HYPERALDOSTERONISM

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CASE PRESENTATION:

A 52 year old woman with no medical history was noted to have mildly elevated blood pressure on a routine physical exam, ~130/80 mmHg. In the subsequent two years, her blood pressure trended higher, ~140/90 mmHg. She was treated with lisinopril. One year later, she was found to have a blood pressure of 180/100 mmHg and serum potassium concentration was 2.3 mmol/L. After treatment with lisinopril, amlodipine, labetolol, and potassium chloride, her serum potassium and blood pressure normalized.

Her physician wondered whether her progressive hypertension and hypokalemia could be due to hyperaldosteronism. Since aldosterone excess has been associated with cardiovascular outcomes independent of blood pressure, she decided to conduct a work-up to evaluate for primary hyperaldosteronism.

INTRODUCTION

Aldosterone is the principal mineralocorticoid in man. Its classical functions include regulation of extracellular volume and potassium homeostasis through its effects on the renal distal convoluted tubule. In addition, the non-classical extra-renal actions of aldosterone, particularly on cardiovascular tissues, are now increasingly recognized and characterized for their role in human health.

Excess production of aldosterone, due to either primary or secondary disorders, is prevalent in the general population, and is an important cause of morbidity and mortality. This chapter reviews the physiology of aldosterone action, as well as the clinical features, biochemical diagnosis, and treatment of hyperaldosteronism.

ALDOSTERONE REGULATION AND ACTION
A. Aldosterone Biosynthesis and Regulation

Aldosterone is synthesized in the zona glomerulosa of the adrenal gland. Its production is restricted to this layer of the adrenal cortex because of zonal-specific expression of aldosterone synthase (CYP11B2). Aldosterone secretion is under the control of three primary factors: angiotensin II, potassium, and adrenocorticotropic hormone (ACTH).

The renin-angiotensin system (RAS) is a principal regulator of aldosterone secretion. Renin, an enzyme produced in the juxtaglomerular apparatus of the kidney, catalyzes the conversion of angiotensinogen (an inactive precursor peptide) to angiotensin I (**Figure 1**). Angiotensin I undergoes further enzymatic conversion by angiotensin-converting enzyme (ACE) to produce angiotensin II. Angiotensin II acts via the adrenal angiotensin receptor to stimulate the release of aldosterone by increasing the transcription of aldosterone synthase. The physiologic role of the RAS is to regulate sodium homeostasis and arterial pressure. For example, renin (and consequently aldosterone) production is stimulated by low tubular sodium or low renal perfusion. Conversely, renin is suppressed by high sodium content or high perfusion pressure. Angiotensin II and other components of the RAS are also expressed locally in the zona glomerulosa and regulate aldosterone production in a paracrine fashion. Through complex negative feedback loops (**Figure 1**), activity of the RAS can be suppressed or enhanced by sodium balance, intravascular volume, and other factors.

Aldosterone secretion is also directly stimulated by potassium (**Figure 1**), which increases transcription of aldosterone synthase in the zona glomerulosa. ACTH is another aldosterone secretagogue, although its effect is modest and transient; prolonged and sustained ACTH infusion leads to a return of aldosterone levels to baseline[1].

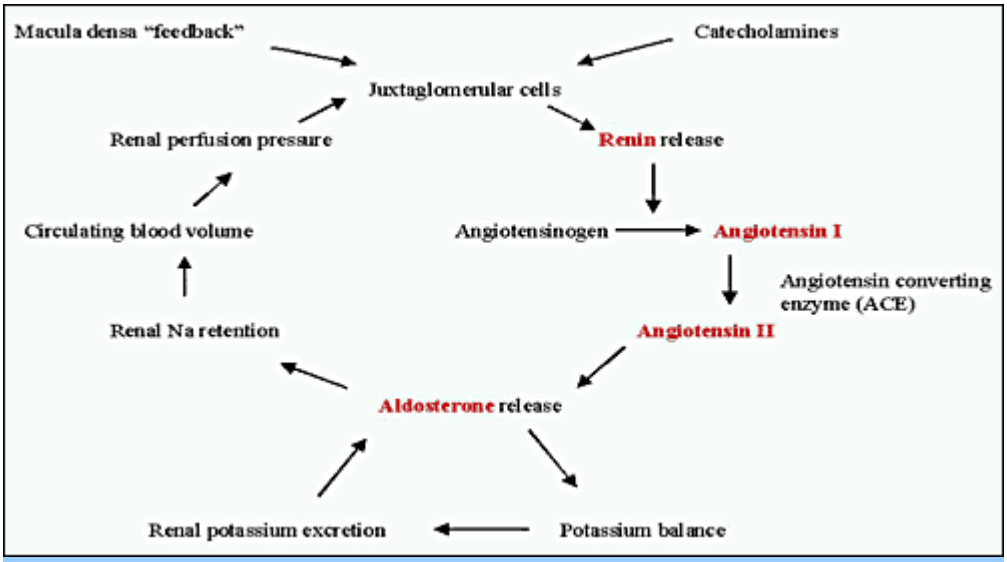


Figure 1. Renin-angiotensin-aldosterone and potassium-aldosterone negative-feedback loops. Aldosterone production is determined by input from each loop. (Adapted and redrawn from Williams GH, Dluhy RG. Disease of the adrenal cortex. In: Fauci AD, Braunwald E, Isselbacher KJ, et al, eds. Harrison's Principles of Internal Medicine. 15th ed. New York: McGraw-Hill, 2001)

B. Physiologic Actions of Aldosterone

The classical physiologic functions ascribed to aldosterone are the regulation of extracellular volume and potassium balance. These effects are mediated through the effects of aldosterone on the distal nephron. Aldosterone binds to the type I mineralocorticoid receptor in the cytosol of distal cortical collecting principal cells. Translocation of the hormone-receptor complex to the nucleus leads to modification of target gene expression, and subsequently increased number of available sodium channels on apical cell membranes. The resulting increase in sodium resorption generates a negative electrical gradient in the tubular lumen, which promotes potassium and hydrogen ion excretion to maintain electrical neutrality[1,2].

C. Pathophysiologic Actions of Aldosterone

Emerging evidence has implicated aldosterone, and specifically activation of the mineralocorticoid receptor, with cardiovascular and cardiometabolic diseases[3]. These non-classical effects of aldosterone have stemmed from dysregulated aldosterone physiology being linked with deleterious end-organ effects. Typically, this has been evidenced by inappropriately elevated levels of aldosterone in the setting of high dietary sodium intake (subclinical or clinical primary hyperaldosteronism). However, some evidence also suggests that inappropriately low levels of aldosterone on a restricted sodium diet, or in response to angiotensin II, are also associated with adverse cardiometabolic consequences[4-6].

Excess aldosterone activity has been associated with or shown to cause cardiac fibrosis, inflammation, and remodeling[7-9], pathologic insulin secretion and/or peripheral resistance, as well as the metabolic syndrome[6,10-15], kidney injury[16], and increased mortality[17-19]. Intervention studies in animal and man have supported these assertions by demonstrating the prevention of these deleterious effects with the use of mineralocorticoid antagonists[17,20]. Taken together, this evolving body of evidence points towards subclinical aldosterone excess, particularly in the milieu of excessive dietary sodium intake, as a modifiable cardio-metabolic risk factor.

