Review Article

Low renin hypertension

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ABSTRACT

Low renin hypertension is an important and often underdiagnosed cause of hypertension. It may be associated with high aldosterone levels as in Conn's syndrome or low aldosterone levels as in Liddle syndrome, and syndrome of apparent mineralocorticoid excess, glucocorticoid remediable hypertension etc. Some forms of essential hypertension are also associated with low renin levels. Hypokalemia may be an important finding in low renin hypertension. The aldosterone to renin ratio helps in correct diagnosis. The treatment varies with etiology hence an accurate diagnosis is essential. Aldosterone antagonists play an important role in medical management of some varieties of low renin hypertension.

Key words: Aldosterone antagonists, hypertension, hypokalemia, low renin hypertension, monogenic hypertension, renin aldosterone ration

Introduction

Renin is produced from the juxta glomerular cells in the kidney. It acts on the angiotensinogen produced in the liver and converts it to angiotensin I. The latter is converted to Angiotensin II by the Angiotensin converting enzyme in the lung. Angiotensin II is a potent vasoconstrictor and acts on the angiotensin receptors. Both high as well as low levels of renin may be associated with hypertension. This article deals with hypertensive disorders associated with low renin levels.

Causes of Low Renin Hypertension

The causes of low renin hypertension are as follows:

- Low renin essential hypertension (LREH)
- Primary aldosteronism
  - Conn's syndrome
  - Glucocorticoid-remediable (GRH)/Familial hyperaldosteronism Type I
  - Familial Type II
- Liddle syndrome
- Mineralocorticoid receptor mutation
- Apparent mineralocorticoid excess (AME)
- Glucocorticoid resistance
- Gordon syndrome
- Congenital adrenal hyperplasia (CAH)

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Low-Renin Essential (Primary) Hypertension

Introduction

Renin measurement in patients with essential (primary) hypertension shows that the plasma renin activity (PRA) is increased in 15 percent patients, normal in 60 percent patients, and reduced in approximately 25 percent patients.[1] Thus, the majority of patients with primary hypertension do not have low renin levels. Low renin levels are seen especially in blacks and in the elderly. Patients with low-renin essential hypertension (LREH) have some unique features.[2] Hypertension is salt-sensitive. The response to life style modification, especially weight reduction, is less compared to response to a diuretic or calcium channel blocker. Patients with LREH may have a lower risk of cardiovascular disease than hypertensive patients with normal or high renin levels. Low renin levels are seen in essential hypertension as there is a higher perfusion pressure at the juxta glomerular cells which suppresses renin release.

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Though the plasma renin activity in LREH is reduced there is increased local angiotensin II activity in the tissues (such as vascular endothelium, kidneys, brain, and adrenal glands). This activation of the renin-angiotensin system within the kidney is not detectable from measurement of the plasma renin activity. This accounts for the fact that angiotensin converting enzyme (ACE) inhibitors are effective in patients even with low plasma renin levels. The plasma angiotensin II level are normal, while adrenal renin content, vascular angiotensin II formation, and the plasma level of prorenin are elevated. Some patients of LREH have mineralocorticoid excess without hypokalemia. In addition, defects in cortisol physiology are seen in LREH, including increased levels of 18-hydroxylated steroids, and activation of the mineralocorticoid receptor by cortisol.

Treatment

Many antihypertensive drugs are effective in LREH.[3] The blood pressure in LREH is salt- and volume sensitive; hence, diuretics are the drugs of choice. However, this has not been found in all studies. Since mineralocorticoid excess plays a role in LREH, mineralocorticoid receptors antagonists such as spironolactone and eplerenone are often effective. Angiotensin converting enzyme inhibitors (ACEI) are effective as the tissue renin is high. However patients with LREH do not respond better to particular antihypertensive agents. Hence measurement of Plasma Renin Activity (PRA) is not part of standard management of patients with essential hypertension. Thus, the treatment of these patients is similar to other patients with essential hypertension.

Primary Hyperaldosteronism

Introduction

Primary hyper secretion of aldosterone is an important under diagnosed cause of hypertension. The classic presenting signs of primary aldosteronism are hypertension and hypokalemia. The most common types are: (1) Aldosterone-producing adenoma, and (2) Bilateral idiopathic hyperplasia. Less common forms include: (1) Unilateral hyperplasia or primary adrenal hyperplasia (caused by micro nodular or macro nodular hyperplasia of the zona glomerulosa, (2) Bilateral macro nodular or micro nodular adrenal hyperplasia with primary aldosteronism (3). Genetic forms include Familial type I (glucocorticoid-remediable aldosteronism [GRA] and Familial hyperaldosteronismType II. Pure aldosterone-producing adrenocortical carcinomas and ectopic aldosterone-secreting tumors (e.g., neoplasms in the ovary or kidney) are some of the other causes. Increasing use of Plasma aldosterone/Plasma renin activity ratio or PAC/PRA ratio as a screening test in hypertensive patients has resulted in increase in the detection of primary aldosteronism (1 to 2 percent before screening to 5 to 10 percent after screening).[4]

Clinical features

The clinical features of primary aldosteronism are determined by the aldosterone.

Absence of edema

Although there is initially sodium and water retention, this is followed within a few days by a spontaneous diuresis (called aldosterone escape) which lowers the extracellular fluid volume almost toward normal. This occurs due to volume expansion once weight gain exceeds 3 kg. The mechanisms responsible for the escape are: increased secretion of atrial natriuretic peptide (ANP); decreased thiazide-sensitive sodium chloride (Na-Cl) co transporter in the distal tubule and pressure natriuresis. In the steady state, both urinary Na and potassium (K) excretion are roughly equal to dietary intake, similar to that in normal subjects.

Hypertension

Hypertension is due to the mild volume expansion which also leads to an increase in systemic vascular resistance that helps to perpetuate the hypertension due to increased endogenous ouabain-like compound. Hypervolemia leads to low plasma renin. Low renin measurements differentiate primary from secondary, hyperreninemic forms of hyperaldosteronism seen in renovascular hypertension, coarctation of the aorta, renin-secreting neoplasms, or diuretic therapy. Blood pressure in primary aldosteronism is significantly elevated, yet malignant hypertension is rare. Primary aldosteronism may be associated with resistant hypertension. Rarely, hypertension is absent in patients with primary aldosteronism.

