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Diagnosis and Treatment of Primary Aldosteronism

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1. Introduction

Primary aldosteronism (PAL) is a clinical disorder characterized by excessive production and release of aldosterone from the cortical zona glomerulosa of the adrenal gland. The high level of circulating aldosterone increases sodium reabsorption with potassium loss in the distal tubule, leading to mild hypernatremia, hypertension (HTN), severe hypokalemia, and alkalosis.^{1,2} Primary aldosteronism, as originally described by Conn in the 1950s.^{3,4} (PAL) is characterized by an increased secretion of aldosterone that seems to be autonomous of the renin-angiotensin system, as the secretion of renin is suppressed. PAL represents the most common form of secondary hypertension.^{5,6} In recent years, the large-scale hypertension trials, It is now widely recognized that PAL is much more common than previously thought, being present in up to 5–13% of unselected hypertensive patients⁷ and in resistant HTN (BP above goal with three or more antihypertensive medications) with a reported prevalence of 20% to 23% in this group of patients.^{5,8} As older age and obesity are 2 of the strongest risk factors for uncontrolled hypertension, the incidence of resistant hypertension will likely increase as the population becomes more elderly and heavier. The prognosis of resistant hypertension is unknown, but cardiovascular risk is undoubtedly increased as patients often have a history of long-standing, severe hypertension complicated by multiple other cardiovascular risk factors such as obesity, sleep apnea, diabetes, and chronic kidney disease.⁵ In ALLHAT, older age, higher baseline systolic blood pressure, LVH, and obesity all predicted treatment resistance as defined by needing 2 or more antihypertensive medications. Overall, the strongest predictor of treatment resistance was having CKD as defined by a serum creatinine of ≥ 1.5 mg/dL. Other predictors of the need for multiple medications included having diabetes mellitus and living in the southeastern United States. African-American participants had more treatment resistance, as did women, such that black women had the lowest control rate (59%) and non-black men the highest (70%).⁸ Furthermore, experimental and clinical studies showed that excess aldosterone has detrimental effects on the heart, brain and kidneys that are partly hypertension-independent.⁹ Patients diagnosed with PAL, compared with patients with essential hypertension seems to increase the left ventricular wall thickness.¹⁰ In addition, aldosterone excess appears to independently increase the risk of cardiac fibrosis.¹¹ Likewise, mineralocorticoid receptor blockage has been showed to diminish the effects of aldosterone

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on PAI-1 levels. In recent years, clinical trials have demonstrated an additive effect of combined ACEI and aldosterone receptor antagonism on cardiovascular morbidity and mortality.^{12,13} The mechanism, named aldosterone escape, referring to chronic ACEI that leads aldosterone to return to baseline concentrations, might clarify the additional effects of aldosterone on PAI-1 levels.^{14,15} We study, administration of an ACEI (fosinopril) and an ACEI plus aldosterone antagonist (spironolactone) both caused a significant decrease in PAI-1 levels, which might be attributed to aldosterone escape.¹⁶

Several studies have shown that patients with either aldosterone-producing adenoma (APA) or idiopathic hyperaldosteronism (IHA) appear to have increased cardiovascular morbidity compared with age-, sex-, and systolic and diastolic BP-matched patients with essential hypertension.^{17,18} Patients with PAL, stroke, MI and significantly increased risk of atrial fibrillation.¹⁹ Optimal BP control and specific management of aldosterone excess by either adrenalectomy or medical treatment with mineralocorticoid receptor (MR) antagonists is fundamental for the prevention of cardiovascular events in patients with PA.²⁰

The adverse effects of aldosterone excess stress the importance of establishing the diagnosis of PAL and its underlying cause. The most common subtypes of PAL are APA (35% of cases) and IHA (60% of cases).²¹ Many other subtypes of PAL have also been described, including primary or unilateral adrenal hyperplasia (2%), pure aldosterone-secreting adrenocortical carcinoma (<1%) and ectopic aldosterone-secreting tumours (e.g. neoplasms in the ovary or kidney) (<0.1%).²²

