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Review Article

Primary Aldosteronism (Conn's Syndrome): Detection and Management

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Abstract

Aim: In this review, we will review Conn's disease and its manifestations, and the best way to manage this condition.

Primary aldosteronism (PA) or Conn's syndrome is an endocrine disorder resulting in excessive production of aldosterone from the adrenal gland(s). Excessive secretion of aldosterone cause increased blood volume, high blood pressure, mild hypernatremia, hypokalemia, and metabolic alkalosis. Hypokalemia is present in 30 - 50% of cases.

Refractory hypertension is one of recognizable signs, as aldosterone works on the kidneys to reabsorb sodium back to the blood and water follows creating hypertension resistant to standard pharmacologic medications. Commonly, it can manifest unilaterally as an adenoma or bilaterally as hyperplasia of both adrenal glands. High blood pressure can lead to kidney disease, cardiovascular morbidity and even a stroke which is why early patient management is very important. Patients with hypertension should be screened if they are showing any one of the followings; adrenal mass, refractory hypertension, hypokalemia, or family history of hypertension or stroke below 40 years of age. The best screening test is the aldosterone/renin ratio that has high sensitivity but low specificity. Adrenal computed tomography is the initial diagnostic procedure to distinguish between APA and bilateral hyperplasia. Adrenal venous sampling is indicated if the adrenal CT was non-conclusive or patients age above 40 years. Management depends on the etiology of the excess aldosterone. Laparoscopic adrenalectomy is the ideal treatment for adrenal adenomas producing the aldosterone. Mineralocorticosteroid antagonists is the preferred treatment of the cases with bilateral adrenal hyperplasia.

Keywords: *Primary Aldosteronism; Hypertension; Hypokalemia Aldosterone; Renin*

Introduction

Primary aldosteronism, PA (Conn's syndrome) named after J. W. Conn who first described it in 1955, in a patient suffering from hypertension with an adrenal adenoma producing aldosterone [1]. PA is the most common cause of secondary hypertension. The prevalence is approximately 6 to 10% of hypertensive patients. It may constitute up to 20% of adult patients with resistant hypertension [2]. Aldosterone regulates blood pressure by increasing sodium reabsorption through the epithelial sodium channel (ENaC) and Na-K ATPase from distal convoluted tubules in the kidneys. This is linked with more urinary potassium excretion, causing hypokalemia and increased water reabsorption which results in increased extracellular and plasma volume leading to hypertension. Nonetheless, normal serum potassium might be found in 30% to 50% of patients, particularly in patients with adrenal hyperplasia or familial aldosteronism. Urinary potassium is increased (more than 30 mmol/day) and the diagnosis relies upon demonstration of increased extracellular fluid (ECF) volume (suppressed plasma renin) and non-suppressible aldosterone production [1].

Usually patients with PA are asymptomatic, however they may have numbness, fatigue or muscle cramping (related to potassium wasting). They can likewise have polydipsia and polyuria from hypokalemia-initiated nephrogenic diabetes insipidus. High blood pressure is often the only sign of PA. Resistant hypertension or hypokalemia in a hypertensive patient are recognized indications to screen for PA Hypertension with direct proinflammatory and profibrotic effects of aldosterone on the walls of vessels causes cardiovascular atherosclerosis [3]. Excessive aldosterone levels are linked to increased risk for cardiovascular ischemic events, heart failure, strokes, renal failure, and premature death. Inhibition of the renin-angiotensin-aldosterone system gives a better outcome to patients with heart failure and after a myocardial infarction [4].

Main causes of PA include aldosterone-secreting adenomas (40%), idiopathic unilateral or bilateral adrenal hyperplasia (60%), aldosterone-producing adrenal carcinoma (rare) and familial hyperaldosteronism (rare). It's worth noting that women are affected two times more than men [5].

The Endocrine Society's clinical practice guidelines 2016 recommended screening of Severe hypertension (> 150/100 mmHg) or drug-resistant hypertension (defined as suboptimally controlled hypertension on a three drugs that including diuretic or hypertension with adrenal incidentaloma or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (< 40 years) and all hypertensive first-degree relatives of patients with primary aldosteronism [6].