Muscle weakness

Muscle weakness can occur in patients with primary aldosteronism esp. if the plasma potassium concentration is less than 2.5 meq/L.

Cardiovascular risks

As compared to patients with other types of hypertension, patients with primary aldosteronism have greater left ventricular mass, increased risk of cardiovascular disease, higher rates of stroke, nonfatal myocardial infarction and atrial fibrillation. There is increased prevalence of microalbuminuria, endothelial dysfunction and less NO mediated dilatation. Metabolic syndrome is found to be more common. Aldosterone-induces inflammation, fibrosis and necrosis in various target organs. These effects of may be mediated by mineralocorticoid receptors in the heart and blood vessels.[5]

Lab evaluation

Albuminuria is common. Hypokalemia is present in many patients with primary aldosteronism who are on an adequate Na intake. Hypokalemia occurs due to the hyper secretion of aldosterone, which increases potassium secretion in the cortical collecting tubule in presence of adequate delivery of sodium and water to the distal tubule. If the distal flow is reduced because of effective circulating volume depletion, then normal potassium balance may be maintained despite the excess mineralocorticoid. The plasma potassium is stable as the potassium-wasting effect of excess aldosterone is counterbalanced by the potassium-retaining effect of hypokalemia (steady state). Progressive hypokalemia does not occur unless some other factor is added i.e. diuretic therapy or further increase in aldosterone secretion. There is metabolic alkalosis due to increased urinary hydrogen excretion mediated by hypokalemia and by the direct stimulatory effect of aldosterone on distal acidification. The persistent mild volume expansion resets the osmostat regulating antidiuretic hormone release upwards with serum sodium concentration between 143 and 148 meq/L. Inhibition of sodium transport in the ascending limb of the loop of Henle during aldosterone escape is associated with a decline in magnesium reabsorption and hypomagnesemia. Aldosterone may raise the glomerular filtration rate (GFR) and renal perfusion pressure independent of systemic hypertension.[6]

Plasma aldosterone/Plasma renin activity Screening

In 2008, the Endocrine Society published evidence-based guidelines for the diagnosis and treatment of primary aldosteronism.[7] Screening is recommended in -

- Hypertension and spontaneous or low dose diuretic-induced hypokalemia
- Severe hypertension (>160 mmHg systolic or >100 mmHg diastolic) or drug-resistant hypertension (defined as sub optimally controlled hypertension on a three drug regime that includes an adrenergic inhibitor, vasodilator, and diuretic)
- Hypertension with adrenal incidentaloma
- Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)
- All hypertensive first-degree relatives of patients with primary aldosteronism

PAC/PRA screening is not recommended in elderly normokalemic patients with mild hypertension or if diagnosis would not change management (e.g., the blood pressure is easily controlled with antihypertensives). The test is performed by measuring a morning (preferably 8 AM), ambulatory, paired, random plasma aldosterone concentration (PAC) and plasma renin activity (PRA) or plasma renin concentration (PRC). Most antihypertensive medications can be continued and posture stimulation is not required. However, mineralocorticoid receptor antagonist (spironolactone and eplerenone) should not be initiated until the evaluation is completed. In patients already receiving spironolactone, therapy should be discontinued for at least six weeks. Other potassium-sparing diuretics, such as amiloride and triamterene, usually do not interfere with testing. Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and direct renin inhibitors could elevate PRC. Thus, in a patient treated with one of these drugs, a detectable PRA level does not exclude the diagnosis of PA. However if PRA or PRC even on one of these drugs is low or undetectable it is suggestive of PA.

The plasma renin activity (PRA) and plasma renin concentration (PRC) are very low in patients with primary mineralocorticoid excess, usually less than 1 ng/mL per hour for PRA and usually undetectable for PRC. Plasma aldosterone (PAC) is increased. (>15 ng/dl) with PAC/PRA ratio >20 in Primary aldosteronism. PAC/PRA ratio is <10 in normal subjects and patients with essential hypertension. Both PRA (or PRC) and PAC are increased and the PAC/PRA ratio is <10 in Secondary hyperaldosteronism (e.g., renovascular disease, renin producing tumors, coarctation of aorta). Both the PRA (or PRC) and PAC are suppressed in cases with an alternate source of mineralocorticoid receptor stimulation (e.g., hypercortisolism, licorice root ingestion). The PAC/PRA ratio is denominator-dependent. (PRA varies from 0.1-0.6 ng/mL per hour hence the PAC/PRA ratio may vary between 27-160). Thus, the cutoff for a "high" PAC/PRA ratio is assay-dependent. Thus an increased PAC is essential for diagnosis. The combination of a PAC above 20 ng/dL and a PAC/PRA ratio above 30 had a sensitivity and specificity of 90 percent for the diagnosis of aldosterone-producing adenoma. Other studies have suggested that a ratio 50 or higher rather than 30, or measurement of the ratio 60 to 90 minutes after a single dose of 25 to 50 mg of captopril or 50 mg of losartan may increase sensitivity.

An elevated PAC/PRA ratio with high PAC does not establish the diagnosis of primary aldosteronism, which must be confirmed by demonstrating non suppressible aldosterone secretion with saline loading. However, confirmatory test is not needed in patients with spontaneous hypokalemia, undetectable PRA or PRC, and a PAC >30 ng/dL; in this setting, the only possibility is primary aldosteronism. In all other situations aldosterone suppression testing is performed. The 2008 Endocrine Society Guidelines suggest fludrocortisone suppression or captopril challenge

tests as two additional alternative confirmatory tests in addition to saline loading.

Oral sodium loading is done after hypertension and hypokalemia are controlled (hypokalemia suppresses aldosterone secretion), and stopping spironolactone and eplerenone for 6 weeks. Patients can be given oral sodium chloride tablets (e.g., two 1 g sodium chloride tablets taken three times daily with food which provide 90 meq of sodium) for three days or patients can consume a 5000 mg per day sodium diet. On the third day of the high sodium diet, serum electrolytes are measured and a 24-hour urine specimen is collected for measurement of aldosterone, sodium and creatinine. The 24-hour urine sodium excretion should exceed 200 meq to document adequate sodium loading. Urine aldosterone excretion >12 mcg/24 hours is consistent with hyperaldosteronism. Sodium loading increases kaliuresis and hypokalemia hence serum potassium should be measured daily and replacement with potassium chloride should be prescribed.

