SEMINARS IN
NEPHROLOGY

Mineralocorticoid Hypertension and Hypokalemia

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Mineralocorticoid hypertension is hypertension associated with the presence of hypokalemia, metabolic alkalosis, and suppression of plasma renin. Mineralocorticoid hypertension represents only 10% of patients with essential hypertension. However, its recognition is important because it is a potentially reversible cause of hypertension. Primary hyperaldosteronism is the most common form of mineralocorticoid hypertension. It is current clinical practice to use the plasma aldosterone-renin ratio and the absolute plasma aldosterone level as screening tests. Confirmatory suppression tests and adrenal imaging are performed in appropriate patients. Three monogenic forms of mineralocorticoid hypertension have been identified including Liddle's syndrome, glucocorticoid-remediable hypertension, and apparent mineralocorticoid excess. In a number of patients with mineralocorticoid hypertension, hypokalemia can be a variable finding. This review highlights mineralocorticoid biology and important features of primary hyperaldosteronism and monogenic hypertension.
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Mineralocorticoid hypertension is a potentially reversible cause of hypertension that is characterized by the triad of hypertension, metabolic alkalosis, and hypokalemia. It refers to hypertension that is caused by increased retention of sodium by the nephron, expansion of the extracellular fluid compartment, and suppression of plasma renin. Of note, edema is not often present because of the sodium-escape phenomenon and normokalemia may be present in some forms of mineralocorticoid hypertension.[1] The potential causes of mineralocorticoid hypertension are presented in Table 1.

The true incidence of mineralocorticoid hypertension in an unselected community-based population is unclear and screening remains a widely debated topic. Certainly it is clear that all hypertensive patients should have their electrolyte levels checked and further testing should be performed if unprovoked hypokalemia is present. Screening of patients with difficult-to-control hypertension, rapid onset of disease, and possibly a strong family history of early onset hypertension and cerebrovascular disease is advisable.

This review discusses the biology of aldosterone followed by a discussion of primary hyperaldosteronism, the most common form of mineralocorticoid hypertension. It also discusses 2 monogenic forms of this class of hypertension: glucocorticoid-remediable hyperaldosteronism (GRA) and apparent mineralocorticoid excess (AME). Additional differential diagnoses also are highlighted, including abnormalities seen in essential hypertension that have been discovered from our understanding of monogenic forms of hypertension.

Mineralocorticoid Secretion and Hormone Action

An understanding of mineralocorticoid hypertension requires an understanding of aldosterone biosynthesis, regulation, and action. The major adrenal hormones are synthesized in different compartments of the adrenal cortex: aldosterone in the zona glomerulosa and glucocorticoids in the zona fasiciculata. Angiotensin II and increased potassium levels primarily regulate aldosterone secretion. Its synthesis requires 11-β hydroxylation followed by zona glomerulosa–specific 18 hydroxylation and 18 oxidation of deoxycorticosterone.[2-5] These latter 2 reactions are mediated by a single,

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Table 1 Differential Diagnosis of Mineralocorticoid Hypertension

Diagnosis based on responsible mineralocorticoid
Aldosterone
Adrenal adenoma
Bilateral adrenal hyperplasia
Adrenal carcinoma
GRA
Cortisol via 11 β-hydroxysteroid dehydrogenase deficiency/inhibition
AME
Licorice and carbenoxolone ingestion
Ectopic ACTH syndrome
?? Essential hypertension variant
?? Pre-eclampsia
Deoxycorticosterone
Congenital adrenal hyperplasia (11-β hydroxylase deficiency and 17-α hydroxylase deficiency)
Glucocorticoid receptor mutations
Metyrapone, mifrestone ingestion

multifunctional, cytochrome P450 enzyme called *aldosterone synthase*, the activity of which normally is suppressed in the zona fasciculata.[6] The absence of aldosterone synthase in the zona fasciculata prevents aldosterone secretion from being regulated by ACTH.

Aldosterone interacts with the mineralocorticoid receptor (MR) to increase sodium transport across epithelial cells of the distal nephron, colon, and salivary gland. The principal cell, located in the cortical collecting tubule, is a key site of potassium regulation and aldosterone activity. The aldosterone-MR complex interacts with the cell nucleus to increase synthesis of aldosterone-induced proteins, and these aldosterone-induced proteins work to open silent luminal Na+ channels and insert new Na+ channels into the lumen.[7-10] Aldosterone also increases the activity and recruitment of basolateral Na+/-K+- adenosine triphosphatase pumps in the principal cell. The resultant increase in Na+ reabsorption promotes K+ secretion via channels in the apical membrane. Aldosterone also stimulates H+ secretion via Na+ transport through its interaction with MRs in the intercalated cells of the kidney cortex.[11]