Patients with primary aldosteronism (PA), when compared with matched essential hypertensives, have increased left ventricular wall and carotid intima media thickness, as well as impaired diastolic and endothelial function[3,21-23]. PA is also associated with higher incidence of cardiovascular outcomes (myocardial infarction and stroke) than essential hypertension with similar degree of blood pressure elevation[24-26]. The excess cardiovascular events associated with hyperaldosteronism appear to be reversible if treatment with mineralocorticoid antagonists (or surgery) is implemented in time[27,28].

EPIDEMIOLOGY OF ALDOSTERONE EXCESS

A. Epidemiology of Primary Hyperaldosteronism

In 1954, Conn first reported the clinical syndrome of hypertension, hypokalemia, and metabolic alkalosis resulting from autonomous production of aldosterone due to an adrenal adenoma – a syndrome that continues to bear his name. Since that time, numerous studies have investigated the prevalence of primary aldosteronism (PA) and reported rates between 0.05% and 14.4% among hypertensive individuals. Disparity in these percentages is probably due to the use of different laboratory screening techniques, study design, and varying population ethnicity and sampling source[10,29-34]. Initial studies primarily diagnosed patients with PA if they had both hypertension and spontaneous (not diuretic-induced) hypokalemia. More recent reports, however, describe hypokalemic

PA in only the minority of PA cases (<40%)[35], and describe an intermediate phenotype of normetensive PA with milder manifestations than the classic hypertensive PA[36].

Accumulating evidence suggests that approximately 10% of hypertensive individuals (mostly sampled from specialty clinics) may have primary hyperaldosteronism[29,37]. In patients with resistant hypertension, the addition of a mineralocorticoid antagonist has been associated with substantial efficacy in blood pressure lowering, suggesting that subclinical hyperaldosteronism may be more prevalent than recognized[38,39]. On-going studies continue to examine the role of mild or subclinical primary aldosteronism in resistant forms of hypertension.

CAUSES OF HYPERMINERALOCORTICOIDISM

Mineralocorticoid excess states (**Table 1**) comprise a group of disorders that can be separated into those mediated by the principal mineralocorticoid, aldosterone, and those caused by non-aldosterone etiologies. This chapter focuses on the former. Non-aldosterone mediated mineralocorticoid excess states, including the syndrome of Apparent Mineralocorticoid Excess (AME) and Liddle's Syndrome are discussed further in Chapter 26 ("Overview of Endocrine Hypertension").

Hyperaldosteronism can result from autonomous secretion of aldosterone from one or both adrenal glands, which is referred to as primary aldosteronism (PA). In this circumstance, the plasma renin activity (PRA) is suppressed (*hyporeninemic hyperaldosteronism*), and the plasma aldosterone to renin activity ratio is elevated. In secondary hyperaldosteronism, increased activation the RAS is the initiating event, and activation of the RAS then results in excess aldosterone production (*hyperreninemic hyperaldosteronism*). Therefore, secondary hyperaldosteronism can be a normal physiologic phenomenon (such as in states of systemic hypovolemia or hypoperfusion), or can manifest as a pathologic entity when activation of the RAS is inappropriate relative to the state of the systemic vasculature. The distinction between primary and secondary causes of hyperaldosteronism is of importance, as the manifestations, as well as the subsequent testing and treatment, differ.

Table 1: Mineralocorticoid-Excess State

Mineralocorticoid Excess with low plasma renin activity

- Primary Aldosteronism (PA)
  - Aldosterone-producing adenoma (APA)
  - Idiopathic bilateral hyperplasia (BAH)
  - Unilateral primary adrenal hyperplasia (UAH)
  - Glucocorticoid-remediable aldosteronism (GRA)
  - Aldosterone-producing adrenocortical carcinoma
- Congenital adrenal hyperplasia (e.g., 11beta-hydroxylase deficiency)
- Syndrome of Apparent Mineralocorticoid Excess (AME)*
- Liddle's syndrome*

Mineralocorticoid Excess with high plasma renin activity (Secondary Hyperaldosteronism)

- Usually Hypertensive
  - Renovascular disease (atherosclerotic, fibromuscular hyperplasia)
  - Coarctation of the aorta
  - Renin-secreting tumors
- Usually Normo- or Hypotensive
  - Reduced Circulating Blood Volume:
    - Gitelman's Syndrome
    - Bartter's Syndrome

▪ Pseudohypoaldosteronism Type I ▪ Diuretic Use (surreptitious or prescribed therapy) ○ Reduced 'Effective' Circulating Blood Volume: ▪ Congestive Heart Failure ▪ Hepatic cirrhosis ▪ Nephrotic Syndrome
*In these disorders, non-aldosterone mediated renal sodium reabsorption results in volume expansion and suppression of both plasma renin activity and plasma aldosterone.

A. Causes of Mineralocorticoid Excess With Low Plasma Renin Activity

1) Primary Hyperaldosteronism: The five subtypes of PA include: aldosterone-producing adenoma (APA), bilateral adrenal hyperplasia (BAH), unilateral adrenal hyperplasia (UAH), glucocorticoid-remediable aldosteronism (GRA), and, rarely, adrenal carcinoma (**Table 1**). Recent advances in genetics have dramatically enhanced our understanding of the pathogenesis of APA, UAH, and BAH, and have raised the question of whether these entities are part of the same spectrum of disorders.

a) APA/BAH/UAH: It is currently estimated that APA or UAH account for 30-40% of PA cases, whereas BAH accounts for the remaining 60%[41-43]. Definitive diagnosis of the cause of PA can be a challenge in individual patients (see Diagnosis Section); however, making the correct diagnosis is of utmost importance, since the treatment for each underlying etiology may be different.

APA's are often small tumors, usually less than 2 cm in diameter. Histopathology of APA reveals hybrid cells which have histological features of both zona glomerulosa and zona fasciculata cells. Unilateral adrenal hyperplasia (UAH), sometimes referred to as primary adrenal hyperplasia, shares many biochemical features with APA. This diagnosis is often made based on evidence of unilateral production of aldosterone (primarily from adrenal vein sampling, see Diagnosis Section) in the absence of a discrete radiographic mass. Similar to APA, the hypertension and biochemical abnormalities with UAH may be cured or substantially ameliorated with unilateral adrenalectomy[43,44].

BAH probably represents a spectrum of disorders[30,45]. The extent of hyperaldosteronism is often milder in BAH compared to APA, and consequently the severity of hypertension, hypokalemia and suppression of PRA is often less.

Genetic Insights Into the Causes of APA/BAH/UAH: Recent advances in the genetics of PA have provided novel insights into the pathogenesis of APA/BAH/UAH. For decades two forms of familial hyperaldosteronism were recognized: FH-I (also known as GRA, described below) and FH-II (a familial disease without unique phenotypic features or known genetic underpinnings). However, Lifton *et al*. recently described a new familial form of PA (FH-III)[46] that was associated with germline mutations in *KCNJ5*, a gene that encodes the inwardly-rectifying potassium channel GIRK4[47]. This family had severe childhood-onset hypertension, hypokalemia, very high aldosterone-to-renin ratio, with marked adrenal enlargement and diffuse hyperplasia of the zona fasiculata.