Saline infusion test can be performed instead of oral test by the intravenous administration of two liters of isotonic saline over four hours (from 8 AM to noon) while the patient is recumbent. The PAC will fall below 5 ng/dL in normal subjects, whereas values above 10 ng/dL suggest primary aldosteronism. A 24-hour urine collection for potassium is required in those cases of hypertension and hypokalemia where PRA is not suppressed, PAC is not elevated, or there is a suspicion of vomiting or laxative abuse. Inappropriate potassium wasting is defined as more than 30 meq/day in a patient with hypokalemia and is a feature of PA. A low rate of potassium excretion suggests either extra renal losses (vomiting, diarrhea) or diuretic treatment with the urine being collected after the diuretic effect has worn off. Aldosterone excretion can also be measured, with high values (>12 mcg/day) on a high sodium diet (urine sodium excretion >200 meq/day) being consistent with primary aldosteronism if the PRA is low. A high-sodium diet can also be given as a provocative test in patients with an initial serum potassium concentration in the normal or low-normal range. Sodium-induced hypokalemia is strongly suggestive of no suppressible hyperaldosteronism.

Classification

Once the diagnosis of primary aldosteronism has been established, a unilateral aldosterone-producing adenoma (APA) must be distinguished from bilateral hyperplasia (idiopathic hyperaldosteronism, IHA). Adenomas account for approximately 35 percent of cases and should be considered for surgical removal. In some patients, APA patients have higher aldosterone secretion rates, with more severe hypertension, more severe hypokalemia, higher plasma (>25 ng/dL) and urinary (>30 mcg/24 hour) levels of aldosterone; these patients are younger (<50 years) than those with IHA. Bilateral adrenal hyperplasia, which accounts for approximately 60 percent of cases, is a milder disease with less hyper secretion of aldosterone and less hypokalemia.

Adrenal CT Endocrine Society Guidelines 2008 state that adrenal CT should be the initial study to determine subtype (adenoma versus hyperplasia) and exclude adrenal carcinoma. CT has superior spatial resolution when compared to MRI for adrenal imaging. The diagnosis of an adrenal carcinoma should be suspected when a unilateral large (>4 cm) adrenal mass is found on CT. An abnormality in both glands suggests adrenal hyperplasia. However CT is not enough and adrenal venous sampling (AVS) is needed as (1) patients with hyperplasia may have normal appearing adrenal glands on CT (2) a solitary unilateral adrenal macro adenoma may be a nonfunctioning cortical adenoma and in patients >40 years of age AVS is required before removing it (3) patients with a unilateral adrenal mass may have bilateral hyperplasia. (4) APAs can be very small [e.g., <3 mm in diameter] and may be missed on CT.

Adrenal vein sampling

Measurement of aldosterone in samples of adrenal venous blood, obtained by an experienced radiologist, is the standard test to distinguish between unilateral adenoma and bilateral hyperplasia. Unilateral disease is associated with a marked (usually fourfold greater than contra lateral adrenal) increase in PAC on the side of the tumor, whereas there is little difference between the two sides in patients with bilateral hyperplasia The Endocrine Society recommends AVS to confirm unilateral disease in all patients with primary aldosteronism who are candidates for surgical management (unilateral adrenalectomy). AVS can be done without cosyntropin stimulation, but continuous cosyntropin infusion (50 mcg per hour started 30 minutes before sequential sampling of the adrenal veins and continued throughout the procedure) is more sensitive. With cosyntropin infusion, the adrenal vein to IVC cortisol ratio is more than 10 : 1; without cosyntropin infusion, an adrenal vein to IVC cortisol gradient of more than 3:1 diagnostic. The right and left adrenal vein plasma aldosterone concentrations (PAC) when divided by their respective cortisol concentrations corrects for the dilutional effect of the inferior phrenic vein flow into the left adrenal vein; are termed cortisol-corrected ratios. A cutoff for the cortisol-corrected aldosterone ratio from high-side to low-side of more than 4 : 1 is used to indicate unilateral aldosterone excess; a ratio less than 3 : 1 is suggestive of bilateral aldosterone hypersecretion. There are few cases of

primary aldosteronism due to an ectopic adrenal adenoma who have low serum aldosterone concentrations in adrenal vein samples and CT or MRI may identify the site of the tumor.

Other tests— Other older tests that are used to distinguish unilateral aldosterone-producing adenomas from bilateral disease before adrenal CT and AVS approach include:

- Posture stimulation test -Patients with bilateral idiopathic hyperplasia have a rise in plasma aldosterone when going from the supine to standing position (due to an enhanced sensitivity of the adrenal zona glomerulosa to the small changes in angiotensin II with standing). In contrast, no such changes are seen in patients with an aldosterone-producing adenoma because their hyper secretion of aldosterone is autonomous and diurnal. The test is performed by measuring plasma renin activity and serum aldosterone at 8 AM (supine), followed by an upright sample at noon after four hours of ambulation. However, this test does not discriminate well between unilateral adenoma and bilateral hyperplasia.
- 18-OH corticosterone Patients with an aldosterone-producing adenoma typically have elevated supine plasma18-OH-corticosterone levels at 8 AM (>100 ng/dL) while patients with bilateral idiopathic hyperaldosteronism do not. However, the accuracy of the test is low, and it does not help with localization
- Radionuclide scintigraphy with 131-I-iodocholesterol has the potential advantage of correlating function with anatomic findings, it is not useful for evaluating small adrenal nodules, as tracer uptake is poor in aldosterone-producing adenomas <1.5 cm in diameter.

Treatment

Unilateral adrenal adenoma or hyperplasia A unilateral adrenal adenoma is responsible for the hyperaldosteronism in 30 to 60 percent of cases of primary aldosteronism, while unilateral hyperplasia is less common (about 3 percent). Surgery is the treatment of choice in unilateral mass. An alternative is medical therapy with a mineralocorticoid receptor antagonist. Aldosterone (mineralocorticoid receptor) antagonists can be used in patients who refuse or are not fit for surgery. Hypertension can be controlled by dietary sodium restriction (<100 meq/day), maintenance of ideal body weight, avoiding alcohol and regular aerobic exercises. Spironolactone (12.5 to 25 mg) is the drug of choice; eplerenone (25 mg once or twice daily) is a newer and more expensive drug; however, has lesser side effects. Dose can be titrated so that the serum potassium levels remains normal. Potassium-sparing diuretics that block the aldosterone-sensitive epithelial sodium channel in the collecting tubules (amiloride, triamterene) can be used for treatment; however, they are now recommended as first line therapy as they do not correct the hyperaldosteronism, though they are effective for hypertension. Hyperaldosteronism is associated with cardiovascular morbidity. In patients showing side effects with aldosteroneantagonists, Amiloride is started at 5 mg twice daily and gradually increased to correct the hypokalemia. If the hypertension persists, thiazide can be added followed by ACEI.[8]In Idiopathic adrenal hyperplasia, patients should be treated with an aldosterone (mineralocorticoid receptor) antagonist.