2. Clinical findings

2.1 Symptoms and signs

The most common findings in PAL, moderate or severe hypertension and hypokalemia. PAL patients are often resistant hypertension, hypertension in these patients usually need to take control of multiple drug use. In recent studies, only a minority of patients with PAL (9–37%) had hypokalemia.²³ Although hypokalemia is considered the hallmark of hyperaldosteronism, the majority of patients with PAL have normal serum potassium levels. Hypokalemia is believed to be a late manifestation of PAL and many patients with PAL may present with HTN well before they develop hypokalemia.^{6,23} Most symptoms of PAL are attributed to hypokalemia, which include muscle weakness, cramping, transient paralysis, palpitations, headache, or polyuria.²²

Half the patients with an APA and 17% of those with idiopathic hyperaldosteronism (IHA) had serum potassium concentrations less than 3.5 mmol/liter.²⁴ Thus, the presence of hypokalemia has low sensitivity and specificity and a low positive predictive value for the diagnosis of PAL. Separation of IHA and APA, IHA to be treated medically, surgically corrected if the APA is very important because of an illness.

2.2 Laboratory findings

The recently published Guidelines for diagnosis and treatment of PAL outlined for the first time the categories of hypertensive patients with relatively high prevalence of PAL who should undergo a screening test.¹ The screening test should be performed in all

patients with: **1)** resistant hypertension; **2)** hypertension grade 2 or 3; **3)** hypertension and spontaneous or diuretic-induced hypokalaemia **4)** hypertension with adrenal incidentaloma; **5)** hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 year); **6)** all hypertensive first-degree relatives of patients with PAL.

There is a general consensus that aldosterone:renin ratio (ARR) is the most reliable available means for PAL screening; however there is no agreement on either the ARR cut-off or whether the absolute aldosterone level should also be taken into account. Aldosterone/renin ratios (ARRs) were calculated from these values using the following Formula (ARR): Plasma aldosterone (ng/dL)/Plasma renin (ng/mL-h). Individuals with an ARR of ≥ 30 were suspected of having primary aldosteronism, while an ARR of <30 was considered normal.¹ However, it is now recognized the prevalence is higher (5-13% of all patients with hypertension) when the PAC to PRA ratio (ARR) is used to screen for PAL. Measurements of PAC and PRA are recommended for the diagnosis of PAL.

Several factors affect ARR, the most important being antihypertensive therapy: mineralocorticoid receptor antagonists and diuretics lead to false-negative results and thus should always be withdrawn for at least 4–6 weeks (6–8 for spironolactone); dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists can potentially, but infrequently, lead to false-negative results²⁵; in contrast, beta-blockers and central α_2 -agonists can cause false positives.²⁶ The direct renin inhibitor aliskiren lowers PRA, resulting in false-positive ARR for renin measured as PRA and false negatives for renin measured.¹

An increased ARR is not diagnostic by itself, and PAL must be confirmed by demonstrating over-production of aldosterone. The Endocrine Society guidelines recommend the following four confirmatory tests; an oral sodium test, saline infusion test, fludrocortisone test and captopril challenge test.¹ Patients should receive 12.8 g sodium chloride for 3 days in the oral sodium loading test. The captopril challenge test shows excellent sensitivity despite relatively low specificity and due to its simplicity can be performed at the outpatient clinic.

