Primary Aldosteronism

Internal Medicine Grand Rounds

University of Texas Southwestern Medical Center

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This is to acknowledge that Jeffrey Penfield, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Penfield will be discussing off-label uses in his presentation.

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Purpose and overview: The purpose of this grand rounds is to review changes in primary aldosteronism that have occurred over the last several years. There is accumulating evidence for increased cardiovascular events with primary aldosteronism. Hypertensive patients with appropriate risk factors should be screened. The complexities of screening and confirmatory testing will be discussed as well as the familial forms of primary aldosteronism and a differential diagnosis.

Learning Objectives:

1. Know the prevalence of primary aldosteronism in both the hypertensive population and those referred to a hypertension center.
2. Know the complexities of the screening tests and confirmatory tests in evaluation of primary aldosteronism.
3. Know the increased risk of cardiovascular disease associated with excess aldosterone production.
4. Understand the familial forms of primary aldosteronism.
5. Be familiar with diseases that should be considered in the differential diagnosis of primary aldosteronism.

History

Aldosterone was isolated from adrenal glands in 1953 by Simpson et al.[1] It was originally called electrocortin but was renamed aldosterone in 1954 by the same authors based on its structure[2,3]. In 1955 Conn described a 34 year old female with hypertension, hypokalemia, hypernatremia and alkalosis with high urinary levels of a sodium retaining corticoid based on a bioassay. He performed a 70 day metabolic balance study on her and measured sodium and potassium in her sweat, saliva and urine. She eventually underwent surgery where a 4 centimeter right adrenal cortical tumor was found and resected. He concluded that her disease was due to excess aldosterone and named it primary aldosteronism[4]. In the same year primary aldosteronism was called Conn's Syndrome in a letter to Lancet.[5]

A decade later, Conn wrote that primary aldosteronism was much more common than previously thought and estimated that 20% of essential hypertension was caused by an aldosterone producing adenoma. In the same paper he also wrote that there were many cases of primary aldosteronism that did not have hypokalemia until late in the disease and that a suppressed renin was important to differentiate this disease from secondary causes of elevated aldosterone levels[6]. The aldosterone renin ratio (ARR) was introduced as a screening test for low renin hypertension in 1973[7] but not suggested as a test for primary aldosteronism until 1981[8].

Clinical course of primary aldosteronism and prevalence

Excess aldosterone secretion in primary aldosteronism has cardiovascular complications beyond the effect on elevated blood pressure. 124 patients with primary aldosteronism referred to a hypertension center were compared to 465 patients with essential hypertension. The blood pressures were equal in both groups, yet the primary aldosteronism patients had a statistically increased history of stroke and myocardial infarction as well as atrial fibrillation and left ventricular hypertrophy. Results are summarized in tables 1 and 2[9]. The increased cardiovascular disease prevalence was confirmed in a later study where patients with primary aldosteronism were compared to patients with essential hypertension. The relative risks for sustained arrhythmias, cerebrovascular events, and coronary heart disease were 4.93, 4.36, and 2.80 respectively.[10]

Table 1. Clinical Characteristics and Risk Factors Parameters of Primary Aldosteronism Patients and Controls Modified from Miliez et al[9].

	Primary Aldosteronism (n = 124)	**Essential Hypertension (n = 465)**	**p Value**
Age (yrs)	52 ± 10	52 ± 10	NS
Men/women (%)	67/33	63/37	NS
SBP (mm Hg)	176 ± 23	174 ± 20	NS
DBP (mm Hg)	107 ± 14	106 ± 14	NS
Heart rate (beats/min)	72 ± 8	72 ± 10	NS
Current or past smokers (%)	42	44	NS
Serum glucose (mmol/l)	6.0 ± 1.3	5.9 ± 1.9	NS
Total cholesterol (mmol/l)	5.4 ± 0.9	5.9 ± 1.1	0.0004
Serum potassium (mmol/l)	3.5 ± 0.3	4.4 ± 0.3	0.0001
Serum creatinine (µmol/l)	92 ± 24	87 ± 36	NS
Urinary potassium (mmol/24 h)	80 ± 37	63 ± 25	0.0003
Active plasma renin (pg/ml)	4.7 ± 2.6	17.5 ± 15.3	0.0001
Plasma aldosterone (pg/ml)	374 ± 174	116 ± 60	0.0001
Aldosterone/renin ratio	94 ± 90	11 ± 10	0.0001
Urinary aldosterone (µg/24 h)	34 ± 17	16 ± 6	0.01

Table 2. Rate of Cardiovascular Events and Cardiac Structure in Primary Aldosteronism Patients and Controls Modified from Milliez et al[9].