Aldosterone Producing Tumors

Less common forms include:

1. Unilateral hyperplasia or primary adrenal hyperplasia (caused by micro nodular or macro nodular hyperplasia of the zona glomerulosa,
2. Bilateral macro nodular or micro nodular adrenal hyperplasia with primary aldosteronism which are pure aldosterone - producing adrenocortical carcinomas and ectopic aldosterone-secreting tumors (e.g., neoplasms in the ovary or kidney).

Familial Hyperaldosteronism

There are two other forms of primary aldosteronism associated with adrenal hyperplasia: familial hyperaldosteronism type I and type II [Figure 1]. Both are rare disorders characterized by autosomal dominant inheritance. The 2008 Endocrine Society Guidelines recommend genetic testing for familial disease in patients with primary aldosteronism, who are younger than age 20 years, or who have a family history of primary aldosteronism or stroke at a young age (<40 years). Familial

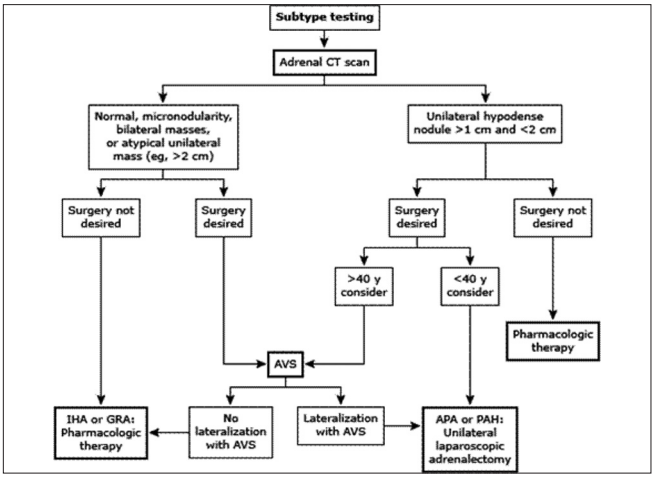

Figure 1: Workup for primary hyperaldosteronism

hyperaldosteronism can be categorized into the following two types:

- Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism).
- Familial hyperaldosteronism type II

Glucocorticoid Remediable Aldosteronism or Familial Hyperaldosteronism Type I

Glucocorticoid-remediable aldosteronism (GRA) is a rare form of hyperaldosteronism in which the hyper secretion of aldosterone is under the control of ACTH. Normally two isozymes of 11-beta-hydroxylase encoded by two genes on chromosome 8 are responsible for the biosynthesis of aldosterone and cortisol. The isozyme in the zona glomerulosa (CYP11B2, aldosterone synthase, P450as) catalyzes the conversion of deoxycorticosterone to corticosterone (controlled by ACTH) and of 18-hydroxycorticosterone to aldosterone. The isozyme in the zona fasciculata (CYP11B1, P450c11) catalyzes the conversion of 11-deoxycortisol to cortisol and does not contribute to aldosterone synthesis. The mutation in patients with GRA is fusion of the promoter region of the gene for CYP11B1 and the coding sequences of CYP11B2, resulting in ACTH-dependent activation of the aldosterone synthase effect on cortisol, corticosterone, and cortisol precursors [Figure 2]. Glucocorticoid-remediable aldosteronism is inherited as an autosomal dominant trait. It is characterized by positive family history and onset of hypertension before age 21. The plasma potassium concentration is normal in more than 50% of cases of GRA in contrast to primary aldosteronism due to an adrenal adenoma. This is because aldosterone release in GRA is under the influence of ACTH; with the normal circadian rhythm of ACTH release, aldosterone secretion is above normal for only part of the day. Aldosterone release is insensitive to potassium loading due to location of aldosterone synthesis in the zona fasciculata. The lack of aldosterone response to dietary potassium also reduces net al.dosterone release. There is marked hypokalemia after thiazide diuretic (which increases sodium delivery to the aldosterone-sensitive potassium secretory site in the cortical collecting tubule). GRA is associated with bilateral adrenal hyperplasia. In patients with GRA, 20 percent can have a cerebrovascular complication, 70 percent of which are hemorrhagic strokes due to ruptured intracranial aneurysms. The increase in hemorrhagic stroke is due to early onset hypertension during the early stages of cerebrovascular development. All patients with genetically proven GRA should undergo screening MR angiography at puberty and every five years thereafter. The diagnosis is suspected on the basis of the history. The plasma aldosterone is elevated and plasma renin activity is suppressed, but the aldosterone-renin ratio is typically not as high as with primary aldosteronism caused by an aldosterone-producing adenoma. The diagnosis is established by dexamethasone suppression testing and demonstration of hyper secretion of 18-carbon oxidation products of cortisol: 18-hydroxycortisol and 18-oxocortisol. However, genetic testing is the gold standard.[9,10] Indications for genetic screening include primary aldosteronism patients with onset at a young age (e.g., <20 years), or a family history of primary aldosteronism or of strokes at a young age (e.g., <40 years).[7]

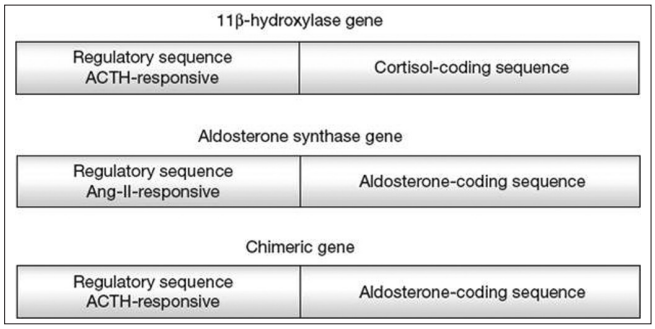

Figure 2: Mutation in glucocorticoid remediable hypertension

Treatment

Physiologic doses of a glucocorticoid (prednisone, dexamethasone, or hydrocortisone) correct the overproduction of aldosterone by diminishing ACTH release. The smallest effective dose of an intermediate-acting glucocorticoid (e.g., prednisone) should be administered at bedtime. Treatment with mineralocorticoid receptor antagonists is also effective and avoids steroid side effects.