Diagnosis: Screening and confirmation

Estimation of the plasma aldosterone/renin ratio (PAR) is recommended as screening test for PA. Both aldosterone and renin levels are dependent upon body position, sodium intake and medications. The PAR might be misleadingly increased in patients with chronic kidney disease, patients taking beta-blockers. Patients taking diuretics, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors may cause false-negatives. On the off chance that the clinical doubt is high, ARR ought to be measured again after stopping the agents mentioned above for two weeks. If clinically feasible substitution with medications such as calcium channel blockers or α 1 -blockers which have minimal effect on plasma aldosterone/renin ratio (PAR) is advised. Mineralocorticoid antagonists should be ideally withheld one month before testing. However, it may be difficult to stop all anti-hypertensive medications and PAR can be checked while using current medications with cautious interpretation of results. Furthermore, hypokalemia must be corrected beforehand because it suppresses aldosterone and in this manner can veil hyperaldosteronism. It should be noted that salt intake should not be limited [6].

Preferably, morning plasma samples (8 - 10o'clock) are collected for aldosterone concentration, plasma renin activity (or direct plasma renin concentration) and PAR. The patient ought to have gotten up for at least 2 hours and blood taken following 15 minutes in sitting position. A high plasma aldosterone concentration (PAC) ≥ 10 ng/dL (277 pmol/L) and low renin (plasma renin activity [PRA] < 1 ng/mL/hour or plasma renin concentration [PRC] less than the lower limit of normal, suggest PA. Direct renin levels can be measured, which

has the advantage of being stored at room temperature. ARR (aldosterone: renin ratio) can be useful but can make a misleading outcome in cut-off values among different laboratories. A ratio of at least 40 (20 ng/dL/h to 40 ng/dL/h) or more than 135 (68 pmol/mU to 135 pmol/mU) has a sensitivity of 73% to 93% and a specificity of 71% to 84%. So, an increase in ARR itself is not diagnostic of PA and that confirmatory testing (for instance, sodium loading) is required to confirm the diagnosis. Confirmatory testing is not required in the patient with spontaneous hypokalemia, undetectable PRA or PRC and a PAC ≥ 20 ng/dL.

Different tests can be utilized which can exhibit the absence of suppressibility of plasma aldosterone level and confirm diagnosis [5,6]. The Endocrine Society's clinical practice guidelines do not determine which of these confirmatory tests ought to be viewed as the highest quality level to affirm or prohibit the diagnosis; consequently, various tests are performed by various studies.

Oral sodium loading, e.g. 2g sodium chloride tablets taken three times daily for three days. Urine aldosterone excretion > 12 mcg/24-hour is consistent with hyperaldosteronism (provided that urine sodium excretion more than 200 mEq/24-hour to document adequate sodium loading). Another confirmatory test that can be used is the saline infusion test which is simpler, less invasive, and with fewer risks. Conversely, this test has a lower specificity and sensitivity than the other tests. The patient receive 2000 ml of 0.9% NaCl intravenously for 4 hours, with measurement of aldosterone levels before and after the test. The test ought to be performed on a lying position in the morning to systemize the impacts of body position and circadian rhythm (cortisol should be measured for test validation). Suppression of aldosterone after saline infusion (aldosterone < 5 ng/dl) rule out PA, and with an aldosterone > 10 ng/dl the diagnosis is proven [8].

Other confirmatory tests include fludrocortisone suppression test and Captopril challenge test. The fludrocortisone suppression test is very tedious and costly and seldom utilized. Moreover, the measurement of aldosterone metabolites tetrahydro-aldosterone and aldosterone-18-glucuronide in 24-h urine can be utilized. However, the measurements in the urine are not a better test than the saline loading test and are not widely available. The diagnosis and the management of Conn disorder are best approached with a multidisciplinary group.

Once excess aldosterone production is documented, the subsequent step is adrenal computed tomography (CT) to distinguish between APA and bilateral hyperplasia. However, some studies indicate that the CT cannot differentiate reliably between bilateral hyperplasia and adrenal adenomas. The adrenal glands may appear normal on CT, or may shows nodular changes in idiopathic adrenal hyperplasia, or may show incidental nonfunctioning adrenal cortical adenoma especially above the 40 years. If the adrenal CT was non-conclusive for unilateral adrenal adenoma (> 1 cm) or age above 40 years bilateral adrenal venous sampling (catheterization of adrenal veins) by an experienced interventional radiologist remains the most precise procedure to distinguish between APA and bilateral hyperplasia. It distinguishes between unilateral adrenal adenoma and bilateral hyperplasia. The aldosterone/cortisol ratio of both adrenal veins is compared. If there is a gradient of > 3, an aldosterone-producing adenoma is diagnosed. If the gradient is < 3, hyperplasia might be suspected [8].