This discovery set off international research efforts to investigate the role of potassium channel mutations in PA. Although the prevalence of *KCNJ5* germline mutations is considered to be extremely low[48-50], investigators have now reported the presence of *KCNJ5* somatic mutations in 30-50% of patients with APA's that were previously

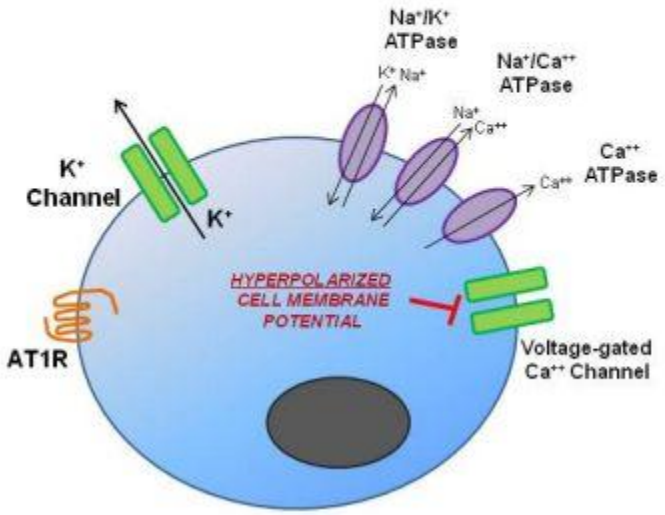
classified as sporadic[48,51-57]. Hence, the discovery of a rare familial form of PA has resulted in the understanding that somatic potassium channel mutations may be a highly prevalent cause of PA. In general, from the reports to date, somatic mutations in *KCNJ5* appear to be associated with female gender, younger age, and higher aldosterone levels; however, these descriptions may reflect a significant sample selection bias.

Normally, adrenal zona glomerulosa cells maintain a hyperpolarized resting membrane potential that is largely regulated by potassium current. Depolarization of the cell (either by angiotensin II or hyperkalemia mediated inhibition of the potassium current) results in the opening of voltage-gated calcium channels, increased intracellular calcium signaling, and stimulation of aldosterone synthase. A gain-of-function mutation in GIRK4 results in sodium influx, cell depolarization, and increased aldosterone synthesis[58,59] (**Figure 2**). In this manner, mutations in channels that regulate the resting potential of zona glomerulosa cells have been implicated in the development of hyperaldosteronism. How these mutations may result in proliferation and adenoma production is less well understood, but it is speculated that aberrant and excessive intracellular calcium signaling may result in hyperplasia (UAH or BAH) and ultimately adenoma (APA). This understanding provoked further international collaborative research, especially among European research teams, to investigate the role of other cell membrane channels involved in maintaining zona glomerulosa cell resting potentials. This research has resulted in the discovery of somatic mutations in the sodium-potassium-ATPase and calcium-ATPase in the pathogenesis of PA[60].

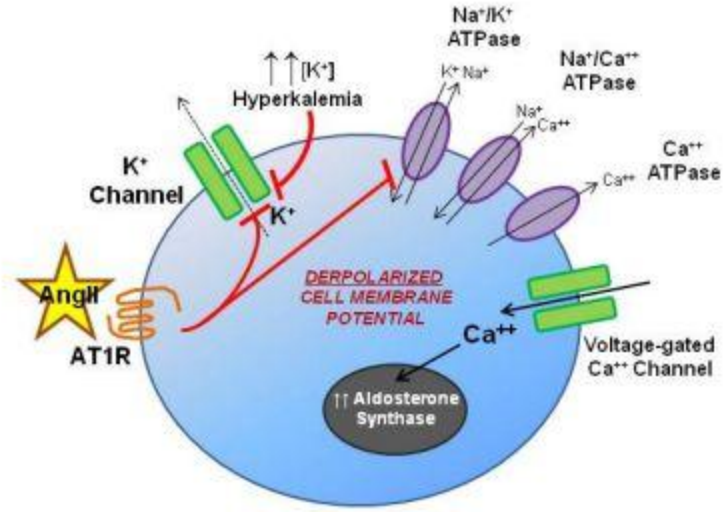
With continued collaborative research, it is expected the number of mutated gene products regulating the resting potential of zona glomerulosa cells implicated in the pathogenesis of PA will grow. Whether the identification of these mutations will translate to treatment modalities remains to be seen.

FIGURE 2: Adrenal zona glomerulosa cell membrane potential and *KCNJ5* mutations.

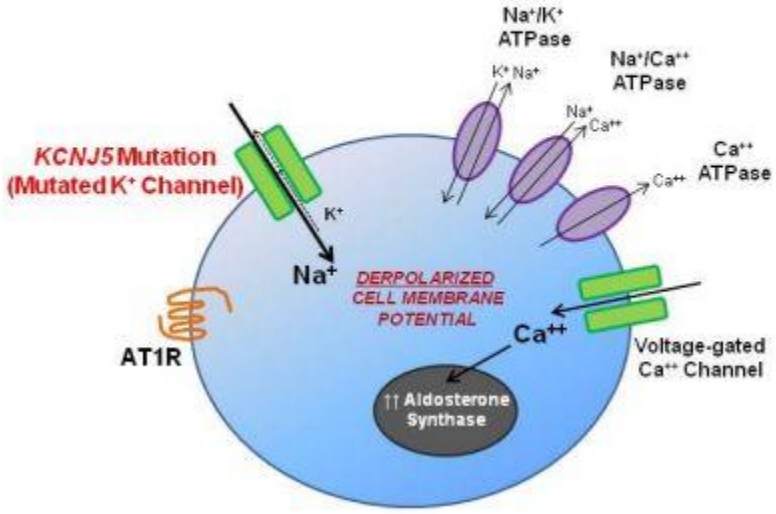
A. Normal resting equilibrium: The normal resting membrane potential of zona glomerulsa cells is hyperpolarized thereby preventing calcium influx by inhibiting voltage-gated calcium channels.



B. Normal aldosterone stimulation: Activation of the angiotensin receptor (AT1R) by angiotensin II (AngII), or extracellular hyperkalemia, results in depolarization of the cell and resultant calcium influx via activated voltage-gated calcium channels. Calcium influx activates signaling to increase expression of aldosterone synthase and ultimately aldosterone production.



C. *KCNJ5* mutations: Mutations in *KCNJ5* result in permeability to Na^+, resultant depolarization, and calcium influx via voltage-gated calcium channels. Similarly, mutant Na^+/K^+-ATPase and Ca^{++}-ATPase result in cell membrane depolarization and calcium influx.



b) Glucocorticoid-remediable aldosteronism: GRA (also known as familial hyperaldosteronism type I) is an autosomal dominant disorder characterized by a chimeric duplication, whereby the 5'-promotor region of the 11β-hydroxylase gene (regulated by ACTH) is fused to the coding sequences of the aldosterone synthase gene in a recombination event. The result is that the aldosterone synthase gene (CYP11B2) is under the control of the promoter for the CYP11B1 gene, typically responsible for cortisol production under the regulation of ACTH. Aldosterone synthesis is therefore abnormally and solely regulated by ACTH[61,62].

c) Adrenal Carcinoma: Adrenal carcinomas are an exceedingly rare cause of primary aldosteronism. At the time of diagnosis, adrenal carcinomas are usually large (>4 cm) and may be producing one or multiple adrenal cortical hormones, including cortisol, aldosterone, and adrenal androgens. Adrenal carcinoma usually cannot be differentiated from adrenal adenoma on the basis of fine needle aspiration. Rather, the diagnosis is based upon evidence of extension of the tumor through the adrenal capsule or a high mitotic index on histological examination.