Primary Hyperaldosteronism Type II

In familial hyperaldosteronism type II, the hyperaldosteronism is not dependent upon ACTH and is not suppressible by dexamethasone. Families with familial hyperaldosteronism type II can have an aldosterone-producing adenoma or idiopathic hyperaldosteronism or both. The genetic defect is different from that of type I disease and is unrelated to abnormalities of the CYP11B2 (aldosterone synthase) gene. Linkage to chromosome 7p22 was described in several families.[11]

Liddle's Syndrome

Liddle's syndrome is a rare autosomal dominant condition in which there is a primary increase in collecting tubule sodium reabsorption and potassium secretion. The cortical collecting tubule contains two cell types: principal

cells (65 percent) and intercalated cells. The principal cells have sodium and potassium channels in the luminal (apical) membrane and Na-K-ATPase pumps in the basolateral membrane.The intercalated cells are primarily involved in hydrogen, bicarbonate, and potassium handling. The principal cells contribute to net sodium reabsorption and are the primary site of potassium secretion [Figure 3]. The intercalated cells are primarily involved in hydrogen, bicarbonate, and potassium handling. In Liddle syndrome there is gain of function mutation of the collecting tubule sodium channel, also called the epithelial sodium channel (ENaC) or the amiloride-sensitive sodium channel. ENaC hyperfunction leads to manifestations of mineralocorticoid excess, such as hypertension, hypokalemia (not universal) and metabolic alkalosis. Most patients present at a young age, but some are not detected until adulthood.

The genetic abnormality in Liddle's syndrome involves mutations in genes on chromosome 16p12 that encode the beta and gamma subunits of the collecting tubule sodium channel, which are called SCNN1B and SCNN1G, respectively. Deletions or substitutions in a short proline-rich segment of the intracytoplasmic C-terminus cause an inability of these subunits to bind with an intracellular ubiquitin protein ligase (Nedd4) that normally removes the luminal sodium channel from the cell surface.[12,13] Patients with Liddle's syndrome have low plasma renin activity,reduced plasma aldosterone concentration and low urinary excretion of aldosterone in contrast to primary aldosteronism. Genetic testing is the most reliable method for establishing the diagnosis of Liddle's syndrome. Therapy in Liddle's syndrome consists of amiloride or triamterene, potassium-sparing diuretics that directly block the collecting tubule sodium channels and can correct both the hypertension and hypokalemia. The mineralocorticoid antagonist spironolactone is ineffective, since the increase in sodium channel activity in Liddle's syndrome is not mediated by aldosterone.

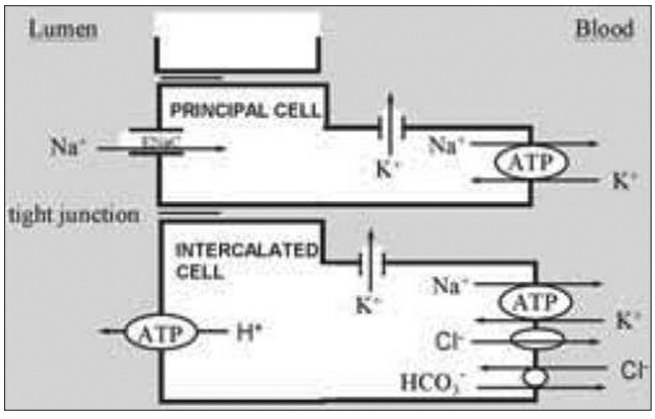

Figure 3: Epithelial sodium channel in the collecting duct

Mineralocorticoid Receptor-Activating Mutation (or Pregnancy-Exacerbated Hypertension)

This is an extremely rare autosomal dominant condition characterized by an early onset of low-renin/low-aldosterone hypertension associated with hypokalemia. Typically, blood pressure levels further increase during pregnancy. This condition is due to a mutation in the mineralocorticoid receptor (MR) that constitutively activates the receptor, which is also activated by progesterone (hence the exacerbation during pregnancy) and spironolactone (explaining the lack of response to spironolactone therapy). Furthermore, it has been shown that cortisone can also activate the mutated MR, contributing to hypertension and hypokalemia in male subjects and in nonpregnant women. Amiloride is the treatment of choice for this genetic form. To date, only one family has been described with this condition.[14]

Apparent Mineralocorticoid Excess Syndromes

The syndrome of apparent mineralocorticoid excess (AME) is a genetic disorder. However, chronic ingestion of licorice or carbenoxolone can result in clinical findings similar to AME. However, plasma aldosterone levels are low in these disorders, rather than elevated, as in primary aldosteronism. The syndrome of AME is due to deficiency in the 11-beta-hydroxysteroid dehydrogenase enzyme type 2 isoform (11-beta-HSD2), which is the kidney isoform of 11-beta-HSD.11-beta-HSD2 normally converts cortisol to cortisone, latter does not bind to the mineralocorticoid receptor. However cortisol binds avidly to the mineralocorticoid receptor like aldosterone. Normally the plasma cortisol concentration is approximately 100-fold higher than the plasma aldosterone concentration. Thus, if cortisol were not converted by 11-beta-HSD2 to cortisone at the aldosterone-sensitive sites cortisol becomes the primary mineralocorticoid. The persistence of cortisol resulting from deficiency in 11-beta-HSD2 leads to an often marked elevation in mineralocorticoid activity.The mutation in the 11-beta-HSD2 gene is located on chromosome 16, which encodes the kidney isoform of 11-beta-HSD. AME is an autosomal recessive trait.