Of importance, cortisol has a high affinity for the MR. However, target tissues possess enzymes such as 11-β-hydroxysteroid dehydrogenase that converts cortisol to cortisone and other inactive metabolites and, as a result, only aldosterone can activate the MR under normal conditions.[12,13]

Primary Hyperaldosteronism

Primary hyperaldosteronism (PA) is the most common form of mineralocorticoid hypertension and remains a challenging diagnosis for most clinicians. The prevalence has varied from earlier estimates of 0.5% to 2.0% to rates of 10% of hypertensive patients with more widespread screening.[14,15] The prevalence varies by the patient population and the referral center. There are 2 main causes of PA. First, adrenal adenomas present in the adrenal cortex can present with autonomous secretion of aldosterone. The secretion can be in response to either angiotensin II or corticotrophin (ACTH). Bilateral adrenal hyperplasia is the second cause in which aldosterone secretion is exaggerated to the response of angiotensin II.

Screening

Screening is a challenging topic. It generally is advocated that patients with unexplained persistent hypokalemia or with diuretic-induced hypokalemia deserve investigation. An important point, however, is that not all patients with PA present with hypokalemia and some reports claim that only 30% of patients with PA present with hypokalemia.[15] Additional clues may prompt screening in these patients. For example, patients with difficult-to-control hypertension requiring 3 or more medications should be screened. Certainly, patients identified with an incidental adrenal mass should be evaluated. Mosso L, et al[16] advocated screening of all patients with stage 2 and 3 essential hypertension, arguing that the prevalence of PA increases with the severity of hypertension. The prevalence of PA in patients with stage 2 and 3 has been reported to be as high as 8% and 13%, respectively.[16] This screening strategy has been challenged secondary to the increased cost of testing and the increased possibility of false-positive results. This reality must be balanced, however, with identifying patients with a potentially curable form of hypertension or at least, in most patients, partial amelioration of hypertension.

Despite a number of different mechanisms of screening including salt suppression and fludrocortisone-suppression tests, these tests are technically difficult to execute in the outpatient setting. This difficulty often deters clinicians from embarking on a search for PA in patients with low to intermediate risk factors. As a result, the aldosterone renin ratio (ARR) has become the most widespread method of screening.

Japanese investigators first proposed the use of these measurements as a screening test for primary aldosteronism in 1981.[17] Subsequent to the initial report on the use of an ARR as a screening test for primary aldosteronism, other investigators have followed up with additional reports.[18-31] However, data on the sensitivity and specificity of the ARR as a screening test for primary aldosteronism have been complicated by disagreement between investigators on the conditions for screening, how to perform the test, which medications influence the results, and the definition of an ARR cut-off value.

A pooled analysis of available data is contained in the article by Montori and Young,[32] which showed the difficulty in assessing the use of ARR. These investigators conducted a systematic review of the literature (from 1966 to 2001) to establish useful test characteristics (sensitivity, specificity, and likelihood ratios at different cut-off values). Only prospective studies were included in the analysis and a total of 16 studies totaling 3,136 participants were evaluated. The investigators discovered that none of the studies evaluated both the ARR and a reference standard independently (ie, a blinded comparison). In addition, only 2 studies evaluated

patients who did not have a positive ratio, thus precluding an estimate of false negatives. They also reported that only 16.7% of the subjects had both a ratio and a confirmatory test performed. Applying the most rigorous of scientific standards, the investigators concluded that there are no published "valid estimates of the test characteristics of the ARR when used as a screening test for primary aldosteronism."[32]

In addition to the use of a ratio to screen for primary aldosteronism, several investigators have recommended the use of a ratio in combination with an absolute level of aldosterone as a screening test for primary hyperaldosteronism. Because the ratio is so dependent on the plasma renin activity level, it is important to view the ratio in light of the absolute PA level. Weinberger and Fineberg[33] studied 434 normotensive and 263 hypertensive subjects as well as 62 primary aldosterone patients (48 with known unilateral adrenal adenoma and 14 with known bilateral adrenal hyperplasia). They reported that the ARR provided complete separation between the patients with primary aldosteronism and the combined hypertensive and normotensive populations. In addition, they reported that the use of an ARR greater than 30 plus an absolute aldosterone level greater than 20 succeeded in differentiating the 2 subtypes with a sensitivity of 90%, a specificity of 91%, a positive predictive value of 69%, and a negative predictive value of 98%. Of note, all hypertensive subjects were withdrawn from antihypertensive therapy for at least 2 weeks before the study. Other investigators have recommended the use of an ARR $>$ 20 and an aldosterone level $>$ 15, but do not report on the sensitivities or specificities of these cut-off values.[34]