Oral sodium loading test: This test is performed to evaluate the suppression of aldosterone by oral sodium loading. The oral sodium loading test is also not practical in hypertensive patients because of their high-salt intake, and the intravenous saline infusion test is not common as it is dangerous for elderly patients or those with left ventricular hypertrophy or a previous myocardial infarction, all of which are commonly complicated by PAL. The most commonly used test to verify the diagnosis oral sodium loading test. Patients should increase their sodium intake to 200 mmol/d (6 g/d) for 3 days, verified by 24-h urine sodium content. Patients should receive adequate slow-release potassium chloride supplementation to maintain plasma potassium in the normal range. Urinary aldosterone is measured in the 24-h urine collection from the morning of d 3 to the morning of day 4. PAL is unlikely if urinary aldosterone is lower than 10 $\mu\text{g}/24\text{ h}$ (27.7 nmol/d) in the absence of renal disease where PAL may coexist with lower measured urinary aldosterone levels. Elevated urinary aldosterone excretion $>12\text{ }\mu\text{g}/24\text{ h}$ ($>33.3\text{ nmol/d}$) at the Mayo Clinic, $>14\text{ }\mu\text{g}/24\text{ h}$ (38.8 nmol/d) at the makes PAL highly likely.

Urinary aldosterone levels greater than 12 mcg/24 hours indicate failure to suppress the aldosterone production by high salt intake and is diagnostic of PAL with over 90% sensitivity and specificity.²²

Saline loading test: Patients stay in the recumbent position for at least 1 h before and during the infusion of 2 liters of 0.9% saline iv over 4 h, starting at 08:00–09:30 h. Blood samples for renin, aldosterone, cortisol, and plasma potassium are drawn at time zero and after 4 h, with blood pressure and heart rate monitored throughout the test. Post infusion plasma aldosterone < 5 ng/dl make the diagnosis of PAL unlikely, and levels >10 ng/dl are a very probable sign of PAL. Values between 5 and 10 ng/dl are indeterminate.³⁴ SLT is contraindicated in patients with severe HTN, chronic kidney failure, HF, cardiac dysrhythmias, or severe hypokalemia.

Captopril challenge test: Patients receive 25–50 mg captopril orally after sitting or standing for at least 1 h. Blood samples are drawn for measurement of PRA, plasma aldosterone, and cortisol at time zero and at 1 or 2 h after challenge, with the patient remaining seated during this period. Plasma aldosterone is normally suppressed by captopril (>30%). The test is considered positive if SA remains greater than 12 ng/dL or ARR is greater than 26.²⁸ This test has a higher sensitivity (100% versus 95.4%) and specificity (67% to 91% versus 28.3%) over the baseline screening tests, and is easier to perform than the SLT.

Fludrocortisone suppression test: Fludrocortisone suppression is the standard test used to confirm the diagnosis of PAL. Fludrocortisone (Florinef) is given 0.1 mg every 6 hours orally together with high oral sodium of 200 mmol (6 g) per day for 4 days. Potassium supplement should be given to maintain a close to normal serum potassium level. Upright SA and PRA are obtained on day 4 of the test. SA greater than 6 ng/dL is indicative of failure to suppress the aldosterone production and is diagnostic of PAL; PRA should be suppressed to less than 1 ng/mL/hour. FST requires hospital admission because of hypokalemia associated with testing as well as the need for frequent blood samples to monitor serum potassium levels. This test is contraindicated in patients with severe HTN or heart failure (HF).^{1,27}

3. Imaging studies

3.1 Adrenal computed tomography

Imaging of adrenal glands by computed tomography (CT) and magnetic resonance imaging (MRI) is frequently used to detect an adrenal mass in patients with positive screening and confirmation tests.²⁹

APA may be visualized as small hypodense nodules (usually <2 cm in diameter) on CT. IHA adrenal glands may be normal on CT or show nodular changes. Aldosterone-producing adrenal carcinomas are almost always more than 4 cm in diameter, but occasionally smaller, and like most adrenocortical carcinomas have a suspicious imaging phenotype on CT.³⁰

A high resolution CT scan with 2–3 mm cuts represents the best available technique for identifying adrenal nodules that can be an APA, primary unilateral adrenal hyperplasia or bilateral adrenal hyperplasia.³¹ According to the Endocrine Society guidelines, MRI, CT or

both should be performed in patients with primary aldosteronism to identify the rare but large aldosterone-producing carcinoma.³² However, as MRI is more expensive and has a lower spatial resolution than CT, MRI has no advantage over CT in subtype evaluation of primary aldosteronism.¹