The syndrome AME is characterized by low birth weight, failure to thrive, and onset of severe hypertension in early childhood with severe target organ damage, hypercalciuria,

nephrocalcinosis and renal failure. These manifestations are accompanied by all of the findings of primary aldosteronism (hypertension, hypokalemia, metabolic alkalosis, and low plasma renin activity) except for the low plasma aldosterone concentration. Patients may have polyuria due to nephrogenic diabetes insipidus induced by chronic hypokalemia.[15]

Lab tests reveal hypokalemia, metabolic alkalosis, low plasma renin activity and low plasma aldosterone levels. The urinary free cortisol to urinary free cortisone ratio as measured on a 24-hour urine collection is a sensitive diagnostic test. If 11-beta-HSD is normal, urinary free cortisone levels exceed urinary cortisol levels, and the ratio of cortisol to cortisone is approximately 0.3 to 0.5. In patients with AME, the ratio is high usually 5 in children and 18 in adults, respectively. Genetic testing to confirm the diagnosis of the syndrome of AME is commercially available.[16]

Treatment of AME consists of reducing endogenous cortisol production or blocking the mineralocorticoid receptor. Dexamethasone in doses of 1.5 to 2 mg/day suppresses ACTH and reduces endogenous cortisol production. However, dexamethasone does not correct the hypokalemia and hypertension in all patients, and has adverse effects if used long-term. Thus, dexamethasone is used only if mineralocorticoid blockade is not effective or not tolerated. Blockade of mineralocorticoid effects can be achieved by decreasing sodium channel activity with amiloride or triamterene or by direct mineralocorticoid receptor blockade with spironolactone or eplerenone. Direct comparison of these agents shows that high doses of spironolactone are required to block the mineralocorticoid effects of cortisol hence of side effects are more. Thus therapy is initiated with drugs with fewer side effects e.g., amiloride or eplerenone. Potassium supplements may be required initially to treat hypokalemia. A thiazide is indicated if hypercalciuria or nephrocalcinosis is present. Transplantation of a kidney with normal 11-beta-HSD2 activity resulting in cure has been reported.

Other AME like conditions

Licorice ingestion— Chronic ingestion of licorice or licorice-like compounds (such as carbenoxolone) induces a syndrome with similar to the syndrome of AME. Small amounts of confectionery licorice (flavored chewing gum and chewing tobacco), produce a rise in blood pressure in normal people. Licorice contains a steroid, glycyrrhetinic acid that inhibits 11-beta-HSD2, the same enzyme that is deficient in AME. Urinary free cortisone is slightly decreased, and the ratio is moderately elevated, but testing is not necessary if a history of licorice ingestion is obtained. Cessation of licorice ingestion results in cure.[17]

Ectopic ACTH syndrome Cortisol can contribute to the excess mineralocorticoid effect in Cushing's syndrome due to ectopic ACTH release (commonly arising from small cell carcinoma of the lung). This occurs as (1) Cortisol secretion is so high that it exceeds the metabolic capacity of 11-beta-HSD2, (2) Very high circulating levels of ACTH inhibit 11-beta-HSD2,[18] (3) Hyper secretion of nonaldosterone mineralocorticoids such as deoxycorticosterone and corticosterone. The diagnosis of the ectopic ACTH syndrome is suggested by hypokalemia, the demonstration of markedly increased 24-hour urinary free cortisol excretion, and elevated serum ACTH. Ectopic ACTH secretion may result in an elevated urinary free cortisol to cortisone ratio, but urinary cortisol and cortisone levels are markedly increased in contrast to the very low levels of urinary free cortisone excretion in the syndrome of AME. A Cushingoid appearance may be present but is less marked in patients with malignancies.

Glucocorticoid Resistance

This autosomal recessive disease is caused by a mutation of the glucocorticoid receptor (GR) gene, affecting the ability of the GR to bind ligands and to activate or repress target genes. The loss of GR action is associated with a feedback elevation of ACTH, which in turn drives an excessive secretion of cortisol and other adrenal derived steroids bearing androgenic and mineralocorticoid properties. Clinically, patients develop a mixed adrenal syndrome. Most commonly, they complain of chronic fatigue, which is a symptom of GR resistance in certain resistant target tissues (e.g. brain and skeletal muscle). Often they develop LRH and metabolic alkalosis, while the lack of effect of cortisol prevents cushingoid features. Hypertension is attributed to the excess of cortisol and to saturation of the 11HSD2 enzyme. Dexamethasone, the effect of which actually depends on the underlying genetic alteration, is the treatment of choice.[19]

Pseudohypoaldosteronism Type II

Pseudohypoaldosteronism type II(or Gordon's syndrome) is a rare genetic form of altered renal salt reabsorption. The genetic defect is transmitted as an autosomal dominant trait. It is due to mutations of the genes encoding for two kinases WNK1 and WNK4 (With no lysine kinase) involved in the regulation of ion transport by Thiazide sensitive co transporter in the distal tubule, resulting in an increased reabsorption of sodium and reduced potassium excretion [Figure 4].[20] Patients present with low-renin and

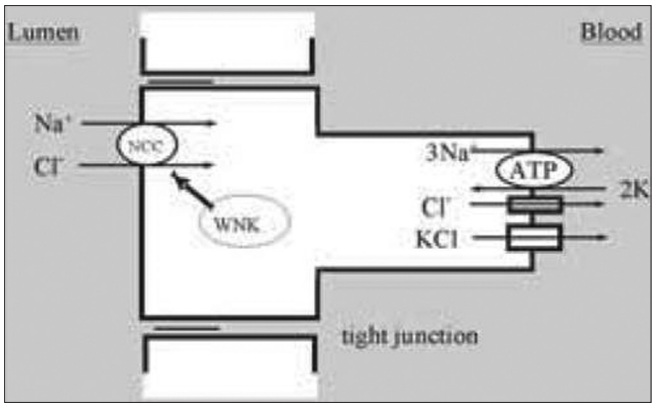

Figure 4: Sodium chloride cotransporter in distal tubule

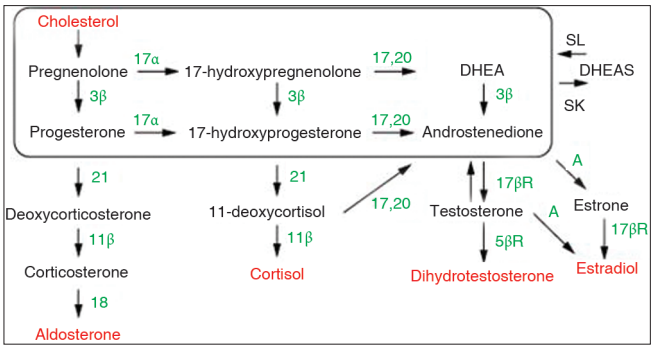

Figure 5: Pathway for adrenal steroid synthesis

normal aldosterone levels. These patients characteristically display high plasma potassium level, hyperchloraemia and metabolic acidosis and therefore have a phenotype that is easily distinguishable from other patients that display normal or low plasma potassium levels.[21,22] The hypertensive phenotype is particularly sensitive to thiazide diuretics.