	Primary Aldosteronism (n = 124)	**Essential Hypertension (n = 465)**	**Odds Ratio (95% CI)**	**p Value**
Stroke (%)	12.9	3.4	4.2 (2.0–8.6)	<0.001
Myocardial infarction (%)	4	0.6	6.5 (1.5–27.4)	<0.005
Atrial fibrillation (%)	7.3	0.6	12.1 (3.2–45.2)	<0.0001
Echocardiographic LVH (%)	34	24	1.6 (1.1–2.5)	<0.01
Electrocardiographic LVH (%)	32	14	2.9 (1.8–4.6)	<0.001

Aldosterone has both genomic and non-genomic effects on vascular endothelium that cause vascular fibrosis, oxidation and inflammation in animal models[3] and patients with elevated aldosterone levels have increased markers of oxidative stress and inflammation[11]. The benefit of mineralocorticoid receptor blockade on cardiovascular events was demonstrated in the RALES trial[12]. The increased cardiovascular risk associated with primary aldosteronism suggests that we should be screening patients with hypertension for this disease so they can be appropriately treated.

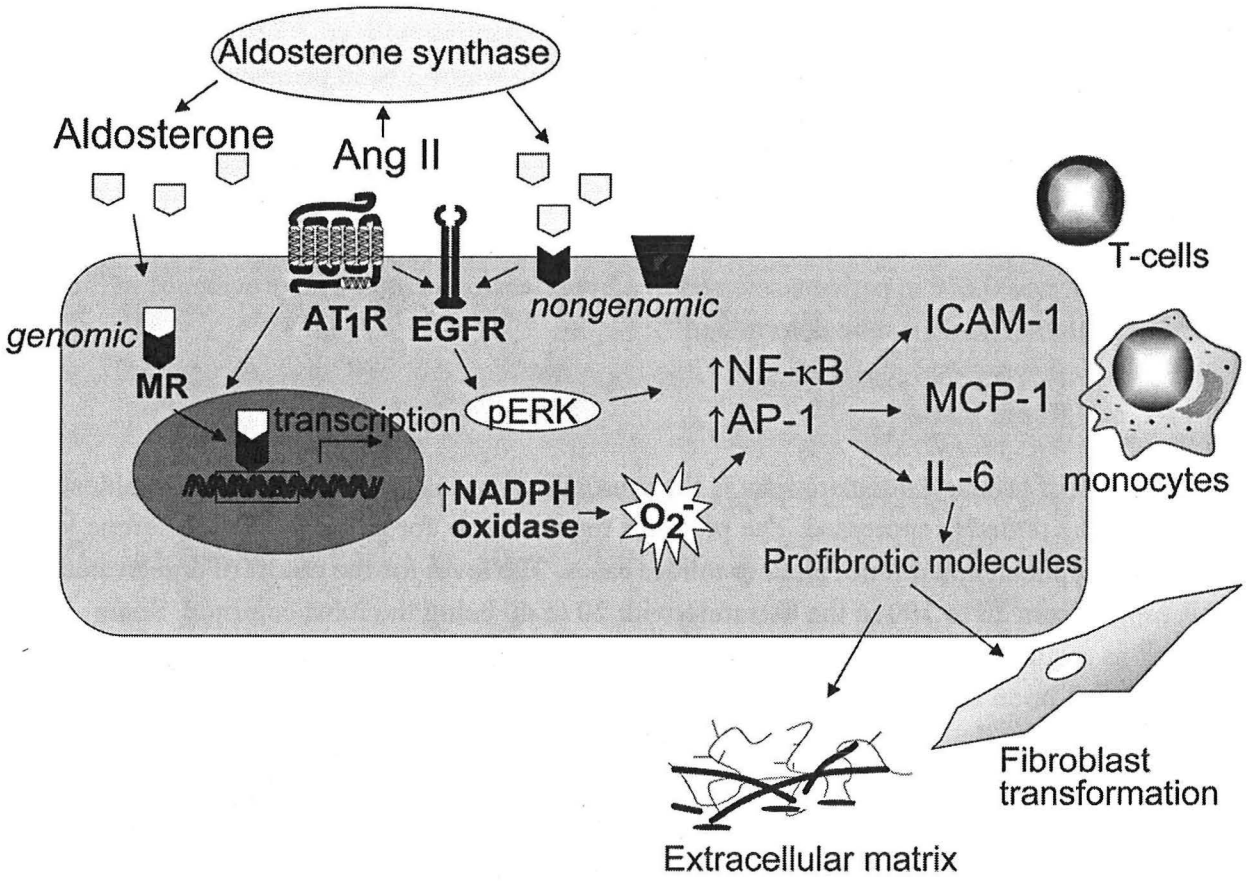


Figure. Cartoon of mechanism(s) of aldosterone-induced vascular fibrosis: aldosterone, acting at the MR, affects the transcription of proinflammatory genes. Aldosterone also causes rapid, transcription-independent effects. Aldosterone activates NADPH oxidases to produce reactive oxygen species (O2–). Ang II increases MR-dependent transcription in VSMCs via its AT1 receptor. Aldosterone and Ang II phosphorylate ERK1/2 through genomic and nongenomic pathways. Nongenomic pathways involve transactivation of the EGFR. Increased oxidative stress and activation of ERK result in the expression of proinflammatory transcription factors, adhesion factors, such as intercellular adhesion molecule (ICAM)-1, and chemokines like MCP-1. Leukocytes secrete inflammatory cytokines (IL-6), which, in turn, promote expression of profibrotic factors, such as TGF-β and PAI-1. Brown, J Hypertension 2008[3]