Testing Conditions

One of the major reasons believed to account for the wide variability of the cut-off values reported is the different conditions under which these tests were performed. Although most investigators recommend that simultaneous plasma renin and aldosterone levels be drawn at 8:00 AM, it is only recently that data were reported assessing the test performance under different conditions. In 2005, Tiu et al[35] conducted a retrospective review of 45 subjects with validated diagnoses of primary aldosteronism and 17 subjects with essential hypertension. A total of 62 subjects with 75 sets of plasma renin, aldosterone, and ARR values from a postural study, and 48 sets of values from a saline suppression test were analyzed. These investigators reported that ARR cut-off levels were significantly affected by the conditions of the test, and depending on when the levels were drawn, the optimal cut-off level varied from between 13.1 and 35.0 ng/dL per ng/mL. When an ARR cut-off level of 35 at 9 AM (recumbent) was compared with a cut-off value of 13.1 at 1 PM (ambulatory), they found a sensitivity of 95.5% and a specificity of 100% (9:00 AM), as compared with a sensitivity of 96.5% and a specificity of 94.1% (13:00 PM). Of note, they found both a sensitivity and a specificity of 100% using an ARR cut-off value of 18.5 performed postsaline infusion.

Although it generally is believed that the only 2 medications that will directly influence the ARR are spironolactone and eplerenone, the evidence documenting the concurrent use of other antihypertensive agents remains scant. In regards to angiotensin-converting enzyme inhibitors, it generally is believed that that these agents increase the plasma renin activity (PRA) and reduce the PA, therefore decreasing the ratio. A positive screen in this setting therefore is regarded as strong evidence of primary aldosteronism and some investigators recommend their use during the test.[36] Calcium channel blockers also have been documented to increase the PRA and decrease the PA, affecting the accuracy of the ARR.[37] The use of antisympathetic agents and β-blockers are believed to suppress renin and yield a falsely high ARR. Overall, most investigators recommend withholding antihypertensive therapy to the degree that it is possible for several weeks before the test. α-blockers impact the ratio minimally and are acceptable agents to use in the diagnostic period.

Although there are no good data defining the optimal conditions and cut-off values of the ARR as a screen for primary aldosteronism, it remains the first step in evaluating patients with hypertension and hypokalemia under the appropriate clinical circumstances. According to current data, the combination of an ARR of 30 or more and an absolute aldosterone level of 20 or greater drawn simultaneously at 8 AM in the setting of no antihypertensive medications and normokalemia in the appropriate patient constitute a positive screen for primary aldosteronism.

Confirmatory Tests

Once an abnormal ARR is seen then the more cumbersome confirmatory tests should be performed. This includes showing a lack of aldosterone suppression with either intravenous or oral saline loading. If aldosterone suppression to salt loading cannot be shown then a diagnosis of PA is highly likely. An alternative, more reliable test is the fludrocortisone-suppression test. With this test plasma aldosterone levels are measured in the upright position at 10 AM after 4 days of 0.1 mg every 6 hours of fludrocortisone acetate. A concomitant high-salt diet of 3 mmol/kg/d is required. The test is positive if aldosterone levels are higher than 5 ng/dL and PRA levels are less than 1.0 ng/mL/h.[15] Serum potassium levels also must be replete for these confirmatory tests to be accurate.

If biochemical confirmation is documented, high-resolution adrenal computed tomography and/or magnetic resonance imaging should be performed. Adrenal computed tomography may be more sensitive in detecting smaller adenomas than magnetic resonance imaging.[38-40] Overall, the sensitivity of adrenal imaging is imperfect. Some investigators recommend proceeding to selective adrenal venous sampling in patients with a high index of suspicion. Adrenal venous sampling is the gold standard for diagnosis but is both technically challenging and operator dependent. This test is also wrought with difficulties. There are no standardized cut-off values that determine the success of identifying lateralization of aldosterone production. Also, testing requires catheterization of the very small adrenal veins without inadvertent dilution of the adrenal hormone levels at the level of the aorta. Often patients may require multiple attempts to secure