Congenital Adrenal Hyperplasia

The adrenal steroid hormones are synthesized in different areas of the adrenal cortex:-Glucocorticoids, androgens, and estrogens in the zona fasciculata and reticularis and Aldosterone in the zona glomerulosa. The substrate for the synthesis of all steroid hormones is cholesterol. The cells of the adrenal cortex either take up cholesterol from the circulation or synthesize cholesterol de novo from acetate. Four distinct cytochrome P450 enzymes are involved in adrenal corticosteroid biosynthesis [Figure 5]. Inherited defects in the enzymatic steps result in different varieties of congenital adrenal hyperplasia (CAH). All varieties of CAH are inherited as autosomal recessive traits. The resulting decrease in cortisol production causes an increase in the secretion of ACTH, which stimulates the production of adrenal steroids up to and including the substrate for the defective enzyme. There may be impaired synthesis of cortisol or impaired synthesis of aldosterone and excessive synthesis of precursor steroids due to the increase in ACTH secretion. In some varieties this results in increases in androgenic hormones (which can cause virilization) and in deoxycorticosterone (which has mineralocorticoid activity and can cause hypertension).[23] The varieties of CAH associated with hypertension include.

CAH Due to CYP17 (17- Alpha-Hydroxylase Deficiency)

The frequency of 17 OH CAH is <1% of all cases of CAH. The gene is located on chromosome10. In CYP 17 deficiency there is increased concentration of 17 desoxy steroids while all other steroids including gonadal steroids are low. Excess of deoxycorticosterone causes hypertension and hypokalemia. Reduced gonadal steroids leads to hypogonadism and undervirilization in an XY infant and sexual infantilism in females at puberty. Low renin and low aldosterone are seen along with high adrenal steroid metabolites (17-hydroxypregnenolone, deoxycorticosterone, and DHEA). Adrenal function should be evaluated with an ACTH stimulation test as follows-ACTH (1 mcg/m^2 IV). Is administered and 60 minutes later, cortisol, progesterone, pregnenolone, 17-alpha-hydroxyprogesterone, 17-alpha-hydroxypregnenolone, DHEA, and androstenedione are measured. Pelvic and abdominal ultrasonography should be performed to determine whether gonads, uterus, and vagina are present. Treatment consists of dexamethasone to control hypertension, testosterone in boys and estrogen in girls.

CAH Due to CYP11B1 (11-Beta-Hydroxylase Deficiency)

CYP11B1, or 11-beta-hydroxylase, deficiency is the second most common cause of congenital adrenal hyperplasia. And accounts for about 5 to 8 percent of cases of CAH. CYP11B1 deficiency may manifest in neonates, children, or adults (late-onset). CYP11B1 deficiency is inherited as an autosomal recessive disorder caused by mutations of the CYP11B1 gene on chromosome 8q21-q22. Deficiency of CYP11B1 results in decreased conversion of 11-deoxycortisol and 11-deoxycorticosterone to cortisol and corticosterone, respectively. The decrease in cortisol production causes an increase in ACTH secretion. The resulting adrenal stimulation leads to excessive production of 11-deoxycortisol, 11-deoxycorticosterone leading to hypertension and over secretion of adrenal androgens. This leads to ambiguous genitalia in newborn females (clitoral enlargement, labial fusion) and penile enlargement in males. Some present in childhood with sexual precocity in boys

and hirsutism and menstrual irregularities in adolescent girls. Hypertension occurs in two-thirds of patients; it is most common in early onset disease and uncommon in patients with late-onset disease Hypokalemia may be present and plasma renin activity is often low, due to the excess mineralocorticoid activity. Hypertension and hypokalemia are the primary clinical manifestations that distinguish CYP11B1 deficiency from other types of CAH. However, some patients with CYP11B1 deficiency are normotensive, and a few have salt-wasting.[24]

Patients with CYP11B1 deficiency have a characteristic set of hormonal findings, and some have hypokalemia e.g. High serum concentrations of 11-deoxycortisol, 11-deoxycorticosterone, and the androgens dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA sulfate), androstenedione, and testosterone. There is increased urinary excretion of the tetra hydro metabolites of 11-deoxycortisol and 11-deoxycorticosterone, which are normally present in trace quantities. Urinary 17-hydroxycorticosteroid excretion is high, because 11-deoxycortisol reacts in the assay for these steroids. Urinary excretion of 17-ketosteroids, most of which are androgen metabolites, is also increased. In affected neonates. The diagnosis is established by high basal and ACTH-stimulated serum 11-deoxycortisol concentrations and increased urinary excretion of tetrahydro-11-deoxycortisol. In adolescents and young adults, basal serum 11-deoxycortisol values may be normal, and ACTH testing is often required to establish the diagnosis. The carriers have no detectable biochemical abnormalities.

Treatment consists of glucocorticoid in sufficient doses to reduce ACTH secretion. Hydrocortisone is used in doses of 10 to 25 mg per m^2 in divided doses. Alternately Dexamethasone, 0.5 mg can be given at bedtime. Spironolactone, amiloride, and calcium channel blockers can be used for hypertension. The genital malformations in affected females need surgical correction. CYP11B1 deficiency can be diagnosed prenatally by measuring tetrahydro-11-deoxycortisol in amniotic fluid or by detection of CYP11B1 gene in DNA from chorionic villus biopsy samples. Prenatal treatment can be effective in preventing development of ambiguous genitals.

Acquired Low Renin, Low Aldosterone Hypertension

Low-renin/low-aldosterone hypertension can be acquired. Several conditions should be considered in the differential diagnosis of acquired forms. First, a very generous dietary sodium intake may underlie this functional phenotype in essential hypertensive patients. Second, drugs may be an important cause. Drugs reducing the renin-angiotensin-aldosterone system (RAAS) activation include beta-blockers and centrally acting agents such as clonidine and alpha-methyldopa. Also, no steroidal anti-inflammatory drugs (NSAIDs) and newer COX-2 inhibitors inhibit the RAAS by suppressing intrarenal prostaglandin and renin secretion directly and by reducing sodium excretion, thus favoring volume expansion and aggravating hypertension. Furthermore, unfractionated heparin (UFH) is a potent inhibitor of aldosterone production; unlike UFH, low-molecular-weight heparins lack effects on aldosterone production.