The prevalence of primary aldosteronism in hypertensive patients was originally thought to be around 1%. With use of screening with the ARR, the prevalence was predicted to be as high as 39%[13]. There is bias in these increased predictions and a much lower prevalence than predicted in the 1990s has been suggested[14]. The prevalence rate is much higher in patients referred to a hypertension specialist. The prevalence also depends on how the diagnosis of primary aldosteronism is made. Requiring confirmation with a suppression testing and improvement with

treatment will result in much fewer cases than simply screening with an ARR. A meta-analysis showed that the rate of confirmed primary aldosteronism was 4.3 % in primary care patients and 9% in referred patients. There were only two studies evaluated in the primary care group. Only 31% and 75% of the patient in these 2 studies with an elevated ARR had a confirmatory saline suppression test suggesting that there was a selection bias for performing the confirmatory test. The prevalence of an elevated ARR was 19.6% and the prevalence of confirmed primary aldosteronism was 9.6% in patients referred to a hypertension center. The prevalence in the general population could not be determined[15].

Aldosterone Renin Ratio

The hallmark of primary aldosteronism is the presence of an inappropriately elevated aldosterone level when the renin is suppressed. The previous requirements for an elevated aldosterone level along with hypokalemia did not pick up milder cases. The level for the cutoff of an elevated ARR ranges from 20 to 100 in the literature with 20 to 40 being the most common. Some institutions require a minimal aldosterone level, most commonly 15. Others will take either an elevated ARR or an aldosterone level above a certain level no matter what the ARR is. This makes determining the prevalence of primary aldosteronism challenging as mentioned above. It also makes it hard to choose the correct ARR in one's own practice. For aldosterone levels, each lab has normal values based on the sodium intake of the patient which by itself is not very useful. Each lab also has reference values for renin. Renin for many years has been measured using a bioassay where renin in plasma is allowed to act on the plasma's endogenous angiotensinogen, producing angiotensin I. Renin activity is expressed in ng of angiotensin I produced per mL of plasma per hour of incubation and is called the plasma renin activity[16]. A newer method is to measure renin concentrations directly. This requires conversion to plasma renin activity so a ratio can be interpreted. The conversion can be 8.2 or 12 depending on the assay used[17]. Direct renin inhibitors will increase renin levels but block the activity of renin resulting in increased direct renin levels but decreased plasma renin activity. With such complex tests there will be wide inter-lab variability. Using two lab values for a ratio multiplies the variability in results. No lab has reference values for ARRs specific for the two tests that they run.

In addition to lab variability, there are many factors that affect the level of both aldosterone and renin values. The position of the patient as well as the time of the day, sodium intake, medications, hypokalemia, and oral potassium loading will affect the results of the ratio. Table 3 lists the affect that these factors will have on the ARR. In addition, oral contraceptives, SSRIs, obstructive sleep apnea and obesity can also affect the ratio. Verapamil, alpha blockers and hydralazine have minimal effect on the aldosterone or renin levels.

Table 3. Taken from the Endocrine Society Practice Guidelines[17]

Factors that may affect the ARR and thus lead to false-positive or false-negative results

Factor	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
Medications			
β-Adrenergic blockers	↓	↓↓	↑ (FP)
Central α-2 agonists (*e.g.* clonidine and α-methyldopa)	↓	↓↓	↑ (FP)
NSAIDs	↓	↓↓	↑ (FP)
K^+-wasting diuretics	→↑	↑↑	↓ (FN)
K^+-sparing diuretics	↑	↑↑	↓ (FN)
ACE inhibitors	↓	↑↑	↓ (FN)
ARBs	↓	↑↑	↓ (FN)
Ca^{2+} blockers (DHPs)	→↓	↑	↓ (FN)
Renin inhibitors	↓	↓↑[1]	↑ (FP)[1] ↓ (FN)[1]
Potassium status			
Hypokalemia	↓	→↑	↓ (FN)
Potassium loading	↑	→↓	↑ (FP)
Dietary sodium			
Sodium restricted	↑	↑↑	↓ (FN)
Sodium loaded	↓	↓↓	↑ (FP)
Advancing age	↓	↓↓	↑ (FP)
Other conditions			
Renal impairment	→	↓	↑ (FP)
PHA-2	→	↓	↑ (FP)
Pregnancy	↑	↑↑	↓ (FN)
Renovascular HT	↑	↑↑	↓ (FN)
Malignant HT	↑	↑↑	↓ (FN)

ACE, Angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; DHP, dihydropyridine; FP, false positive; FN, false negative; HT, hypertension; NSAID, nonsteroidal antiinflammatory drug; PHA-2, pseudohypoaldosteronism type 2 (familial hypertension and hyperkalemia with normal glomerular filtration rate).