Plasma 18-hydroxycorticosterone or iodocholesterol adrenal scan have limited clinical utility. Genetic testing that can detect mutations can confirm Glucocorticoid-suppressible hyperaldosteronism. Somatic mutations in *KCNJ5*, *CTNNB1, ATP1A1*, *ATP2B3* and *CACNA1D* are found in more than 50 percent of resected aldosterone producing adenoma [7].

Cardiovascular and cerebrovascular complications

PA cause vascular endothelial dysfunction, decreased vascular compliance, heart fibrosis and prothrombotic changes in plasma. Multiple studies demonstrate that inhibiting the mineralocorticoid receptor is highly successful in heart failure treatment [4].

Patients with PA have an increased morbidity from myocardial infarction, atrial fibrillation and left ventricular hypertrophy, diastolic dysfunction, compared with patients with essential hypertension with similar blood pressure controls. Milliez., *et al*. for the first time determined that patients with PA are more prone to cardiovascular complications than essential hypertension patients, including atrial

fibrillation (7.3% versus 0.6%) and myocardial infarction (4.0% versus 0.6%) and left ventricular hypertrophy (prevalence 32% versus 14%). Overall, abundant levels of aldosterone may be a risk factor for arrhythmic disorders occurring either through left ventricular hypertrophy or through heart fibrosis [9].

Renal damage is more typical in patients with primary hyperaldosteronism than patients with essential hypertension, as estimated by 24-h urinary albumin excretion. Urinary loss of potassium and hydrogen ions traded for sodium at the distal nephron may bring about hypokalemia and metabolic alkalosis [10].

Fifty four percent of stroke incidence is ascribed to hypertension worldwide [11]. There was higher frequency of strokes primary hyperaldosteronism compared with patients with essential hypertension (12.9% versus 3.4%) [10]. The German Conn registry indicates comparative prevalence rates for German patients (12.8%) for cerebrovascular disorders including transient ischemic attacks (TIA), stroke and cerebrovascular stenosis [12].

Aldosterone abundance influences both ischemic stroke and hemorrhagic stroke leading to an increase in stroke rates. Glucocorticoid-receptive aldosteronism patients would, in general, demonstrate an early beginning of the hemorrhagic stroke and ruptured intracranial aneurysms. Besides, cerebral vascular fibrosis increases the incidence of vessel rupture [8].

For the most part, cerebrovascular events happen in 10% to 20% in patients with primary hyperaldosteronism. In 2018, Monticone., *et al*. demonstrated that the risk of stroke is 2.58 times more likely in primary hyperaldosteronism than in essential hypertensive patients (95% CI, 1.93 to 3.45) [13].

Surgical treatment

Treatment of choice of aldosterone-producing adenoma, carcinoma, and unilateral macronodular hyperplasia, is laparoscopic adrenalectomy. Pretreatment with mineralocorticoid antagonist such as spironolactone is required to prevent postoperative hypoaldosteronism. Frequently, this pretreatment likewise improves left ventricular cardiovascular function and therefore the preoperative condition of the patient. Spironolactone ought to be suspended one week before the operation or at the most at the time of medical procedure and ought to be routinely checked for serum potassium, blood pressure, renin, and aldosterone. Postoperative hypoaldosteronism with hyperkalemia and hypotension is relieved with 50 - 100 μg fludrocortisone daily [14]. Excision of the adenoma improves hypokalemia in practically all patients and normalize hypertension in 33 - 80% of cases, Overall, hypertension in patients with adenomas after adrenalectomy can be better managed with fewer drugs more effectively. Surgically treated patients demonstrated no measurable distinction in the incidence of atrial fibrillation in comparison to age-coordinated essential hypertensive patients. This accentuates the significance of early acknowledgment of patients who may require adrenalectomy to reduce the risk of atrial fibrillation [14].

Medicinal treatment

Adrenalectomy in idiopathic bilateral adrenal hyperplasia is infrequently effective in these patients and better be treated with pharmacologic treatment.