2) Congenital Adrenal Hyperplasia: Other mineralocorticoid-excess states with low plasma renin activity include congenital adrenal hyperplasia (CAH), the syndrome of apparent mineralocorticoid excess (AME), and Liddle's syndrome. CAH, most often diagnosed in infancy, results from inherited defects in enzymes that regulate cortisol biosynthesis. Ineffective glucocorticoid synthesis (depending on the enzymatic block) can result in excess mineralocorticoid (such as 11-deoxycorticosterone) and androgen production as precursors are shunted from blocked to unblocked pathways[63]. Sometimes there is marked virilization of female infants in the most severe form of CAH. When adequately treated with glucocorticoids, however, abnormal mineralocorticoid production is reversed[63].

3) Apparent Mineralocorticoid Excess and Liddle's syndrome: AME results from abnormal activation of the Type I mineralocorticoid receptor in the kidney by cortisol, secondary to an acquired (licorice ingestion or chewing tobacco) or congenital deficiency of the renal isoform of the enzyme 11β-OH steroid dehydrogenase (11β-HSD). The 11β-HSD2 isoenzyme normally metabolizes cortisol to the inactive compound cortisone in the renal distal convoluted tubule[63,64]. However if there is 11β-HSD deficiency, the Type I mineralocorticoid receptor is no longer 'protected' from activation by cortisol. In Liddle's syndrome, constitutive activation of the renal epithelial sodium channel (ENaC) results from activating mutations in the ENaC gene. In both AME and Liddle's syndromes, the intrinsic renal abnormalities described lead to unregulated and excessive sodium reabsorption, and therefore a biochemical phenotype of suppressed PRA, hypokalemia, and undetectable levels of plasma aldosterone[64].

B. Causes of Mineralocorticoid Excess With High Plasma Renin Activity (Secondary Aldosteronism)

Secondary hyperaldosteronism is the result of the hypersecretion of aldosterone as a consequence of increased activation of the renin-angiotensin system (RAS). The subgroups are best understood by contrasting the etiologies that usually produce hypertension from those that do not (**Table 1**).

1) Usually Normo- or Hypotensive: The most common causes of secondary aldosteronism are medical illnesses that result from a reduction in perceived or effective circulating blood volume, such as congestive heart failure and nephrotic syndrome. Secondary hyperaldosteronism in these disorders is the result of renal baroreceptor activation and thus a physiologic response to the decompensated state. Importantly, treatment and correction of the underlying medical illness results in reversal of the activated RAS.

Diuretic use can also cause secondary hyperaldosteronism. The findings can mimic those seen in renovascular hypertension, especially in a hypertensive patient. With chronic diuretic use, moderate to severe extracellular and intravascular volume depletion results in renal hypoperfusion, increased release of renin, and subsequently excessive aldosterone production. In rare occasions, surreptitious use of diuretics can produce misleading biochemical findings. A high degree of suspicion should be

present in the appropriate setting, such as unexplained hypokalemia in a medical or paramedical worker or an individual attempting to lose weight using pharmacologic methods.

2) Usually Hypertensive: It is important to distinguish renal vascular *disease* from renal vascular *hypertension*. While a large proportion of the adult population may have renal vascular disease (defined as a 50% or greater decrease in renal artery luminal diameter), only a small portion of these patients experience critical renal hypoperfusion and ischemia[40]. Therefore, documentation of both *structural* and *functional* abnormalities is required before therapeutic intervention in such patients.

Renovascular hypertension remains the most common cause of secondary aldosteronism associated with hypertension, and is defined as hypertension associated with either unilateral or bilateral ischemia of the renal parenchyma. There are numerous causes of this disorder. Atherosclerosis of the renal arteries is the most common, accounting for 90% of cases. Fibromuscular dysplasia accounts for less than 10% of cases[40]. In these disorders, decreased renal perfusion causes tissue hypoxia and decreased perfusion pressure, thereby stimulating renin release from the juxtaglomerular cells, resulting in excessive aldosterone release. Coarctation of the aorta can produce a similar pathophysiology due to renal hypoperfusion.

Although renal vascular hypertension can affect patients of all ages, it is commonly seen in older adults (>50 years) due to the increased prevalence of atherosclerosis in this population. When found in patients less than 50 years of age, renal vascular hypertension is more common in women, usually as a result of fibromuscular dysplasia of one of both of the renal arteries[40].

In very rare cases, juxtaglomerular cell tumors of the kidney that hypersecrete renin have been described[65]. Such patients often have severe hypertension, accompanied by elevated renin and aldosterone levels, hypokalemia, and a mass lesion in the kidney. Confirmation includes documentation of unilateral renin secretion in the absence of renal artery stenosis. While very rare, such cases are important to diagnose, as surgical removal of the tumor can be curative.

CLINICAL FEATURES OF HYPERALDOSTERONISM

The clinical features of hyperaldosteronism are non-specific and variable, often resulting in or associated with hypertension (Table 2). Renal potassium wasting can result in hypokalemia. But the phenotype depends largely on the underlying cause and the degree of the aldosterone excess, as well as the presence of other co-morbidities. The classic features of moderate-to-severe hypertension, hypokalemia, and metabolic alkalosis are highly suggestive of mineralocorticoid excess (usually primary aldosteronism). In the majority of cases, however, only subtle clues of hyperaldosteronism exist, such as the recent onset of refractory hypertension (defined as refractory to treatment with three classes of antihypertensives, including a diuretic)[29,35].

Table 2. CLINICAL MANIFESTATIONS OF PRIMARY HYPERALDOSTERONISM
Classic Manifestations • Hypertension • Hypokalemia • Hypervolemia • Metabolic alkalosis

Other Manifestations

- Due to hypertension
  - Headaches
  - Retinopathy (rare)
- Due to hypokalemia
  - Neuromuscular symptoms (cramps, paresthesias, weakness)
  - Nephrogenic diabetes insipidus
  - Cardiac arrhythmia
  - Glucose intolerance / impaired insulin secretion
- Due to direct actions of aldosterone on the cardiovascular system
  - Cardiac Hypertrophy/Fibrosis
  - Vascular smooth muscle hypertrophy
- Due to a reset osmostat
  - Mild hypernatremia

A. Clinical Manifestations of Primary Hyperaldosteronism

Hypertension is common among patients with PA. Hypertension results from inappropriately high aldosterone secretion because of plasma volume expansion and increased peripheral vascular resistance. Hypertension may be severe or refractory to standard antihypertensive therapies. However, some patients are normotensive or have minimal blood pressure elevations and, as a result, severe hypertension is not a *sine qua non* for this diagnosis[36,66].

Spontaneous hypokalemia in any patient with or without concurrent hypertension warrants consideration of hyperaldosteronism as the etiology. Additionally, patients that develop severe hypokalemia after institution of a potassium-wasting diuretic (such as hydrochlorothiazide or furosemide) should be investigated. It should be noted that in the majority of cases of PA serum potassium levels are normal[29,35].