1 Renin inhibitors lower PRA but raise DRC. This would be expected to result in false-positive ARR levels for renin measured as PRA and false negatives for renin measured as DRC.

For an ideal test the patient would stop any diuretics for at least 4 weeks and other interfering medicines at least two weeks before testing and blood pressure could be managed with verapamil, alpha blockers and hydralazine. Potassium would be treated with oral supplements. The potassium supplement would be stopped two days before testing to avoid aldosterone stimulation from intestinal absorption of potassium. The patient should be upright for two hours and the blood drawn at 8 AM in the sitting position in a quiet room and without a tourniquet. The potassium should not be less than 3.5 to avoid aldosterone suppression, because aldosterone secretion in primary aldosteronism responds to hypokalemia though it does not respond to angiotensin II.

This might be able to be done in a research setting, but is not practical for a screening test in clinical practice. This was demonstrated in a trial of 25 patients with essential hypertension and 25 patients with primary aldosteronism. They attempted to follow the Endocrine Society Guidelines[17] and stop all interfering medications before screening the subjects with an ARR. Only 26 of 50 patients could be studied under optimal conditions. Of the 25 primary aldosteronism patients, 7 had potassium levels less than 3 meq/L and 6 had serious adverse events requiring hospitalization[18]. An alternative is to interpret the results based on what medicines and other factors are affecting the ratio. This approach is typically done in most practices. If there is either a high or low clinical suspicion for the disease and the ratio does not match, the ratio can be repeated after changing medications or the patient can proceed to a confirmatory test.

Use of the ARR has resulted in increased cases of primary aldosteronism being diagnosed and many of these cases were not associated with hypokalemia. This was demonstrated in a retrospective review of five hypertension centers. All five centers over time changed from screening with hypokalemia and elevated aldosterone levels to an elevated ARR. The rate of primary aldosteronism increased by 5 -15 fold and the prevalence of hypokalemia was quite low at 9 to 37 percent. Since bilateral adrenal hyperplasia tends to be milder, this accounted for the majority of new cases detected. However, the number of aldosterone producing adenomas increased in all centers by 1.3 to 6.3 fold indicating that screening with the ARR will result in more surgically curable cases. This paper also demonstrated the variability in the use of the ARRs. Two groups used ratios of greater than 20 with an aldosterone level of more than 15. One group used a ratio of 40 with an aldosterone level greater than 15. Another required a ratio of 25 and another required a level of 30 and neither required an absolute cutoff for aldosterone.

Guidelines on the diagnosis, workup and treatment of primary aldosteronism were published in 2008. Recommended values for the ARR could not be determined. Instead they decided to leave clinicians the flexibility to judge for themselves[17]. Most hypertensive specialists will evaluate the aldosterone and renin levels together with the clinical suspicion for primary aldosteronism and

not depend on a ratio. If the levels appear inaccurate, the levels can be repeated after stopping interfering medicines and controlling the potassium level. Or they can proceed to a confirmatory test realizing that random aldosterone and renin levels are merely a screening test. On the other hand, clinicians with little or no experience in evaluating these levels will want a ratio to guide them. The ARR I recommend is 20 with an aldosterone level greater than 10 to justify referral to a specialist for further evaluation.

The incidence of primary aldosteronism is higher than we once anticipated and hypokalemia is not seen in the majority of patients and there are increased cardiovascular events in this disease. Therefore should all hypertensive patients be screened? To answer this one must consider the cost of screening both from a patient safety standpoint and fiscally. The cost of aldosterone and renin levels performed at the Mayo Clinic is 450 dollars and with 75 million hypertensive patients in the United States, the cost for screening all of them would be 34 billion dollars. When a low risk population is screened, there will be many false positives that will require further testing and inappropriate changes in therapy. Therefore to be effective, the following patients should be screened: Patients with diuretic induced hypokalemia or spontaneous hypokalemia; Patients with resistant hypertension defined as a blood pressure greater than 140/90 on three blood pressure medicines at maximal doses including a diuretic; Hypertensive patients with a family history of primary aldosteronism in order to exclude hereditary causes of primary aldosteronism.

Confirmatory testing.

Once the patient has a positive screening test, the next step is to confirm the findings with a suppression test. There is less controversy over the values required for confirmatory testing. But there are 4 to choose from. The mechanism in each is to fully suppress angiotensin II production and then measure aldosterone levels to see if it also suppresses.

The easiest test to perform is the captopril suppression test. As originally described in 1983, 25 mg of Captopril is given and aldosterone and renin levels are drawn before and 2 hours after the captopril is given. A positive test for primary aldosteronism is an ARR of greater than 50 and an aldosterone level of greater than 15 after the captopril[19]. This test has the lowest sensitivity and specificity and is the least used test in the literature. It has been used as a screening test instead of a confirmatory test in some centers.

