone: renin ratio in primary aldosteronism. Hypertension. 2010;55(1):83–89.
http://www.ncbi.nlm.nih.gov/pubmed/19933925

26. Weinberger MH, Fineberg NS. The diagnosis of primary aldosteronism and separation of two major subtypes. Arch Intern Med. 1993;153(18):2125–2129.
http://www.ncbi.nlm.nih.gov/pubmed/8379804

27. Young WF Jr. Primary aldosteronism: a common and curable form of hypertension. Cardiol Rev. 1999;7(4):207–214.
http://www.ncbi.nlm.nih.gov/pubmed/10423672

28. Pizzolo F, Raffaelli R, Memmo A, et al. Effects of female sex hormones and contraceptive pill on the diagnostic work-up for primary aldosteronism. J Hypertens. 2010;28(1):135–142.

29. Mulatero P, Rabbia F, Milan A, et al. Drug effects on aldosterone/plasma renin activity ratio in primary aldosteronism. Hypertension. 2002;40(6):897–902.
http://www.ncbi.nlm.nih.gov/pubmed/12468576

30. Mulatero P, Monticone S, Bertello C, et al. Evaluation of primary aldosteronism. Curr Opin Endocrinol Diabetes Obes. 2010;17:188–193.
http://www.ncbi.nlm.nih.gov/pubmed/20389241

31. Mulatero P, Stowasser M, Loh KC, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from f ve continents. J Clin Endocrinol Metab. 2004;89(3):1045–1050.

32. Fraser R, Beretta-Piccoli C, Brown JJ, et al. Response of aldosterone and 18-hydroxycorticosterone to angiotensin II in normal subjects and patients with essential hypertension, Conn's syndrome, and nontumorous hyperaldosteronism. Hypertension. 1981;3(3 Pt 2):I87–I92.

33. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(3):3266–3281.

34. Harvey A, Kline G, Pasieka JL. Adrenal venous sampling in primary hyperaldosteronism: comparison of radiographic with biochemical success and the clinical decision-making with "less than ideal" testing. Surgery. 2006;140(6):847–853.
http://www.ncbi.nlm.nih.gov/pubmed/17188130

35. Young WF Jr, Klee GG. Primary aldosteronism. Diagnostic evaluation. Endocrinol Metab Clin North Am. 1988;17(2):367–395.
http://www.ncbi.nlm.nih.gov/pubmed/3042391