Table 2 Diagnostic Testing for Primary Hyperaldosteronism

Test	Strategy	Result Consistent With PA
Screening		
Plasma renin activity (ng/mL/h)	Optimal testing when off antihypertensive medications interfering with renin- angiotensin axis and normokalemic	<1.0
Plasma aldosterone (ng/dL)		<20
ARR		>30
Confirmatory		
Intravenous salt loading	Administration of 2 L of isotonic saline over 4 hours	Plasma aldosterone >10 ng/dL
Oral salt loading	1 g sodium chloride tablets taken 3 times daily and potassium supplementation for 3 days	24-hour urine aldosterone excretion >14 g/24 h
Fludrocortisone-suppression test	Fludrocortisone acetate (0.1 mg every 6 hours) with high-salt diet and potassium supplementation	Plasma aldosterone <5 ng/dL and plasma renin <1.0 ng/mL/h

accurate samples. Potentially, ACTH infusion may increase the accuracy of the test.[41] Unilateral disease has been found to be associated with a marked (usually >4-fold) increase in plasma aldosterone on the side of the tumor, whereas there is little difference between the 2 sides in patients with bilateral hyperplasia. The simultaneous measurement of cortisol concentrations aid in confirming the adrenal vein has been cannulated adequately. The cortisol level in the adrenals should be 2 times or more than that of the peripheral values.[36] Table 2 summarizes biochemical screening and confirmatory strategies for patients with suspected PA.

Ideally, the primary goal of identifying PA caused from an adenoma is to surgically excise an aldosterone-producing adenoma and effectively cure a patient of hypertension. Unfortunately, this is not always the case because hypertension often persists, although at improved levels, after adrenalectomy. The long-term surgical cure rate of patients with primary aldosteronism varies widely, and causes of persistent hypertension are not completely established. Rates of surgical cure vary from as low as 33% to as high as 73%. Several reports have indicated that cure is more likely to be achieved in younger patients with a shorter duration of hypertension, with a family history of hypertension in no more than 1 first-degree relative, and preoperative use of 2 or fewer antihypertensive agents.[42,43] The current optimal surgical approach is laparoscopic adrenalectomy. Although published data are limited, some centers have advocated percutaneous ablative therapy, including percutaneous acetic acid injection and radiofrequency ablation for unilateral adrenal adenomas.[44] Subtotal adrenalectomy generally has been disappointing in bilateral adrenal hyperplasia because only a minority of patients have a clinically significant hypotensive response.[45]

Medical Management

Medical treatment of PA includes the blockade of aldosterone at the MR via spirinolactone or eplerenone. It is the preferred approach for the treatment of PA from bilateral adrenal hyperplasia. Spirinolactone is more cost effective but has many unwanted antiandrogen and progesterone side effects. There are little data on the more selective MR antagonist, eplerenone, in the treatment of PA, and its use in PA has been extrapolated from experience with spirinolactone and its use in the treatment of essential hypertension. Hyperkalemia is an adverse event that must be monitored in patients on these agents, especially if patients are on other hyperkalemia-inducing medications and have chronic kidney disease.

There are a paucity of prospective studies comparing surgical versus medical treatment of adrenal adenomas. Some studies have failed to show an adverse cardiovascular event associated with MR antagonism instead of the surgical approach.[46] Others studies have shown a lack of improvement in left ventricular hypertrophy.[47] These latter data are consistent with recent literature that aldosterone excess is associated with vascular disease and inflammation as well as cardiac fibrosis.[14] Clinicians should proceed with surgical excision of functioning adenomas if medically feasible and medically treat patients with high surgical risk or bilateral adrenal hyperplasia.

GRA

GRA was first described in 1966 and is an autosomal-dominant form of low renin hypertension in which aldosterone excess is present under the influence of ACTH rather than angiotensin II.[48] The molecular basis for this disorder was described by Lifton et al[49] after their cloning of 11-β hydroxylase, which catalyzes the last step of cortisol synthesis and aldosterone synthase needed for the final step of aldosterone synthesis. Two genes that reside in tandem on chromosome 8, CYP11B1 and CYP11B2, encode these enzymes. The 2 genes are 95% homologous but differ in 5 prime sequences, allowing for the functional zonation seen in the adrenal cortex. Specifically, cortisol secretion is regulated by ACTH and aldosterone secretion is mediated primarily by angiotensin II and hyperkalemia. GRA results from a chimeric gene that is formed from an unequal crossover of sequences at meiosis.[49,50] This hybrid possesses both the promoter gene of the 11-β hydroxylase enzyme and the

coding region of the aldosterone synthase gene. The result is that the aldosterone synthase gene and in turn aldosterone secretion is under the control of ACTH.

This disorder presents with early onset hypertension that can be moderate to severe at presentation. The genotype and phenotype, however, can vary between and within families. Kindreds have been described with normotension. Explanations of the variation in blood pressure include self-selected dietary salt restriction, concomitant inheritance of blood pressure–lowering genes, and decreased penetrance of the gene.[51] Dluhy et al[52] reported kindreds who had normal blood pressure and increased urinary levels of the vasodilator kalekrein, which serves to protect against hypertension.[52] To date, a perfect unchallenged mechanism to explain phenotypic variations in blood pressure does not exist.