In contrast to the captopril suppression test, the fludrocortisone suppression test is difficult to perform but is considered the gold standard for confirmation. In this test fludrocortisone is given at a dose of 0.1 mg every 6 hours and oral sodium loading of 20 meq three times per day is given with meals. An aldosterone level at 10 AM on the 4th day of greater than 6 ng/dl is considered a positive test [20]. Most centers admit the patient to the hospital because of the need to measure potassium every 6 hours and give supplements to prevent hypokalemia which can suppress the aldosterone level. Because of these requirements this test is not used frequently.

The saline infusion test as described in 1971 requires 2 liters of intravenous saline while recumbent over 4 hours. An aldosterone level is measured at the end of the infusion. The test is positive if the aldosterone level is greater than 5 ng/dl[21]. Some authors have chosen a level of greater than 10 as a positive test. A level of 5 to 10 could be considered consistent with bilateral adrenal hperplasia. This test is the preferred test for the nephrology division at the VA North Texas Healthcare System because we have a dedicated nurse that performs this test in our procedure room.

Oral salt loading requires 150 to 200 meq of sodium per day for three days confirmed with a 24 hour urine for sodium. This can be accomplished with a high salt diet or supplements of sodium chloride tablets. A 24 hour urine aldosterone level of greater than 12 mcg is considered a positive test. This test avoids the need to give intravenous saline but requires collection of 24 hour urine with the associated unreliability for an adequate collection. The cutoff for a positive test in the literature ranges from 10 to 20. This test avoids problems with episodic release of aldosterone seen in a single serum sample done with the saline infusion test.

Imaging

Once primary aldosteronism is confirmed, lateralization should be determined. Imaging with computed tomography or magnetic resonance imaging is unreliable because of incedentalomas or aldosterone producing adenomas that are too small to image or unilateral adrenal hyperplasia. Nwariaku et al. at this institution showed that the concordance rate between imaging and adrenal vein sampling was only 54%. This was particularly true when both adrenal glands were abnormal[22]. Adrenal vein sampling should therefore be done prior to imaging with CT or MRI so that the results do not influence the interpretation of the adrenal vein sampling.

Adrenal vein sampling has many pitfalls that need to be recognized before the results can be properly interpreted. A catheter is placed into both adrenal glands where both aldosterone and cortisol can be sampled. The cortisol is used to determine if the adrenal vein was properly sampled. A ratio between the sampled adrenal vein and the inferior vena cava is determined. Similar to the other values in this disease, there is controversy about what ratio should be used. At a minimum, the ratio of the adrenal vein to inferior vena cava cortisol ratio should be greater than 3[23]. Cortisol levels are inexpensive and can be done rapidly in less than an hour where aldosterone levels are expensive and are usually sent to outside labs. So ideally the radiologist would take the samples and wait for the cortisol results before removing the sheaths and sending the patient home. Most centers will infuse cosyntropin so that episodic release of cortisol will not affect the results, but again this is not standardized. Some centers will cannulate both femoral veins so that simultaneous samples can be obtained to avoid episodic secretion. Once the samples are determined to be adequate the samples can be sent for aldosterone levels. To determine lateralization the aldosterone cortisol ratio of one gland is compared to the ratio of the contralateral gland. A ratio of greater than 4 suggests lateralization and is an indication for surgical removal of that adrenal gland.

Sampling is never perfect and this can affect the results that the clinician has to use for interpretation. The right adrenal vein drains into the inferior vena cava and is frequently confused with hepatic veins even with the assistance of venography. It is a small vein with a very limited blood flow draining into a high flow vena cava. Even with a good location of the catheter tip the sample is usually contaminated with vena cava blood. The left adrenal vein drains into the left renal vein. Because it is the only vein that drains into the left renal vein and the angle is better, it is much easier to sample than the right adrenal vein. The left adrenal vein is larger than the right reducing the chance that blood will contaminate the sample from the renal vein. However the left phrenic vein drains into it diluting the sample. Sampling a branch that is not draining the aldosterone producing adenoma could give a false negative result on lateralization. Complications are rare and include thrombosis of the vein with infarction and loss of the gland or hemorrhage.

An alternative approach for lateralization is I131 labeled norcholesterol (NP59) scanning. It requires iodide loading and like other radio pharmaceuticals it is very expensive. It loses it sensitivity for adenomas less than 3 cm in size and is hard to obtain. Most centers prefer the use of adrenal vein sampling if they have radiologists experienced in this procedure.