36. Daunt N. Adrenal vein sampling: how to make it quick, easy, and successful. Radiographics. 2005;25 Suppl 1:S143–158.
37. Mulatero P, Bertello C, Sukor N, et al. Impact of different diagnostic criteria during adrenal vein sampling on reproducibility of subtype diagnosis in patients with primary aldosteronism. Hypertension. 2010;55(3):667–673.
http://www.ncbi.nlm.nih.gov/pubmed/20124107
38. Rossi GP, Pitter G, Bernante P, et al. Adrenal vein sampling for primary aldosteronism: the assessment of selectivity and lateralization of aldosterone excess baseline and after adrenocorticotropic hormone (ACTH) stimulation. J Hypertens. 2008;26(5):989–997.
http://www.ncbi.nlm.nih.gov/pubmed/18398342
39. Bergström M, Juhlin C, Bonasera TA, et al. PET imaging of adrenal cortical tumors with the 11beta-hydroxylase tracer 11C-metomidate. J Nucl Med. 2000;41(2):275–282.
http://www.ncbi.nlm.nih.gov/pubmed/10688111
40. Hennings J, Sundin A, Hagg A, et al. 11C-metomidate positron emission to-mography after dexamethasone suppression for detection of small adrenocortical adenomas in primary aldosteronism. Langenbecks Arch Surg. 2010;395(7): 963–967.
http://www.ncbi.nlm.nih.gov/pubmed/20644954
41. Hennings J, Lindhe O, Bergstrom M, et al. [11C]metomidate positron emission tomography of adrenocortical tumors in correlation with histopathological findings. J Clin Endocrinol Metab. 2006;91(4):1410–1414.
http://www.ncbi.nlm.nih.gov/pubmed/16403816
42. Burton TJ, Mackenzie IS, Balan K, et al. Evaluation of the sensitivity and specificity of (II) C-metomidate positron emission tomography (PET)-CT for lateralizing aldosterone secretion by Conn's adenomas. J Clin Endocrinal Metab. 2012;97(1):100–109.
43. Ghose RP, Hall PM, Bravo EL. Medical management of aldosterone-producing adenomas. Ann Intern Med. 1999;131(2):105–108.
http://www.ncbi.nlm.nih.gov/pubmed/10419425
44. Bravo EL. Primary aldosteronism. Issues in diagnosis and management. Endocrinol Metab Clin North Am. 1994;23(2):271–283.
http://www.ncbi.nlm.nih.gov/pubmed/8070422
45. Catena C, Colussi G, Nadalini E, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch Intern Med. 2008;168(1):80–85.
http://www.ncbi.nlm.nih.gov/pubmed/18195199
46. Struthers A, Krum H, Williams GH. A comparison of the aldosterone-blocking agents eplerenone and spironolactone. Clin Cardiol. 2008;31(4): 153–158.
47. 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.
http://www.ncbi.nlm.nih.gov/pubmed/21451421
48. Catena C, Colussi G, Lapenna R, et al. Long-term cardiac effects of adrenalectomy or mineralocorticoid antagonists in patients with primary aldosteronism. Hypertension. 2007;50(5):911–918.
http://www.ncbi.nlm.nih.gov/pubmed/17893375
49. Sukor N, Kogovsek C, Gordon RD, et al. Improved quality of life, blood pressure, and biochemical status following laparoscopic adrenalectomy for unilateral primary aldosteronism. J Clin Endocrinol Metab. 2010;95(3):1360–1364.
http://www.ncbi.nlm.nih.gov/pubmed/20089615
50. Celen O, O'Brien MJ, Melby JC, et al. Factors influencing outcome of surgery for primary aldosteronism. Arch Surg. 1996;131(6):646–650.
http://www.ncbi.nlm.nih.gov/pubmed/8645073
51. Sawka AM, Young WF, Thompson GB, et al. Primary aldosteronism: factors associated with normalization of blood pressure after surgery. Ann Intern Med. 2001;135(4):258–261.
http://www.ncbi.nlm.nih.gov/pubmed/11511140
52. Litchfield WR, Anderson BF, Weiss RJ, et al. Intracranial aneurysm and hemorrhagic stroke in glucocorticoid-remediable aldosteronism. Hypertension. 1998;31(1 Pt 2):445–450.
53. Lifton RP, Dluhy RG, Powers M, et al. A chimaeric 11 beta-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature. 1992;355(6357):262–265.
53a. From Lifton RP et al., Nature Genetics. 1992;2:66–74.
http://www.ncbi.nlm.nih.gov/pubmed/1303253
54. Fogari R, Preti P, Zoppi A, et al. Prevalence of primary aldosteronism among unselected hypertensive patients: a prospective study based on the use of an aldosterone/renin ratio above 25 as a screening test. Hypertens Res. 2007;30(2):111–117.