Third, a low-renin/low aldosterone status may result from a marked reduction in nephron number and function. These conditions include diabetic nephropathy, chronic glomerulonephritis, congenital solitary kidney, unilateral nephrectomy or ageing. Finally, RAAS suppression may be a physiological response to a RAAS-independent activation of the mineralocorticoid receptor in target tissues. For instance, excessive liquorice intake and ectopic production of ACTH by neoplastic cells, and deoxycorticosterone (DOCA) producing adrenocortical tumors as already discussed above are other acquired causes of low renin hypertension.

Diagnostic Workup of Genetic Low-Renin/Low-Aldosterone Forms

In patients with a suspected genetic form of low-renin/low aldosterone, the differential diagnosis is based on a pharmacological test, which can help to distinguish between the different forms and the type of inheritance (dominant or recessive). Briefly, patients whose blood pressure levels are not reduced after treatment with spironolactone (100 mg daily) for at least 2 months could be affected by Liddle's syndrome, an MR-activating mutation or, more probably, by essential hypertension. If blood pressure levels are high and potentially harmful, conventional antihypertensive drugs should be used and the response to spironolactone evaluated under these treatments. Patients responding to spironolactone therapy can be further subdivided according to cortisol to cortisone metabolite ratio. This ratio reflects the activity of the 11HSD2 enzyme. Patients with a normal ratio may have an excess of DOC production, as in some forms of congenital adrenal hyperplasia (CAH) associated with 11beta-hydroxylase or 17alpha-hydroxylase deficiency (sporadic DOC-producing adrenocortical tumors have to be taken into account). Patients with a high cortisol to cortisone metabolite ratio are probably affected by the

apparent mineralocorticoid excess syndrome (AME) or by a glucocorticoid resistance syndrome (ectopic ACTH production and excess liquorice consumption also need to be excluded). However, patients with glucocorticoid resistance are distinguished from patients with AME, as they display high levels of plasma and urinary cortisol, whereas in patients with AME these levels are normal [Figure 6].[25]

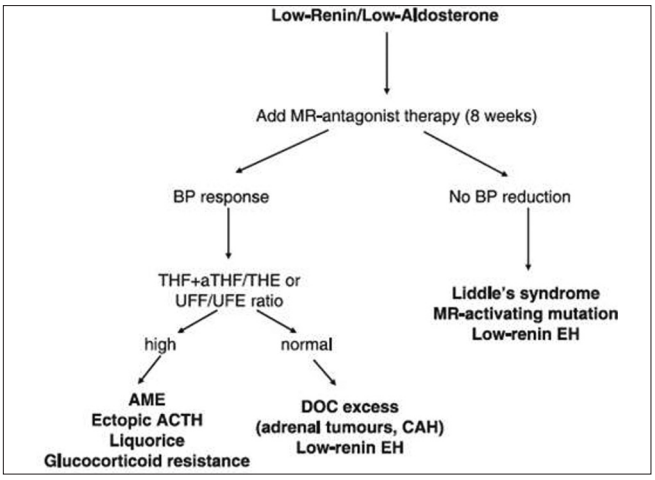

Figure 6: Diagnostic work up for low rennin hypertension

Treatment

The treatment algorithm recommended by the British Hypertension Society (BHS) is based on renin profiling.[26] Caucasian individuals less than 55 years have higher renin levels than older and black individuals of African descent. The guidelines recommend for the former subgroup, in the absence of compelling indications, treatment should be initiated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [A drugs] or β-blockers [B drugs]). For individuals in the latter group, a calcium channel blocker (C drugs) or a diuretic (D drugs) should be the first line of therapy. If two drugs are required in order to control blood pressure, the combinations (A or B) + (C or D) can be given and, in the case of further treatment failure, (A or B) + C + D. The concomitant use of -β blockers and diuretics might be diabetogenic especially in patients at high risk. If the hypertension is resistant to treatment, the addition of low dose spironolactone is suggested. The parameters which allow reliable prediction of the response to treatment are plasma renin activity, age, sex and race e.g. black race and female gender respond well to hydrochlorothiazide. Black subjects have good response to calcium channel blocker.

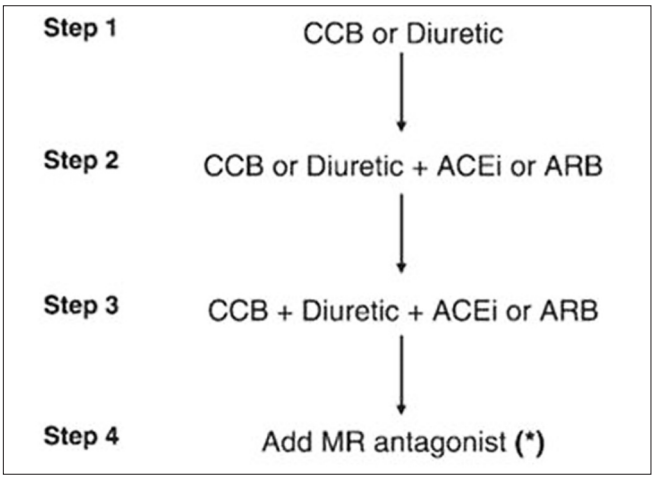

Figure 7: Treatment algorithm for low rennin hypertension (British Hypertension society)

Resistant hypertension, defined as a failure of three or more concomitant antihypertensive medications, including diuretics, to lower blood pressure below 140/90 mmHg, is a common clinical problem, affecting up to 30% of hypertensives. Low-dose MR-antagonists provide significant additive blood pressure reductions in such patients as approximately 60–70% of resistant patients are generally found to be low-renin. Low-renin resistant patients respond much better to the addition of amiloride/hydroclorothiazide rather than other diuretic combinations that did not include a drug acting on the ENaC. More extensive studies are needed to define more clearly treatment guidelines for resistant hypertension. An algorithm for low-renin essential hypertension treatment is suggested in Figure 7.

Conclusion

Low renin hypertension is an important under diagnosed form of hypertension. It is in addition an important cause of resistant hypertension. Renal sodium profiling is important for diagnosis. Some forms are genetic and correct diagnosis is important for treatment. Some varieties of low renin hypertension especially those associated with hyperaldosteronism are associated with increased cardiovascular morbidity and mortality. Recognition of this hypertension is important as the treatment depends on the diagnosis.

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