Hereditary forms

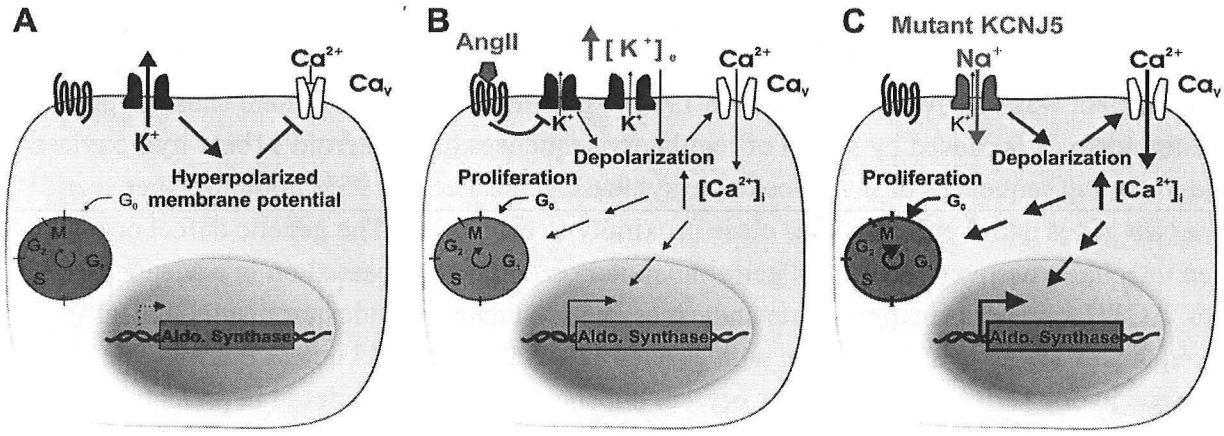
There are familial forms of primary aldosteronism that need to be considered so that appropriate therapy and family screening can be performed. There are three known hereditary forms designated as familial hyperaldosteronsim (FH) I, II and III. Familial hyperaldosteronsim type I is also called glucocorticoid remediable aldosteronism and was originally described in 1965. The genetic defect was discovered by Lifton in 1992[24]. It is an autosomal dominant cause of primary aldosteronism. It is caused by fusion of regulatory sequences of the steroid 11beta-hydroxylase gene to coding sequences of the aldosterone synthase gene. There is 95% homology between these two genes and they are in very close proximity to each other. The genetic defect occurs when unequal crossover occurs as a germline mutation and is then passed on in a Mendelian form. ACTH stimulates inappropriate and excessive production of aldosteronism. Clinical consequences are early hypertension with strokes before the age of 45 unless treated. The incidence in one series was less than 1 percent but should still be considered in patients with a family history of primary aldosteronism and early hypertension. Diagnosis can be suspected if there are elevated levels of 18-oxocortisol or 18-hydroxycortisol and confirmed with demonstration of the hybrid gene by long PCR. However none of these tests are commercially available. The diagnosis can also be made with a dexamethasone suppression test. An aldosterone level is measured after four days of dexamethasone and should be suppressed less than 5 ng/dl.

Familial hyperaldosteronsim II is clinically indistinguishable from non-hereditary primary aldosteronism. The diagnosis is made by confirming primary aldosteronism in 2 family members in a patient who also has this disease. It can cause either bilateral adrenal hyperplasia or an

aldosterone producing adenoma. It has an autosomal dominant inheritance pattern. The incidence is around 7 percent in patients with primary aldosteronism in one series. The gene has not yet been identified but linkage analysis has located it on chromosome 7.

Familial hyperaldosteronsim III has only been found in a single family and is of academic but not clinical interest. A father and his two daughters all had severe hypertension, aldosteronism and severe adrenal hyperplasia with a paired adrenal weight of up to 81 grams (normal less than12 grams) diagnosed between the ages of 4 and 7. All three had bilateral adrenalectomies. Genome wide sequencing of adrenal adenomas from 22 unrelated patients with adrenal producing adenomas showed mutations of KCNJ5 in 8 of these patients. KCNJ5 in the above family was also shown to be mutated.

KCNJ5 is a K specific channel that is open in the resting state and causes hyperpolarization of the adrenal glomerulosa cells. Depolarization of the cell can be caused either by a high extracellular K concentration that limits K exit or by closing the channel when angiotensin II binds to its extracellular receptor. Depolarization in turn opens voltage regulated Ca channels allowing Ca to enter the cell that turns on both aldosterone synthase and cell proliferation. Mutations in KCJN5 reduce the selectivity for K and increases inward sodium influx. Leakage of sodium into the cell keeps it depolarized resulting in excess aldosterone synthesis and cellular proliferation that results in an adenoma that is not suppressed by low levels of angiotensin II but can be partially suppressed by hypokalemia[25].



Proposed mechanism underlying aldosterone-producing adenoma and Mendelian aldosteronism. (A) Adrenal glomerulosa cells have a high resting K+ conductance, which produces a highly negative membrane potential (2). (B) Membrane depolarization by either elevation of extracellular K+ or closure of K+ channels by angiotensin II activates voltage-gated Ca2+ channels, increasing intracellular Ca2+ levels (1). This provides signals for increased expression of enzymes required for aldosterone biosynthesis, such as aldosterone synthase, and for increased cell proliferation. (C) Channels containing KCNJ5 with G151R, T158A, or L168R mutations conduct Na+, resulting in Na+ entry, chronic depolarization, constitutive aldosterone production, and cell proliferation. Choi, et al. Science 2011[25]

Differential

Before treatment is given for primary aldosteronism or for cases of resistant hypertension and/or hypokalemia that do not have an elevated ARR, one must consider an appropriate differential. Table 4 shows a list of secondary hypertension that should be considered initially in all patients presenting with hypertension.