PA results in extracellular volume expansion secondary to excess sodium reabsorption. However, after the retention of several liters of isotonic saline, an escape from the renal sodium-retaining actions of aldosterone occurs in part due to the increased secretion of atrial natriuretic peptide. Therefore, peripheral edema is rarely a feature of PA if cardiac and renal functions are normal.
Metabolic alkalosis occurs secondary to renal distal tubule urinary hydrogen ion secretion. It is usually mild, causing no significant sequelae, and may go unnoticed. Hypomagnesemia and mild hypernatremia (likely secondary to resetting of the osmostat) can also be observed.
Rarely, patients experience neuromuscular symptoms, including paresthesias or weakness, due to the electrolyte disturbances caused by the hyperaldosteronism. Nephrogenic diabetes insipidus, caused by renal tubule antidiuretic hormone resistance due to the hypokalemia, can cause nocturia and mild polyuria and polydipsia. In severe cases of hypokalemia, cardiac arrhythmias occur and can be life threatening.

B. Clinical Manifestations of Secondary Hyperaldosteronism

Secondary causes of hyperaldosteronism have broad phenotypic variation and cannot be stereotyped by classical manifestations. Renovascular etiologies, as well as coarctation of the aorta, almost always result in hypertension. In contrast, diuretic use (whether surreptitious or prescribed) causes secondary hyperaldosteronism due to sodium and volume depletion. Secondary hyperaldosteronism in renal “salt-wasting” syndromes such as Gitelman’s and Bartter’s syndromes, and pseudohypoaldosteronism Type I (due to resistance to the actions of aldosterone on the kidney) result in mild hypotension due to

excess sodium loss. Similarly, illnesses such as congestive heart failure, nephrotic syndrome, and hepatic cirrhosis exhibit a reduction in the 'effective' circulating blood volume and are associated with hypotension, despite avid salt retention and total body sodium overload.

DIAGNOSIS OF HYPERALDOSTERONISM

Secondary causes of hypertension (including hyperaldosteronism) should be considered initially in all hypertensive individuals. A thorough medical history and physical examination can greatly assist the clinician in deciding which patients should be further evaluated and what tests should be performed. Although the sensitivity of testing for hyperaldosteronism increases when limited to patients with moderate-to-severe hypertension, many patients with hyperaldosteronism have mild to moderate hypertension. The recent onset of refractory or accelerated hypertension, especially in a patient known to be previously normotensive, can be a valuable clinical clue. Therefore, the clinician must remain vigilant to the possibility of hyperaldosteronism, especially in the appropriate clinical setting.

A. Diagnosis of Primary Aldosteronism

Who to Screen for PA

The Endocrine Society has published clinical practice guidelines for the diagnosis and treatment of patients with PA[29]. The task force recommends screening the following subtypes of patients deemed to be at high-risk for PA:

1) Patients with stage 2 (>160–179/100–109 mm Hg), stage 3 (>180/110 mm Hg), or drug-resistant hypertension should be screened for PA.
2) Patients should be screened if they have hypertension associated with either spontaneous or diuretic-induced hypokalemia.
3) Patients with hypertension and an incidentally discovered adrenal adenoma.
4) Patients with hypertension with a family history of early-onset hypertension or cerebrovascular accident at age less than 40 years.
5) All hypertensive first-degree relatives of patients with PA, although there is insufficient data from prospective studies to support this recommendation.

GRA should be considered in patients with early-onset hypertension (<20yr) in the setting of a suppressed PRA. A family history of PA or early cerebral hemorrhage (<40yr) should also raise suspicion for GRA. Screening of GRA kindreds has revealed that most affected individuals are not hypokalemic[29,67].

How to Screen for PA

Evaluation for PA begins with hormonal screening, specifically determination of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) with validated, sensitive assays, for calculation of a plasma aldosterone to renin ratio (ARR). An ARR ratio less than 20 is seen in normotensive or essential hypertensive subjects. In most studies, an ARR > 20 is considered suspicious for PA. An ARR >30, especially in the setting of a PAC $\geq$ 15 ng/dL, has been shown to be 90% sensitive and 91% specific for the diagnosis of PA[29,68], whereas a ratio of >50 is virtually diagnostic of PA[68]. Interpretation of the ARR should be made after confirming that the PRA is relatively suppressed in the setting of inappropriately high endogenous aldosterone production.

To optimize the initial screening evaluation for PA, several aspects of the testing conditions must be considered[69]. To begin with, the ARR is most sensitive when collected in the morning, after patients have been ambulatory for 2 hours, and have been seated for 5-15 minutes prior to blood drawing[29]. Hypokalemia should also ideally be corrected prior to screening as it directly inhibits aldosterone release. Furthermore, drugs that alter aldosterone or renin secretion can result in false positive or false negative results. Beta-adrenergic blockers and central alpha agonists lower PRA secretion and often produce a false positive ARR in patients with essential hypertension. Diuretics, ACE-inhibitors (ACEI) and angiotensin receptor blockers (ARB) and dihydropyridine calcium channel blockers (CCB) can increase PRA and result in false negative screening results. *However, if the ARR while on ACEi, ARB, CCB, or central alpha-blocker therapy is high, with frankly elevated PAC and suppressed PRA, the likelihood of primary aldosteronism remains very high.* The mineralocorticoid receptor antagonists spironolactone and eplerenone, as well as renin inhibitors, can cause false negative ARR by virtue of raising the PRA. If a PRA is suppressed while on a mineralocorticoid receptor antagonist, the ARR may still be interpretable; however, in the context of an unsuppressed PRA, mineralocorticoid receptor antagonists should be discontinued for weeks-to-months until the PRA is suppressed, before the ARR is informative.

Understanding the impact of various medications on the ARR helps in the interpretation of results. When possible, it is ideal to withdraw the antihypertensive agents described above that affect the ARR 2-4 weeks prior to screening for PA; spironolactone and eplerenone, because of longer effect duration, should be stopped at least 4-6 weeks prior to testing. However, withdrawal of anti-hypertensives may not be feasible in patients with moderate to severe hypertension. Medications with neutral effects on the ARR, such as non-dihydropyridine calcium channel blockers, hydralazine, or alpha-blockers, can be used instead to control arterial pressure during the screening evaluation.

In addition to the ARR, new studies have implicated other biomarkers that may have a high sensitivity for screening PA. Titers of angiotensin II type I receptor autoantibodies are elevated in PA, and have been shown to exhibit discriminatory capability in distinguishing patients with APA, BAH, essential hypertension, and normotension[70]. Additionally, emerging evidence has implicated a complex cross-talk between adrenal hormones and parathyroid hormone regulation[71,72]; parathyroid hormone levels may be able to distinguish those with PA from an APA[73].

CASE PRESENTATION *(continued)*:

Blood testing for serum aldosterone and plasma renin activity revealed an aldosterone of 15 ng/dL (0.42 nmol/L) and PRA below the detection limit of the assay at <0.6 ng/mL/h (<0.6 mcg/L/h). The ARR was calculated to be at least 25 or greater.

This testing was done while on lisinopril, amlodipine, and labetolol. Given that the ARR was calculated to be at least 25 or greater, the patient's physician pursued additional testing to confirm the diagnosis of primary hyperaldosteronism.