Another expected presentation in patients with GRA is hypokalemia, although normokalemia seems to be the typical presentation unless patients are placed on potassium-sparing diuretics. The reason is unclear but may be related to the influence of aldosterone on the circadian rhythms of ACTH release. A blunted aldosterone response to dietary potassium in GRA subjects also may explain the minimized potassium losses.[52]

An important clinical feature associated with GRA is early onset hemorrhagic stroke and ruptured aneurysms, with an associated high mortality rate of 60%. As a result, screening has been recommended every 5 years after puberty with a magnetic resonance imaging angiography.[53]

Diagnosis requires a high index of suspicion because the presence of normal blood pressure and potassium can be deceptive. Early onset of disease, a family history of early onset hypertension and cerebral hemorrhage, refractory hypertension, and hypokalemia with potassium-wasting diuretics may prompt investigation. Plasma renin levels are usually less than 0.278 ng/L/s. Aldosterone and ARRs also will be high, but are not specific. A confirmatory diagnosis can be made with either a dexamethasone-suppression test, measurement of urinary 18/hydroxy/oxy steroids, or direct genetic testing.[14,52] The suppression test is useful in showing the dependence of aldosterone on ACTH and requires 0.5 mg of dexamethasone every 6 hours for 2 days to suppress ACTH. Serum aldosterone levels should be suppressed to undetectable levels (<4 ng/dL). Increased urinary levels of 18/hydroxy/oxy steroids (2 times the upper limit of normal) reflect the increased activity of aldosterone synthase in the zona fasciculata. These tests, although highly suggestive, need confirmation with genetic testing by Southern blot. This test is available through the International Registry of GRA at www.brighamandwomens.org/gra.

Treatment of this disorder manipulates the dependence of aldosterone secretion on ACTH. Low doses of glucocorticoids effectively suppress ACTH release via feedback suppression. The typical dose for adults ranges from 0.125 to 0.25 mg dexamethasone or 2.5 mg to 5 mg of prednisone. Careful monitoring for signs and symptoms of oversuppression must be monitored. Normotension is the primary goal of treatment rather than normalization of biochemical parameters because this may induce unwanted cushingoid features. Mineralocorticoid receptor antagonists such as spironolactone and eplerenone have been used successfully, as have sodium epithelial channel antagonists, such as amiloride.

AME

AME is an autosomal-recessive disorder that is marked by juvenile hypertension, hypokalemic alkalosis, hyporeninemia, and hypoaldosteronism. The pathophysiology is caused by lack of activity in the 11-β hydroxysteroid dehydrogenase type 2 enzyme (11βHSD2). This enzyme catalyzes the conversion of cortisol to cortisone, rendering it unavailable to the MR.[54] The ensuing inappropriate binding of cortisol to the MR results in sodium retention and volume expansion with subsequent suppression of aldosterone and renin. The hallmark of AME is an apparent high mineralocorticoid state secondary to cortisol binding to the MR in the absence of aldosterone.[55] Worldwide, fewer than 100 cases have been identified and it is most common in consanguineous families. The affected gene is located on chromosome 16q22 and more than 33 different mutations have been defined. Presentation of AME includes childhood low birth weight, short stature, hypokalemia, and hypertension. Some patients suffer from complications related to hypokalemia including rhabdomyolysis and nephrogenic diabetes insipidus. Renal cysts, hypercalciuria, nephrocalcinosis, and renal insufficiency also have been reported. End-organ damage related to hypertension is invariably seen in patients with AME, including hypertensive retinopathy and left ventricular hypertrophy.[54-57] Diagnosis is made in several ways. The plasma renin and aldosterone levels must be low and exclusion of 11-β hydroxylase and 17-α hydroxylase deficiencies and a deoxycorticosterone-producing tumor must be performed. Urinary studies can be performed and these may reflect high levels of cortisol metabolites, 5 β-tetrahydrocortisol (THF) and 5 α-THF, although tetrahydrocortisone (THE) levels may be low. The THF + 5 α THF/THE ratio in AME range from 6 to greater than 70, as compared with a ratio of 1 in normal persons. A high urinary free cortisol to urinary free cortisone ratio will be diagnostic. DNA analysis is required to confirm the diagnosis.[54-57]

Treatment involves blockade of the MR with high doses of spirinolactone or eperlenone and potassium repletion. Suppression of cortisol with dexamethasone (which has little affinity for the MR) has had variable success. Thiazide diuretics can be used to treat hypercalcuria and in some cases can reverse nephrocalcinosis. Removal of the adrenal glands has restored blood pressure in only 60% of affected patients.[55] One case report documented cure of AME with kidney transplantation, which restores 11-βHSD2 activity.[59]