Table 4: Secondary causes of hypertension

Ingestion/Medications	Hereditary	Endocrine	Kidney related	Other
Calcineurin inhibitors	Polycystic kidney disease	Hyperthyroidism	Ask-Upmark kidney (segmental renal hypoplasia)	Non-compliance
Oral contraceptives	Gordon's syndrome	Hypothyrodism	Renal artery stenosis	Pregnancy
MAOIs	Liddle's Syndrome	Hyperparathyrodism	Chronic kidney disease	White Coat Hypertension
Corticosteroids	11 β hydroxylase deficiency	Pheochromocytoma		Scleroderma
Heavy ethanol use	Apparent mineralocorticoid excess	Cushing's Disease		Sleep apnea
Nicotine	Neurofibromatosis	Acromegaly		Obesity
Cocaine	Fibromuscular dysplasia	Primary aldosteronism		Anemia
Amphetamines		Renin secreting tumor		Fever
Midodrine		ACTH secreting tumor		Coarctation of the aorta
Heavy metals		Cortisol producing adenoma		
Erythropoietin				

For hypokalemia one must consider diuretic use or hereditary causes that resemble diuretic use. Use of thiazide diuretics and loop diuretics will cause both an elevated renin and aldosterone levels and should be discontinued at least 4 weeks before obtaining aldosterone and renin levels. Barter's syndrome is a variety of 5 different gene mutations that affect different proteins in the thick ascending limb of the loop of Henle and mimic loop diuretic use. Some varieties can present in young adults. Gittleman's syndrome is caused by a mutation in the sodium chloride transporter in the distal tubule and mimics thiazide use[26,27]. The features are less severe than Bartter's syndrome and can present in adulthood. Both syndromes have hypokalemia and elevated aldosterone levels but can be differentiated from primary aldosteronism based on low blood pressure and elevated renin levels.

Gordon's syndrome is associated with hypertension, hyperkalemia and metabolic acidosis and is also called pseudohypoaldosteronism type II. Renin is suppressed and aldosterone can be elevated resulting in an elevated ARR. It is caused by mutations in WNK1 or WNK4 kinases

that affect the thiazide sensitive sodium chloride co-transporter (NCC) in the distal tubule. These patients can present as adults with hypertension resistant to non-thiazide blood pressure medications but respond to treatment with thiazide diuretics or low sodium diets[28,29].

Liddle's syndrome can cause hypokalemia and hypertension with suppressed renin and aldosterone levels with a low ARR. It is caused by an activating mutation in the gene for the epithelial sodium channel (ENaC) in the distal tubule. This channel in normal health is up-regulated by aldosterone and causes resporption of sodium in exchange for potassium and hydrogen ions, but cannot be down regulated in Liddle's syndrome. Amiloride blocks ENaC and is effective in treating the hypertension and hypokalemia but spironolactone is not. This response to amiloride can be used to diagnose Liddle's syndrome

Licorice ingestion should be considered in patients with hypertension and hypokalemic metabolic alkalosis with suppressed renin and aldosterone levels. Cortisol can bind to aldosterone receptors and circulates at a much higher concentration than aldosterone. In order to prevent cortisol from interacting with aldosterone receptors in the kidney, 11 beta - hydroxysteroid dehydrogenase type II breaks down and inactivates cortisol. Glycyrrhetinic acid in licorice can inhibit this dehydrogenase and causes a disease similar to apparent mineralocorticoid excess. 100 mg of glycyrrhetinic acid can cause an increase in blood pressure and this is the amount found in around 50 grams of licorice candy[30,31]. Because the licorice plant is not native to the United States, licorice induced hypertension was thought to be only a problem in Europe and Asia where it is readily available. Over time, the availability of licorice in the United States has increased due to overseas marketing. So much so that in October of 2011, the United States Food and Drug Administration placed a warning on its consumer updates website warning Halloween celebrants to avoid ingesting too much black licorice because it could cause low potassium levels, edema, hypertension, heart failure and irregular heart rhythms.

Licorice root is quite sweet and has a distinct taste. This unique taste is used in chewing tobacco to improve the flavor and can cause an increase in blood pressure in tobacco chewers. A case of an elderly man with a severe case of licorice induced hypertension because he swallowed his tobacco juice instead of spitting it out was described at the Dallas VA Medical Center in 1980[32].

The inherited form of apparent mineralocorticoid excess is a rare autosomal recessive cause of hypertension. Most cases present in early childhood with failure to thrive, hypertension and hypokalemic metabolic alkalosis. They have a high mortality rate if not treated. These children have a mutation in the gene encoding 11β-hydroxysteroid dehydrogenase type 2 enzyme. Milder phenotypes have been described with only partial inactivation of the enzyme and these patients may present in adulthood. Treatment consists of mineralocorticoid receptor antagonists, salt restriction and potassium supplements[33,34].