Confirming the Diagnosis

In patients with a positive ARR, subsequent confirmation or exclusion of autonomous aldosterone secretion is necessary. Methods to demonstrate autonomy of aldosterone production focus on volume-expanding maneuvers. Options for volume expansion include oral sodium loading and intravenous

saline infusion. Other confirmatory testing can be done by fludrocortisone suppression and captopril challenge[29].

When prescribing the oral sodium loading test to confirm PA, patients should be instructed to consume a high sodium (200 mmol/day) diet for 4 days. This is best accomplished by adding 4 boullion packets per day to a regular diet (each packet contains 1100 mg, or 48 mmol, of sodium). Sodium chloride tablets can also be used, though in our experience these may be poorly tolerated due to gastrointestinal upset. On the fourth day of high dietary sodium intake, a 24-hour urine collection for urinary aldosterone, creatinine, and sodium is collected. Oral salt loading should result in extra- and intra-vascular volume expansion and RAS suppression in normal individuals. Aldosterone excretion greater than 12 to 14 ug/d in the presence of a urinary sodium excretion greater than 200 mmol/24 hours confirms the diagnosis of PA. The advantage of oral sodium loading is that it is easier for both the patient and clinician, as it can be performed on an outpatient basis without using hospital resources. However, this should not be performed on patients with severe uncontrolled blood pressure or moderate to severe, untreated hypokalemia. Blood pressure and potassium levels should be monitored during the testing, as hypertension and hypokalemia can be further precipitated or exacerbated with dietary sodium loading[29,74].

For the saline suppression test, 2-3 liters of isotonic saline are infused (500cc/h) over 4 hours. This test should not be performed in patients with compromised cardiac function due to the risk of pulmonary edema. Intravascular volume expansion should suppress the RAS. In normal subjects, PAC decreases below 5 ng/dL at the end of the saline infusion; levels greater than 10 ng/dL are considered diagnostic of autonomous aldosterone production. Values between 6 and 10 ng/dL are considered indeterminate[74,75].

CASE PRESENTATION *(continued)*:

The patient was advised to undergo an oral salt suppression study. Before initiating the study, her physician advised her to obtain a home sphygmomanometer and instructed her on how to use it. The patient was advised to continue taking her potassium chloride supplements. The patient consumed 200 mmol of sodium by ingestion of broth packets at home for 4 consecutive days. She reported her daily blood pressure to her physician daily, and it was found to rise from 120/80 mmHg to 148/90 mmHg. Her serum potassium was checked on the 2nd day of oral sodium consumption and was found to be 3.6 mmol/L.

On the 4th day of the study, the patient began a 24 hour urine collection which was submitted on the day 5. Analysis of the urine revealed a 24-hour urine sodium of 310 mmol and an aldosterone of 25.5 mcg/24h.

The physician confirmed the diagnosis of primary hyperaldosteronism.

Identifying the Cause and Source of PA

Once the biochemical diagnosis of primary hyperaldosteronism has been confirmed, further testing is required to determine the etiology and location of the disorder. Distinguishing between APA, BAH, and less common forms of PA, such as GRA, is important. Unilateral adrenalectomy cures hypertension in 30-70% of patients with APA or UAH, and invariably reverses hypokalemia[44,76]. In contrast, bilateral

adrenalectomy in BAH cures hypertension in only <20% of patients[44,77]. Hence, the treatment of choice is surgical in APA or UAH, and medical therapy is generally favored in BAH and GRA.

Biochemical characteristics can assist with the diagnosis of the various causes of PA. Young age (<50 years old), severe hypokalemia (<3.0 mmol/L), high plasma aldosterone concentrations (> 25 ng/dl), and high urinary aldosterone excretion (>30 ug/24hr) favor the diagnosis of APA versus BAH. The presence of a classical unilateral Conn's adenoma in addition to a serum potassium < 3.5 mmol/L or estimated glomerular filtration rate > 100 mL/min/1.73 m^2 is nearly 100% specific for an APA[78]. However, while sensitive or specific, these clinical tools lack validation in large cohorts, and therefore cannot be relied upon as a means to determine the underlying etiology in individual patients[29,43,68].

Patients with PA should undergo radiographic evaluation of the adrenal glands to localize the source and define the anatomy for potential surgical approaches. Computed tomography (CT) scanning with thin-slice (3mm) spiral technique is the best radiographic procedure to visualize the adrenal glands, and serves primarily to exclude large masses that may represent adrenocortical carcinoma, which are usually more than 4 cm in size. Observation of a solitary hypodense adrenal nodule, usually < 2 cm in size, supports the diagnosis of APA. Adrenal adenomas typically are lipid-rich on CT scan (<10 HU), and have a greater than 50% washout of contrast after 10-15 minutes. However, even when biochemical features suggestive of APA are present, only one-third to one-half of patients have positive CT findings for a solitary adenoma[79,80]. It is also not uncommon for both adrenal glands to be anatomically abnormal in patients with primary aldosteronism. Furthermore, it is emphasized that a radiographic abnormality does not correlate with a functional equivalent. Non-functioning adrenal 'incidentalomas' are not rare, especially in patients above the age of 40; these are radiographically indistinguishable from APA, and can co-exist with an APA in the ipsilateral or contralateral adrenal gland. Therefore, data suggest that adrenal anatomy determined by CT scanning may wrongly predict etiology as well as lateralization of hyperaldosteronism in a significant proportion of patients[79,81].

Adrenal vein sampling (AVS) is a localization technique that is considered to be the 'gold standard' for distinguishing unilateral versus bilateral disease in PA[29,79,81]. AVS involves sampling from the right and left adrenal veins, as well as from the inferior vena cava (IVC), for measurement of aldosterone and cortisol concentrations. Many favor performing AVS with adrenocorticotropin (ACTH) stimulation, which can be administered continuously or as a bolus, and may minimize stress-induced fluctuations in aldosterone secretion during the procedure as well as maximize aldosterone secretion from an APA[29,35,82]. However, other studies indicate that ACTH does not significantly improve the diagnostic accuracy of the procedure, in part because it may increase secretion from the contralateral side more than from the APA and therefore blunt lateralization[83]. Our practice is to employ ACTH stimulated data to aid in confirming the location of the catheters in the adrenal venous circulation by maximizing the 'selectivity-index' (described below), but we do not find ACTH stimulated data particularly useful in interpreting the 'lateralization-index' (described below).

Multiple variables derived from AVS can be used to determine lateralization of aldosterone hypersecretion[84]. **Cortisol-corrected aldosterone ratios (A/C ratio)** are determined by dividing the aldosterone concentrations from each location sampled by the cortisol concentration in the same location to correct for dilutional effects. We recommend the following approach when interpreting results from an AVS:

STEPWISE APPROACH TO AVS TERMINOLOGY AND INTERPRETATION:

Index of Terms:

- **The IVC Ratio** = [aldosterone from IVC]/[cortisol from IVC]
- **Selectivity Index** = [cortisol from each adrenal vein]/[cortisol from IVC]
- **Lateralization Index** = A/C ratio from dominant side / A/C ratio from non-dominant side
- **Contralateral Index** = A/C ratio from non-dominant side / IVC Ratio

Stepwise Interpretation:

1) Calculate the "IVC Ratio" to determine the baseline corrected aldosterone.