An acquired form of AME can be seen with licorice ingestion. Licorice is present as a sweetener in chewing gum and tobacco. It is also a confectionary sweet in Europe and is present in some herbal teas. A mild form of AME is induced by licorice because glycyrrhizic acid and its hydrolytic product, glycyrrhetinic acid, are potent competitive inhibitors of 11-β hydroxysteroid dehydrogenase. Licorice given to normal volunteers results in an increase in the THF + 5 α THF/

THE ratio, an increase in plasma cortisol half-life, and a decrease in cortisone values. Such changes also were documented in patients who ingested licorice and presented with a mineralocorticoid excessδlike state. Patients can present with hypertension and hypokalemic myopathy and cardiac arrhythmias after licorice ingestion.[55,60,61]

Cushing's syndrome also can present with signs and symptoms of mineralocorticoid excess, particularly in the subgroup caused by ectopic ACTH production. Ectopic ACTH syndrome is associated with marked hypersecretion of cortisol and incomplete metabolism of cortisol as a result of an overload in the metabolizing enzyme.[62]

AME is a rare disorder that many clinicians likely will not encounter. However, mild impairments in 11-βHSD2 activity have been identified in some patients with essential hypertension.[58] The exact mechanism and role of this impairment is unclear and data have been varied. Heterozygote mutations of the gene have been described in hypertensive patients who did not display classic features of AME and similar mutations also have been seen in patients with low renin hypertension. Decreased activity of the enzyme, as shown by high urinary cortisol to urinary cortisone ratios, has been seen in patients with essential hypertension without evidence of gene mutations. Recent studies also have shown gene polymorphisms of the enzyme affecting sodium handling, salt sensitivity, and responsiveness to diuretics in patients with essential hypertension. The precise role of this gene in essential hypertension remains to be explored.[63,64]

Conclusions

A potentially treatable cause of secondary hypertension is mineralocorticoid hypertension. Often these forms of hypertension are clinically apparent by the presence of hypokalemia and metabolic alkalosis. However, in many cases low potassium may not be present. Other clues to a mineralocorticoid hypertension must be identified. These include difficult-to-control hypertension, an incidental adrenal adenoma, and in monogenic forms a strong family history of early onset hypertension. Treatment is directed toward decreasing the level of the responsible mineralocorticoid or blockade of the MR.