Table 5: Differential diagnosis of primary aldosteronism

	Blood pressure	Renin	Aldosterone	Potassium	Genetic testing
Primary aldosteronism	high	low	high	low or normal	FH I only
Low renin hypertension	high	low	low or normal	normal	no
Malignant hypertension	high	high	high	low	no
Renal artery stenosis	high	high	high	low or normal	no
Renin secreting tumor	high	high	high	low or normal	no
Gittleman's syndrome	low	high	high	low	yes
Bartter's syndrome	low	high	high	low	yes
Liddle's syndrome	high	low	low	low or normal	yes
Gordon's syndrome	high	low	normal or high	high	yes
Licorice	high	low	low	low	no
Apparent mineralocorticoid excess	high	low	low	low	yes

FH I: Familial hyperaldosteronsim type I (Glucocorticod remdial aldosteronism). Liddle's syndrome will respond to amiloride but not spironolactone. Gordon's syndrome will respond to thiazide diuretics and/or low sodium diet.

Treatment

The desired goal in evaluating a patient for primary aldosteronism is to demonstrate the presence of an aldosterone producing adenoma that can be removed for a resolution of the hypertension, cardiovascular risks and electrolyte disorders. Laparoscopic adrenalectomy offers faster recovery time and can be done on patients with more comorbidities than an open adrenalectomy. Patients with bilateral adrenal hyperplasia typically do not respond to adrenalectomy and adrenalectomy is not indicated in these patients. There are some cases of unilateral adrenal hyperplasia without adenomas that respond to adrenalectomy. There are also cases of very small adenomas that are not visualized by imaging, but are found when the gland is removed and dissected.

Medical treatment can be offered if the patient is too ill or not willing to proceed with surgical removal or in patients with bilateral adrenal hyperplasia when demonstrated with adrenal vein sampling. Spironolactone was discovered in 1959 and is effective in lowering blood pressure and treating the electrolyte disorders in primary aldsoteronism. It does have significant side effects related to antagonism of the androgen receptor and antagonism of the progesterone receptor. This non specificity results in gynecomastia, impotence and decreased libido in males and menstrual irregularities and mastodynia in females and might limit the dose needed to fully suppress the effects of aldosterone.

Epleronone is a newer mineralocorticoid receptor blocker that is more selective and does not have the androgen and progesterone related side effects of spironolactone. The ½ life of eplerenone is less than spironolactone and requires twice daily dosing. Eplerenone at 100- 300 mg was compared to spironolactone at 75-225 mg in 141 patients with primary aldosteronism. Blood pressure progressively improved over 16 weeks in both groups. Eplerenone was better tolerated but was not as effective as spironolactone in lowering blood pressure. Seven patients (10%) of patients in the spironolactone group dropped out because of side effects vs. none in the epleronone group. Spironolactone reduced the diastolic blood pressure by 12.5 mm of Hg vs only 5.6 mm Hg in the epleronone group[35]. Efficacy studies have shown that eplerenone should be dosed at 2 to 3 times the dose of spironolactone. The recommended dose of eplerenone for hypertension is 50 mg twice daily (100 mg total dose per day) and is not FDA indicated for primary aldosteronism. Spironolactone is FDA indicated for primary aldosteronism at a maximum dose of 400 mg per day.

Alternatives to mineralocorticoid receptor blockers include amiloride if hypokalemia cannot be controlled. Another alternative is the new aldosterone synthase inhibitor currently called LCI699. This drug was studied in 14 patients with primary aldosteronism at a dose of 0.5 mg twice daily for 2 weeks and then increased to 1 mg BID for another two weeks. The plasma potassium levels improved and the blood pressure decreased with a decrease in the aldosterone levels. A potential advantage of an aldosterone synthase inhibitor over a mineralocorticoid receptor antagonist is less stimulation of non-genomic effects of aldosterone which are not mediated by the mineralocorticoid receptor.

Conclusions

The prevalence of primary aldosteronism in the hypertension population is not known but it most likely is much less than the 10 to 20 percent frequently quoted in the literature. A more reasonable estimate is somewhere between 1 and 5 percent. There is however a significant increased risk of cardiovascular events in patients with excess aldosterone production and patients with the appropriate risk factors should be screened with both aldosterone and renin levels. Perfect testing conditions for screening are very difficult to obtain and there is no agreement on what the appropriate ARR is for a positive test. Screening tests should always be confirmed with a confirmatory suppression test. The most commonly used confirmatory tests are the saline infusion test and the oral salt loading test. Like the aldosterone-renin ratio, there no consensus on the best confirmatory test or the appropriate values for a positive test.

The decision on which adrenal gland to remove should be based on adrenal vein sampling and not by imaging for the presence or lack of adrenal nodules. If there is lateralization, adrenalectomy is the most effective treatment. Medical treatment currently includes spironolactone or eplerenone. Aldosterone synthase inhibitors will most likely be used in the future.

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