Half of APAs are <20 mm in diameter and up to 42% are <6 mm in diameter, therefore, most patients with primary aldosteronism attributable to an APA who can be cured with surgery have a small or very small tumor.³³ Other surgically curable subtypes of primary aldosteronism, such as primary aldosteronism caused by primary unilateral adrenal hyperplasia or multinodular unilateral adrenocortical hyperplasia, have nodular lesions that are also most often very small (<10 mm in diameter), which makes them hardly detectable with CT or MRI. In addition, a nonfunctioning adrenal mass (incidentaloma) can also be present in a patient with primary aldosteronism either with a small APA or with unilateral adrenocortical hyperplasia, both of which are undetectable with CT. Moreover, in a patient with primary aldosteronism, an adrenal nodule can be an APA, a macronodule of hyperplasia attributable to idiopathic hyperaldosteronism,³⁴ or a macronodule attributable to primary unilateral adrenal hyperplasia.³⁵

3.2 Adrenal venous sampling

There are an increasing number of reports that adrenal vein sampling (AVS) is the gold standard test to differentiate unilateral from bilateral disease in patients with PAL. The Endocrine Society guidelines state that AVS is the “standard test to differentiate unilateral from bilateral causes of [primary aldosteronism].”¹ Adrenal venous sampling is a difficult procedure as the right adrenal vein is small, with the success rate depending on the proficiency of the angiographer. AVS is expensive, technically demanding and carries a tiny, but not negligible, risk of adrenal-vein rupture.³⁶

In a study where AVS was used as the gold standard for diagnosis, CT scans mistakenly suggested that one-quarter of patients had an APA; correctly identified a unilateral or bilateral excess of aldosterone only in half of all patients; falsely suggested a bilateral adrenal hyperplasia in one-fifth of patients with a unilateral source of aldosterone excess; and in some patients identified an APA in the wrong adrenal gland.³⁴

Rapid cortisol assays during AVS to monitor cortisol levels can reduce the failure rate of AVS. We have developed a new rapid cortisol assay using immunochromatography, in which cortisol concentrations can be measured within 6 min. (briefly explain false positive rates etc., in this method- should this be used in conjunction with CT?) Using this technique, the success rate of AVS has improved to 93%.³⁷

4. Treatment

At our institution, we support the recommendation from the Endocrine Society guidelines¹ that a lateralized aldosterone secretion should be demonstrated before undertaking surgery in patients who are candidates for general anesthesia and wish to achieve long-term cure. The goal of treatment for PAL is focused on the normalization of circulating aldosterone or aldosterone receptor blockade to prevent the morbidity and mortality associated with HTN,

hypokalemia and end-organ damage.²⁹ Management strategies should take patient characteristics and desires into consideration. Surgical treatment may not be appropriate for all patients with unilateral hypersecreting adrenal mass but may be reasonable for those with bilateral hypersecretion.

4.1 Medical treatment

Medical management with a mineralocorticoid receptor (MR) antagonist is recommended for patients who do not undergo surgery. Medical treatment is recommended for patients with bilateral hypersecreting adrenal lesions or for those with unilateral lesion who are not optimal for or who do not want surgical treatment (see Pharmacotherapy for hyperaldosteronism). Medications that block aldosterone action are effective for the treatment of hypokalemia and HTN and these include nonselective (spironolactone) and selective aldosterone receptor antagonists (eplerenone). Amiloride is not an aldosterone receptor antagonist and is not effective in controlling HTN in PAL but may be used for its potassium sparing property.

Prior studies on the efficacy of spironolactone in treating resistant HTN have used 25 to 50 mg daily dosing, whereas true PAL may require larger daily doses up to 100 to 400 mg. The onset of action on BP may be slow. Measurements of PRA are not necessary but may be an indication that an optimal dose of the medication has been prescribed when it is no longer suppressed.