References

1. Hall JE, Granger JP, Smith MJ Jr, et al: Role of renal hemodynamics and arterial pressure in aldosterone "escape". Hypertension 6:I183-1192, 1984
2. White PC, New MI, Dupont B: Congenital adrenal hyperplasia. N Engl J Med 316:1519-1522, 1987
3. White PC: Disorders of aldosterone biosynthesis and action. N Engl J Med 331:250, 1994
4. Mitra A, Batlle D: Aldosterone deficiency and resistance. acid-base and electrolyte disorders, in Du Bose, Hamm (eds): A Companion to Brenner and Rector's the Kidney. Philadelphia, Saunders, 2002, pp 413-433.
5. Batlle D, Kurtzman N: Clinical disorders of aldosterone metabolism. Dis Mon 30:(8):1-55, 1984
6. Taymans SE, Pack S, Pak E, et al: Human CYP11B2 (aldosterone synthase) maps to chromosome 8q24.3. J Clin Endocrinol Metab 83:1033, 1998
7. Minuth WW, Gilbert P, Gross P: Appearance of specific proteins in the apical plasma membrane of cultured renal collecting duct principal cell epithelium after chronic administration of aldosterone and arginine vasopressin. Differentiation 38:194, 1988
8. Verrey F: Early aldosterone action: Toward filling the gap between transcription and transport. Am J Physiol 277:F319, 1999
9. Masilamani S, Kim GH, Mitchell C, et al: Aldosterone-mediated regulation of ENaC alpha, beta, and gamma subunit proteins in rat kidney. J Clin Invest 104:R19, 1999
10. Shimkets RA, Lifton R, Canessa CM: In vivo phosphorylation of the epithelial sodium channel. Proc Natl Acad Sci U S A 95:3301, 1998
11. Hays SR: Mineralocorticoid modulation of apical and basolateral membrane H+/OH−/HCO3− transport processes in rabbit inner stripe of outer medullary collecting duct. J Clin Invest 90:180, 1992
12. Funder JW: Mineralocorticoids, glucocorticoids, receptors and response elements. Science 259:1132, 1993
13. Kenouch S, Coutry N, Farman N, et al: Multiple patterns of 11β-hydroxysteroid dehydrogenase catalytic activity along the mammalian nephron. Kidney Int 42:56, 1992
14. Stewart P: Mineralocorticoid hypertension. Lancet 353:1341-1347, 1999
15. Mulatero P, Dluhy RG, Giacchetti G, et al: Diagnosis of primary aldosteronism: From screening to subtype differentiation. Trends Endocrinol Metab 16:114-119, 2005
16. Mosso L, Carvajal C, Gonzalez A, et al: Primary hyperaldosteronism and hypertensive disease. Hypertension 42:161-165, 2003
17. Hiramatsu K, Yamada T, Yukimura Y, et al: A screening test to identify aldosterone producing adenoma by measuring plasma renin activity: Results in hypertensive patients. Arch Intern Med 141:1589-1593, 1981
18. Brown M, Cramp H, Zammit V, et al: Primary hyperaldosteronism: A missed diagnosis in essential hypertensives? Aust N Z J Med 26:533-538, 1996
19. Fardella C, Mosso L, Gomez-Sanchez C, et al: Primary hyperaldosteronism in essential hypertensives: Prevalence, biochemical profile, and molecular biology. J Clin Endocrinol Metab 85:1863-1867, 2000
20. Gallay B, Ahmad S, Xu L, et al: Screening for primary hyperaldosteronism without discontinuing hypertensive medications: Plasma aldosterone-renin ratio. Am J Kidney Dis 37:699-705, 2001
21. Gordon R, Ziesak M, Tunny T, et al: Evidence that primary aldosteronism may not be uncommon: 12% incidence among antihypertensive drug trial volunteers. Clin Exp Pharmacol Physiol 20:296-298, 1993
22. Hamlet S, Tunny T, Woodland E, et al: Is aldosterone/renin ratio useful to screen a hypertensive population? Clin Exp Pharmacol Physiol 12: 249-252, 1985
23. Kreze A, Okalova D, Vanuga P, et al: Occurrence of primary aldosteronism in a group of ambulatory hypertensive patients. Vnitr Lek 45: 17-21, 1999
24. Kumar A, Lall S, Ammini A, et al: Screening of a population of young hypertensives for primary hyperaldosteronism. J Hum Hypertens 8:731-732, 1994
25. Lazurova I, Schwartz P, Trejbal D, et al: Incidence of primary aldosteronism in hospitalized hypertensive patients. Bratisl Lek Listy 100:200-203, 1999
26. Lim P, Dow E, Jung R, et al: Prevalence of primary aldosteronism in the tayside hypertension clinic population. J Hum Hypertens 14:311-315, 2000
27. Loh K, Koay E, Khaw M, et al: Prevalence study on primary aldosteronism among Asian hypertensive patients in Singapore. J Clin Endocrinol Metab 85:2854-2859, 2000
28. Mosso L, Fardella C, Montero J, et al: High prevalence of undiagnosed primary aldosteronism among patients with essential hypertension. Rev Med Chil 127:800-806, 1999
29. Rossi G, Rossi E, Pavan E, et al: Screening for primary aldosteronism with a logistic multivariate discriminate analysis. Clin Endocrinol 49: 713-723, 1998
30. Gordon R, Stowasser M, Tunny T, et al. High incidence of primary aldosteronism in 199 patients referred with hypertension. Clin Exp Pharmacol Physiol 21:315-318, 1994