http://www.ncbi.nlm.nih.gov/pubmed/17460380
55. White PC, Speiser PW Steroid 11 beta-hydroxylase deficiency and related disorders. Endocrinol Metab Clin North Am. 1994;23(2):325–339.
http://www.ncbi.nlm.nih.gov/pubmed/8070425
56. Biglieri EG, Herron MA, Brust N. 17-hydroxylation deficiency in man. J Clin Invest. 1966;45(12):1946–1954.
http://www.ncbi.nlm.nih.gov/pubmed/4288776
57. Malchoff CD, Malchoff DM. Glucocorticoid resistance in humans. Trends Endocrinol Metab. 1995;6(3):89–95.
http://www.ncbi.nlm.nih.gov/pubmed/18406688
58. Farman N, Rafestin-Oblin ME. Multiple aspects of mineralocorticoid selectivity. Am J Physiol Renal Physiol. 2001;280(2):F181–192.
58a. From Walker BR, Edwards CR. Endocrinol Metab North Am. 1994;23: 359–377.
59. Funder JW, Pearce PT, Smith R, et al. Mineralocorticoid action: target tissue specificity is enzyme, not receptor, mediated. Science. 1988;242(4878):583–585.
http://www.ncbi.nlm.nih.gov/pubmed/2845584
60. Palermo M, Quinkler M, Stewart PM. Apparent mineralocorticoid excess syndrome: an overview. Arq Bras Endocrinol Metabo. 2004;48(5):687–696.
61. Miettinen HE, Piippo K, Hannila-Handelberg T, et al. Licorice-induced hypertension and common variants of genes regulating renal sodium reabsorption. Ann Med. 2010;42(6):465–474.
http://www.ncbi.nlm.nih.gov/pubmed/20597806
62. Howlett TA, Drury PL, Perry L, et al. Diagnosis and management of ACTH-dependent Cushing's syndrome: comparison of the features in ectopic and pituitary ACTH production. Clin Endocrinol (Oxf). 1986;24(6):699–713.
63. Christy NP, Laragh J. Pathogenesis of hypokalemic alkalosis in Cushing's syndrome. N Engl J Med. 1961;265:1083–1088.
http://www.ncbi.nlm.nih.gov/pubmed/13879332
64. Ritchie CM, Sheridan B, Fraser R, et al. Studies on the pathogenesis of hypertension in Cushing's disease and acromegaly. Q J Med. 1990;76(280): 855–867.
http://www.ncbi.nlm.nih.gov/pubmed/2217688
65. Ulick S, Wang JZ, Blumenfeld JD, et al. Cortisol inactivation overload: a mechanism of mineralocorticoid hypertension in the ectopic adrenocorticotropin syndrome. J Clin Endocrinol Metab. 1992;74(5):963–967.
http://www.ncbi.nlm.nih.gov/pubmed/1569172
66. Walker BR, Campbell JC, Fraser R, et al. Mineralocorticoid excess and inhibition of 11 beta-hydroxysteroid dehydrogenase in patients with ectopic ACTH syndrome. Clin Endocrinol (Oxf). 1992;37(6):483–492.
67. Tsigos C, Kamilaris TC, Chrousos GP. Adrenal diseases. In: Eastman RC, ed. Diagnostic Radiology. Philadelphia: BC Decker; 1996: 125.
68. Oldfield EH, Chrousos GP, Schulte HM, et al. Preoperative lateralization of ACTH-secreting pituitary microadenomas by bilateral and simultaneous inferior petrosal venous sinus sampling. N Engl J Med. 1985;312(2):100–103.
http://www.ncbi.nlm.nih.gov/pubmed/2981108
69. Botero-Velez M, Curtis JJ, Warnock DG. Brief report: Liddle's syndrome revisited—a disorder of sodium reabsorption in the distal tubule. N Engl J Med. 1994;330(3):178–181.
http://www.ncbi.nlm.nih.gov/pubmed/8264740
70. Yamashita Y, Koga M, Takeda Y, et al. Two sporadic cases of Liddle's syndrome caused by de novo ENaC mutations. Am J Kidney Dis. 2001;37(3): 499–504.
http://www.ncbi.nlm.nih.gov/pubmed/11228173
71. Shimkets RA, Warnock DG, Bositis CM, et al. Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. Cell. 1994;79(3):407–414.
72. Abriel H, Loffing J, Rebhun JF, et al. Defective regulation of the epithelial Na+ channel by Nedd4 in Liddle's syndrome. J Clin Invest. 1999;103(5):667–673.
73. Wang C, Chan TK, Yeung RT, et al. The effect of triamterene and sodium intake on renin, aldosterone, and erythrocyte sodium transport in Liddle's syndrome. J Clin Endocrinol Metab. 1981;52(5):1027–1032.
74. Achard JM, Hadchouel J, Faure S, et al. Inherited sodium avid states. Adv Chronic Kidney Dis. 2006;13(2):118–123.
http://www.ncbi.nlm.nih.gov/pubmed/16580612
75. Geller DS, Farhi A, Pinkerton N, et al. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. Science. 2000; 289(5476):119–123.
http://www.ncbi.nlm.nih.gov/pubmed/10884226