Spironolactone is a nonselective MR antagonist with significant antiandrogenic and progestational activities responsible for its most common side effects (gynecomastia, erectile dysfunction and abnormal menstrual cycles)². Eplerenone is a selective MR antagonist without antiandrogen or progesterone agonist activity: it has 60% of the potency of spironolactone in vivo and should be administered twice daily given its short half-life. Combined therapy with a small dose of spironolactone and amiloride may alleviate these undesirable consequences.²⁹ Eplerenone, a more selective mineralocorticoid receptor blocker, also effectively reduces BP in patients with resistant hypertension. Eplerenone has a better adverse reaction profile because it has substantially less binding affinity to androgen and progesterone receptors than spironolactone.

4.2 Surgical treatment

Laparoscopic adrenalectomy is currently the best treatment, and can be performed during a short hospital stay at a very low operative risk.³⁸⁻³⁹ This surgery has cured primary aldosteronism in 33–72% of patients and resulted in marked improvements in 40–50% of patients.^{40,41} Approximately one-third of all PAL patients has clear lateralization of aldosterone production and will benefit from unilateral adrenalectomy. Laparoscopic adrenalectomy is the most suitable therapy for APA or unilateral adrenal hyperplasia. After adrenalectomy hypertension is cured in around 50% of patients with APA (range 33–70%) [3] with the remaining patients showing a significant reductions in blood pressure and number of antihypertensive drugs. Chronic suppression of the renin-angiotensin axis may cause transient postoperative hypoaldosteronism and a liberal sodium diet should be allowed to prevent hyperkalemia after the surgery. An I.V. infusion of 0.9% sodium chloride

every 8 to 12 hours may be necessary to avoid postoperative intravascular volume depletion. All antihypertensive medications, especially spironolactone and amiloride, should be withheld and other BP medications may be cautiously reinstituted as needed within a few days. The data on follow-up assessment of the remaining adrenal gland after surgery is scanty. Postoperative SA, PRA, and ARR are commonly repeated.¹⁷ These authors also periodically obtained CT scan in their patients at 1 to 3 yearly intervals because they have observed that the remaining adrenal gland could slowly increase in size, become nodular or develop adenoma after surgery.

Of note, adrenalectomy in APA patients has also been reported to improve self-assessed quality of life.⁴² A recent study suggests that, for reasons which are incompletely understood, unilateral adrenalectomy may be beneficial in carefully selected patients with bilateral PA.⁴³

5. Conclusion

Until recently, aldosterone excess was thought to play a minor role in the development of hypertension. Beginning in the early 1990s, however, reports from investigators worldwide have found that primary aldosteronism is common in patients with hypertension, with prevalence rates of 10 to 15%. In patients with severe or resistant hypertension, the prevalence of primary aldosteronism is even higher, with a prevalence of approximately 20%. Approximately 30% to 60% of APA patients are improved or have resolution of HTN and hypokalemia with normal SA and PRA after unilateral adrenalectomy. HTN is normally resolved within 1 to 6 months and patients with persistent HTN are more likely to be older, require more than two antihypertensive drugs preoperatively, or have a longer duration of HTN or underlying renal dysfunction. The postoperative BP in those with persistent HTN is usually easier to control with fewer medications. The cardiovascular complications of patients who achieve optimal BP control with or without medications eventually decrease to the levels of those with essential HTN. Partial reversal of renal dysfunction, regression of LVM and improved diastolic left ventricular function have been demonstrated after successful treatment of PAL. It has been reported that adrenalectomy for APA is more cost-effective than long-term medical therapy.

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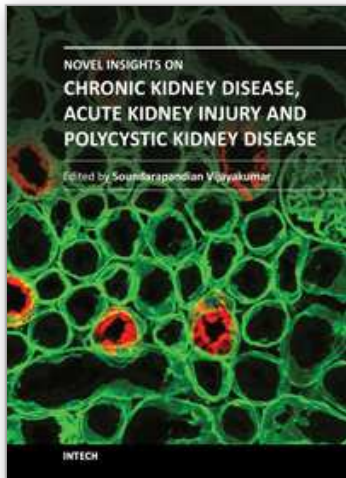
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