2) Calculate the "Selectivity-Index" to confirm the location of each catheter within the adrenal venous circulation. In general, a selectivity-index >2 is preferred to confirm sampling of adrenal venous blood, and ideally this ratio should be 3-4 or higher to maximize confidence. Enhancement of the selectivity-index following ACTH can also increasing confidence that the catheter is located in the adrenal vein.

3) Calculate the "Lateralization-Index" to determine whether aldosterone concentrations lateralize to one side. A lateralization-index > 4 is consistent with an APA, whereas a lateralization index <4 is either indeterminate or suggestive of BAH.

4) Calculate the "Contralateral-Index" to support the diagnosis of an APA. In the setting of unilateral APA/UAH, it is expected that aldosterone production from the contralateral gland will be suppressed, and therefore the contralateral-index will be < 1.

Using this approach, AVS has a sensitivity of 95% and a specificity of 100% to detect unilateral disease[81]. Adrenal vein sampling may not be necessary in patients with a high probability of APA by biochemical criteria, and a >1cm unilateral adrenal nodule with an anatomically normal contralateral gland if they are less than 40 years old[29,81]. In all cases, if adrenal vein sampling is performed, it should be done by an experienced angiographer to increase the likelihood of a successful procedure[81,84].

When GRA is suspected, direct screening by either Southern blot or long polymerase chain reaction can be performed to detect the gene duplication[29].

B. Diagnosis of Secondary Aldosteronism

When there is clinical suspicion for renovascular hypertension, and initial screening has revealed a normal or elevated PRA, further testing for renovascular hypertension should be considered. Clinical features that should raise suspicion for renovascular hypertension include abrupt-onset hypertension, unexplained acute or progressive renal dysfunction, renal dysfunction induced by ACE inhibitors, asymmetric renal dimensions, or suspicion of fibromuscular disease in a young patient. Importantly screening is only recommended if intervention will be pursued if a significant lesion is detected[85,86].

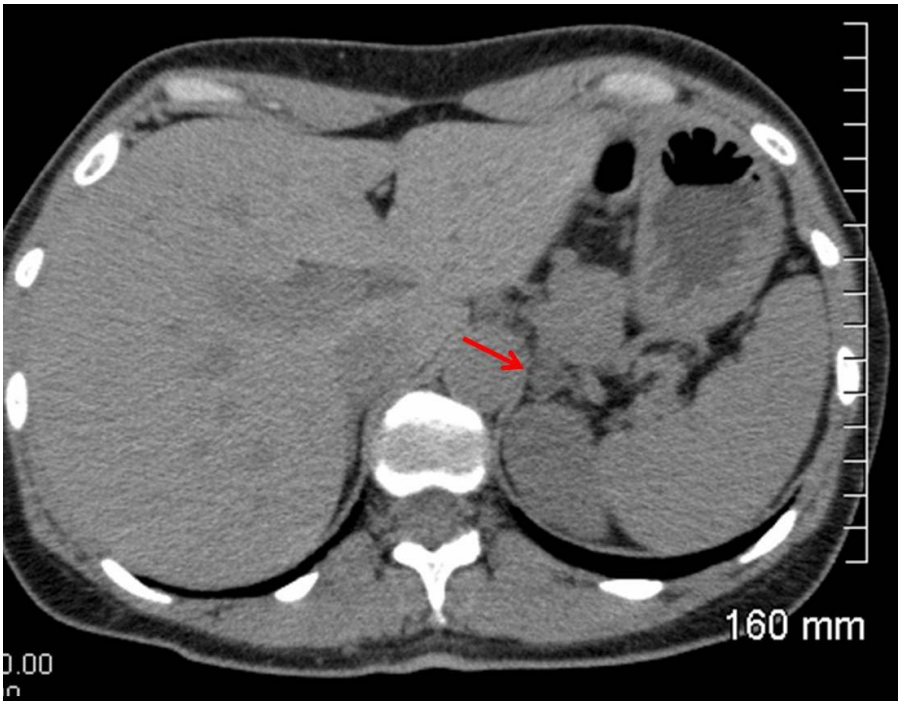
The diagnosis of renovascular hypertension requires two criteria: 1) the identification of a significant arterial obstruction (*structural* abnormality), and 2) evidence of excess renin secretion by the affected kidney (*functional* abnormality)[87]. Structural abnormalities can be detected by a variety of imaging techniques. The gold standard is renal arteriography, but computed tomography (CT) scanning, duplex Doppler ultrasonography, and magnetic resonance angiography are reasonable noninvasive

alternatives[85,88]. Despite the multiple screening options, there is currently no single test that if negative completely excludes a stenotic lesion in the real arteries. Choosing among the various options is largely dependent on degree of clinical suspicion, availability of the technology, cost of the examination, physician experience in performing and interpreting the results, and. The presence of renal insufficiency is an important consideration in determining the most appropriate diagnostic approach.

Evaluating the functional significance of a stenotic lesion in the renal arteries can be accomplished by captopril renography. For this procedure, 25-50 mg of captopril is administered one hour before a radioisotope is injected. Under normal conditions, administration of an ACE inhibitor reduces angiotensin II-mediated vasoconstriction and leads to relaxation of the efferent arteriole and an increase in glomerular filtration rate (GFR). This response is attenuated if the afferent blood flow is fixed by the presence of a stenotic lesion, and thus the difference between radioisotope excretion between the two kidneys is enhanced. Delayed excretion on the affected relative to the unaffected side provides functional evidence of renal artery narrowing[89]. Although the captopril renogram is not recommended as a screening test for renal artery stenosis because of variable sensitivity and specificity depending on the populations studied[85], it is a tool for assessing the clinical significance of a stenotic lesion, and has high positive and negative predictive values for beneficial revascularization results[89].

CASE PRESENTATION *(continued)*:

A CT scan with intravenous contrast was performed and revealed an 8 mm left adrenal mass. The density of this mass was 10 HU, and it displayed >50% washout of contrast following 10 minute delay.



The patient underwent adrenal venous sampling to confirm unilateral left-sided APA versus bilateral disease. AVS revealed an IVC A/C ratio of 2.6 and a selectivity index of 2.5. Following administration of cortrosyn, the selectivity index rose to >100. The A/C ratio from the right adrenal vein was 1.06 and the A/C ratio from the left adrenal vein was 72.5. The patient's physician felt confident that the sampling results reflected adrenal venous blood based on a selectivity index >2. Given that the lateralization index (72.5/1.06=68.4) was well above 4 and that the contralateral index (1.06/2.6=0.41) was well below 1, the patient was diagnosed with a left-sided aldosterone producing adenoma (APA).

TREATMENT OF HYPERALDOSTERONISM
A) Treatment of Primary Hyperaldosteronism

Treatment for PA depends on the underlying etiology. Surgery is most often the treatment of choice for APA, and is often performed with laporoscopic techniques (anterior or posterior approaches)[90], which reduce patient recovery time and hospital cost. Resection of APA may cure or ameliorate hypertension, and invariably reverses hypokalemia. Unilateral adrenalectomy cures hypertension in 30-70% of patients with APA or UAH[44,77]. Data suggests that resolution of hypertension after adrenalectomy for PA is less likely if there is family history of hypertension and use of two or more antihypertensive agents

pre-operatively[44,76,91]. Caution should be exercised in the perioperative and postoperative management of APA patients. Pre-operatively, hypertension and hypokalemia should be well controlled, which may require the addition of a mineralocorticoid receptor antagonist[29]. Post-operatively, suppression of aldosterone secretion in the contralateral adrenal gland is expected, and may result in a transient hyporeninemic hypoaldosterone state. As a result, some patients exhibit post-operative salt wasting, mild hyperkalemia, and are at increased risk of dehydration and orthostatic hypotension if sodium restricted. Potassium and mineralocorticoid receptor antagonists should be withdrawn after surgery. PAC can be measured post-operatively as an indication of surgical response, however, re-equilibration of PRA post-operatively can take several weeks to months. Blood pressure tends to show maximal improvement 1-6 months post-operatively. For patients who are not operative candidates, or choose not to undergo surgery, medical management of hyperaldosteronism should be pursued[29], as described below for BAH.