Mineralocorticoids antagonists

Mineralocorticoid antagonists are utilized to block the effect of excess aldosterone on the receptor. Essentially, starting dosage of 12.5 - 25 mg/day spironolactone and depending on blood pressure and clinical manifestations, with up titration the dose at 4-week intervals. Close observation of blood pressure, electrolytes and creatinine are fundamental to detect hyperkalemia or increase in serum creatinine. In general, spironolactone ought not to be given in renal deficiency, in any case, studies demonstrate that supervised managed treatment with spironolactone in low dosages is likewise tolerated in dialysis patients. In hypokalemia, this typically remunerates rapidly after the beginning of spironolactone therapy. However, the impact on blood pressure can take a few weeks to start seeing improvements [15].

The maximum dose is 400 mg spironolactone per day possible to give patients because of the side effects of this medication. In men, it can cause gynecomastia, erectile dysfunction, and decreased libido, and in women, it can cause mastodynia and cycle disturbances. The frequency of gynecomastia in men increases greatly with increases dosages of spironolactone and can reach more than fifty percent for dosages above 150 mg.

At the point when the side effects of spironolactone can happen, a change to eplerenone could be advised. The effectiveness of eplerenone in treating hypertension is established, however, its adequacy is lower than spironolactone and it would require a higher dosage (50 - 200 mg/day). On the off chance that blood pressure isn't returning to normal levels, more antihypertensive must be utilized. However, it ought to be noticed that the utilization of spironolactone frequently lessens the number of antihypertensive medications used [13].

Potassium-sparing diuretics

Potassium-sparing diuretics generally act by inhibiting the luminal epithelial sodium channel (ENaC). A dosage of 2.5 - 20 mg for every day of amiloride is used. In Germany, amiloride is just accessible as a mix arrangement with hydrochlorothiazide. Nonetheless, monotherapy with amiloride is normally insufficient to satisfactorily control blood pressure. Triamterene, which is additionally accessible just as a joined hydrochlorothiazide readiness, is utilized at a measurement of 50 - 200 mg/day. Potassium-saving diuretics ought not to be utilized for hyperkalemia, extreme hyponatremia or renal insufficiency [2].

Other antihypertensive medications

ACE inhibitors reduce circulating angiotensin II levels and have been utilized effectively in patients with idiopathic adrenal hyperplasia. This achievement is presumably because of the way that idiopathic adrenal hyperplasia is angiotensin-dependent, however aldosterone-producing adenoma is as a rule not. Treatment with spironolactone may invigorate the renin-angiotensin system and lead to safe hypertension with increased levels of angiotensin II. Some of these patients respond well to treatment with ACE inhibitors. Significantly, patients are prompted before starting treatment with ACE inhibitors that the bundle supplement contains hyperaldosteronism as a contraindication [1].

The utilization of calcium antagonists, Nifedipine (20 - 40 mg/day), for instance, has been used for treatment of idiopathic bilateral hyperplasia and aldosterone-producing adenoma, prompting hypotension and aldosterone levels to decrease.

Salt restriction (< 2 g/day or < 100 mEq/day), weight control, smoking cessation and an active lifestyle are also helpful to lower blood pressure [2].

Upgrading healthcare team outcomes

In patients with suspected PA, it is important to keep up an inter-professional collaboration between the primary care physician, endocrinologist, and the laboratory staff. The workup of suspected PA includes plasma aldosterone to plasma renin ratio, ideally be performed early in the morning before 8 am. Confirmatory tests including oral sodium loading or saline infusion require opportune blood draws by laboratory staff and cautious guidance to the patient for sodium loading to take into consideration precise and reliable results. Adrenal CT and possible AVS will be done after confirmation of diagnosis of PA. It is essential to altogether to interpret the results and objectives of treatment as this will help the inter-professional correspondence with primary care physician, or surgeon if the patient is a careful possibility for adrenalectomy. An intensive clarification of the treatment choices ought to be given to the patient to enable them to be a part of the medical team in decision making [16].

Conclusion

PA is the most common cause of secondary hypertension. Screening of PA is performed by measuring a morning blood sample for PAC and PRA or PRC. Subtype testing should start with an adrenal glands CT scan. Adrenal vein sampling is performed for subtypes diagnosis. is indicated to accurately localize the source of aldosterone production in equivocal cases.

The hypertension can be either treated with surgery or with pharmacologic therapy depending on the etiology of the excess aldosterone. The treatment relies upon the disease subtypes where normalizing blood pressure and reversal of associated comorbidities is achieved. Undiagnosed or inadequately treated PA results in increased cardiovascular morbidity and mortality.

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