31. Lim P, Rodgers P, Cardale K, et al: Potentially high prevalence of primary aldosteronism in a primary-care population. Lancet 353:40, 1999
32. Montori V, Young W: 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 31:619-632, 2002
33. Weinberger M, Fineberg N: The diagnosis of primary aldosteronism and separation of two major subtypes. Arch Intern Med 153:2125-2129, 1993
34. Young W: Primary aldosteronism. A common and curable form of hypertension. Cardiol Rev 7:207-214, 1999
35. Tiu T, Choi C, Shek C, et al: The use of aldosterone-renin ratio as a diagnostic test for primary hyperaldosteronism and its test characteristics under different conditions of blood sampling. J Clin Endocrinol Metab 90:72-78, 2005
36. Lyons D, Kem D, Brown R, et al: Single dose captopril as a diagnostic test for primary aldosteronism. J Clin Endocrinol Metab 57:892-896, 1983
37. Nadler J, Hsueh W, Horton R: Therapeutic effect of calcium channel blockade in primary aldosteronism. J Clin Endocrinol Metab 60:896-899, 1985
38. Gleason PE, Weinberger MH, Pratt JH, et al: Evaluation of diagnostic tests in the differential diagnosis of primary aldosteronism: Unilateral adenoma versus bilateral micronodular hyperplasia. J Urol 150:1365, 1993
39. Radin DR, Manoogian C, Nadler JL: Diagnosis of primary hyperaldosteronism: Importance of correlating CT findings with endocrinologic studies. AJR Am J Roentgenol 158:553, 1992
40. Doppman JL, McGill JR, Miller DL, et al: Distinction between hyperaldosteronism due to bilateral hyperplasia and unilateral aldosteronoma: Reliability of CT. Radiology 184:677, 1992
41. Young WF, Stanson AW, Thompson GB, et al: Role for adrenal venous sampling in primary aldosteronism. Surgery 136:1227, 2004
42. Lumachi F, Ermani M, Basso SM, et al: Long-term results of adrenalectomy in patients with aldosterone-producing adenomas: Multivariate analysis of factors affecting unresolved hypertension and review of the literature. Am Surg 71:864-869, 2005
43. Sawka AM, Young WF, Thompson GB, et al: Primary aldosteronism: Factors associated with normalization of blood pressure after surgery. Ann Intern Med 135:258-261, 2001
44. Minowada S, Fujimura T, Takahashi N, et al: Computed tomography-guided percutaneous acetic acid injection therapy for functioning adrenocortical adenoma. J Clin Endocrinol Metab 88:5814, 2003
45. Kawasaki T, Omae T, Tanaka K, et al: Remission or recurrent hyperaldosteronism resulting from subtotal adrenalectomy of adenomatous hyperplastic adrenal glands. J Clin Endocrinol Metab 33:474-480, 1971
46. Ghose RP, Hall PM, Bravo EL: Medical management of aldosterone-producing adenomas. Ann Intern Med 131:105-108, 1999
47. Rossi GP, Sacchetto A, Pavan E, et al: Remodeling of the left ventricle in primary aldosteronism due to Conn's adenoma. Circulation 95:1471-1478, 1997
48. Rich GM, Ulick S, Cook S, et al: Glucocorticoid-remediable aldosteronism in a large kindred: Clinical spectrum and diagnosis using a characteristic biochemical phenotype. Ann Intern Med 116:813, 1992
49. Lifton RP, Dluhy RG, Powers M, et al: A chimeric 11β-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. Nature 355:262, 1992
50. Pascoe L, Curnow KM, Slutsker L, et al: Glucocorticoid-suppressible hyperaldosteronism results from hybrid genes created by unequal crossovers between CYP11B1 and CYP11B2. Proc Natl Acad Sci U S A 89:8327-8331, 1992
51. McMahon GT, Dluhy RG: Glucocorticoid-remediable aldosteronism. Cardiol Rev 12:44-48, 2004
52. Dluhy RG, Lifton RP: Glucocorticoid-remediable aldosteronism (GRA): Diagnosis, variability of phenotype and regulation of potassium homeostasis. Steroids 60:48-51, 1995
53. Litchfield WR, Anderson BF, Weiss RJ, et al: Intracranial aneurysm and hemorrhagic stroke in glucocorticoid-remediable aldosteronism. Hypertension 31:445-450, 1998
54. Stewart PM, Corrie JE, Shackleton CH, et al: Syndrome of apparent mineralocorticoid excess. A defect in the cortisol-cortisone shuttle. J Clin Invest 82:340-349, 1988
55. Quinkler M, Stewart PM: Hypertension and the cortisol-cortisone shuttle. J Clin Endocrinol Metab 88:2384-2392, 2003
56. Dave-Sharma S, Wilson RC, Harbison MD, et al: Examination of genotype and phenotype relationships in 14 patients with apparent mineralocorticoid excess. J Clin Endocrinol Metab 83:2244-2254, 1998
57. Wilson RC, Krozowski ZS, Li K, et al: A mutation in the HSD11B2 gene in a family with apparent mineralocorticoid excess. J Clin Endocrinol Metab 80:2263-2266, 1995
58. Mariniello B, Ronconi V, Sardu C, et al: Analysis of the 11beta-hydroxysteroid dehydrogenase type 2 gene (HSD11B2) in human essential hypertension. Am J Hypertens 18:1091-1098, 2005
59. Palermo M, Cossu M, Shackelton CHL: Cure for apparent mineralocorticoid excess by kidney transplantation. N Engl J Med 329:1787-1788, 1998
60. Farese RV Jr, Biglieri EG, Gomez FR, et al: Licorice- induced hypermineralocorticoidism. N Engl J Med 325:1223-1227, 1991.
61. Whorwood CB, Sheppard MC, Stewart P: Licorice inhibits 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid levels and potentiates glucocorticoid hormone action. Endocrinology. 132:2287–2292, 1993
62. 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 74:963-967, 1992
63. Williams TA, Mulatero P, Filigheddu F, et al: Role of HSD11B2 polymorphisms in essential hypertension and the diuretic response to thiazides. Kidney Int 67:63-67, 2005
64. Mariniello B, Ronconi V, Sardu C, et al: Analysis of the 11beta-hydroxysteroid dehydrogenase type 2 gene (HSD11B2) in human essential hypertension. Am J Hypertens 18:1091-1098, 2005