BAH is best treated medically with the use of a mineralocorticoid receptor (MR) antagonist. However, it should be noted that in situations of grossly asymmetric BAH (where AVS indicates that one adrenal gland is clearly producing the vast majority of aldosterone), unilateral adrenalectomy can be considered to 'debulk' the major contributor to aldosterone excess if it may improve the patient's quality of life or overall well-being. When medical therapy is pursued in the vast majority of BAH cases, the available options are eplerenone or spironolactone[92]. Spironolactone doses required are usually between 50 mg and 400 mg per day, usually administered up to twice daily. Studies have reported reductions in mean systolic and diastolic blood pressure of 25% and 22%, respectively[93,94]. However, while it is effective for controlling blood pressure and hypokalemia, the use of spironolactone is limited by side effects. Gynecomastia and erectile dysfunction often occur during long-term treatment in males due to the anti-androgenic actions of spironolactone. The incidence of gynecomastia in males after 6 months of use at a dose of > 150 mg/d was as high as 52%[95]. In women, spironolactone may lead to menstrual dysfunction, primarily intermenstrual bleeding. Fatigue and gastrointestinal intolerance are other common side effects. Epleronone, which has similar antagonistic actions at the type I renal MR, has no anti-androgen activity since it does not bind to androgen or progesterone receptors, and therefore has fewer side effects. It is felt to have 60% of the MR antagonist potency of spironolactone[29]. However, compared to prior spironolactone usage, with eplerenone there is increased uncertainty in dosing, lack of clinical trial evidence for use in this indication, and markedly increased cost.

When blood pressure is not controlled with spironolactone/eplerenone, or side-effects limit tolerability, the addition of other antihypertensive therapies may be required. Potassium-sparing diuretics, such as triamterene or amiloride, have been used, although they are usually are not as effective as spironolactone[96]. The dihydropyridine calcium channel antagonists have also been shown to effectively reduce blood pressure. Dietary sodium restriction (< 100 mmol/day), regular aerobic exercise, and maintenance of ideal body weight contribute to the success of pharmacologic treatment for hypertension in BAH.

Glucocorticoid-remediable aldosteronism (GRA) can be successfully treated with low doses of glucocorticoids such as dexamethasone[67]. By inhibiting ACTH release, the abnormal production of aldosterone can be suppressed. The lowest dose of glucocorticoid that can normalize blood pressure and potassium levels should used to minimize side effects. PRA and PAC can be measured to assess treatment effectiveness and prevent overtreatment. The MR antagonists eplerenone and spironolactone are alternative treatments of hypertension in GRA[97].

B. Treatment of Secondary Hyperaldosteronism

Renal artery stenosis is managed through medical therapy alone or combined with revascularization. The goal of treatment is blood pressure control, as well as prevention of decline in renal function and secondary cardiovascular disease[85,88]. For renal artery fibromuscular dysplasia, primary angioplasty is the recommended endovascular procedure. In the case of atherosclerotic renovascular disease, angioplasty with stent placement is preferred over angioplasty alone, because data suggest improved outcomes in ostial renovascular stenosis. However, it must be noted that there is a paucity of level 1 data from randomized control trials demonstrating that revascularization has survival advantage in atherosclerotic renovascular disease[98]. In all cases, an experienced interventional angiographer should perform angioplasty. Surgery for repair of renal vascular hypertension is reserved for patients with prior unsuccessful angioplasties.

Aggressive medical therapy should also be instituted, and may be sufficient in many patients with atherosclerotic renovascular hypertension. Given the central role of the RAS in the pathophysiology of the disease, ACE inhibitors and ARB are the agents of choice for medical management, and have anti-hypertensive as well as renoprotective effects. Caution must be taken, however, as initiation of either agent can rarely be associated with precipitation of acute renal failure, particularly in patients who have critical, bilateral renal artery stenosis. As a corollary, acute deterioration of renal function after initiation of these medications in patients with hypertension should prompt clinicians to consider the diagnosis of bilateral renal artery stenosis[40,85].

CASE PRESENTATION *(continued)*:

Following a discussion of the diagnosis and prognosis with the patient, the patient expressed a strong desire to pursue surgical resection of the left-sided APA. Given that the patient was a healthy and active individual, her physician concurred. A laparoscopic left adrenalectomy was performed without complication. Pathology revealed a 9 mm adrenal cortical adenoma. Anti-hypertensive medications were held post-operatively, and the patient experienced no hypo- or hyper-kalemia. Following surgery, her blood pressure improved to 120-135/70-80 mmHg without any medications. She was prescribed lisinopril 10 mg daily, and since the addition of this single anti-hypertensive medication, her blood pressure has remained between 100-120/50-60 and her serum potassium has normalized.

TAKE HOME POINTS

1) Physiologic aldosterone regulation plays a crucial role in maintaining volume and potassium homeostasis; however, inappropriate regulation of aldosterone results in adverse systemic, vascular and metabolic consequences.

2) Hyperaldosteronism can be seen in a broad range of phenotypes. Approaching the case of hyperaldosteronism by assessing plasma renin activity and hypertensive status is a simple method to narrow the potential etiologies.

3) Breakthroughs in genetic research have resulted in a major paradigm shift in understanding the causes of primary hyperaldosteronism and aldosterone producing adenomas. Germline and somatic mutations in membrane channels, such as potassium channels, that maintain the resting potential of zona glomerulosa cells have been implicated in a large subset of aldosterone producing adenomas.

4) The diagnosis of primary hyperaldosteronism requires a meticulous and organized approach. We recommend approaching the diagnosis with an initial screening test (ARR); when the ARR is >20-30 and the PRA is suppressed, confirmation of PA is warranted. Confirmation of autonomous aldosterone excess using sodium suppression tests should prompt imaging studies to localize the source of aldosterone excess. We recommend that adrenal venous sampling should be considered in nearly all cases to confirm the location as unilateral or bilateral, and prevent erroneous diagnoses and treatment plans. In young patients (<40 years) with sufficiently high ARR (>30), low potassium (< 3.0 mmol/L), and a unilateral adrenal adenoma, it may be reasonable to forego AVS and proceed directly with unilateral adrenalectomy.

5)) The treatment of PA depends on the cause of the disease. In cases of unilateral disease (APA or UAH), surgical resection of the tumor typically results in cure of hyperaldosteronism, and substantial improvements in blood pressure and potassium. Minimally invasive surgery should be considered in patients who are young, healthy, and without contraindications that would increase surgical risk. In cases of bilateral disease, and in unilateral disease where surgery is not preferred, medical management with mineralocorticoid antagonists is usually effective.

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