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Primary hyperaldosteronism – a practical approach from the cardiologist perspective

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Abstract

Primary hyperaldosteronism is the most common cause of endocrine secondary hypertension in the general population. Studies report a prevalence of primary hyperaldosteronism ranging from 10% of patients with BP > 180 mmHg and up to 20% of those with resistant hypertension. Regardless of the primary or secondary cause of hyperaldosteronism, increased levels of aldosterone can cause resistant hypertension and electrolyte imbalance. Moreover, individuals with primary hyperaldosteronism have an increased risk of long-term cardiovascular complications (stroke, coronary artery disease, atrial fibrillation, and heart failure) compared with those with essential hypertension. Given the increasing prevalence of primary hyperaldosteronism and the known impact on CV morbidity, early diagnosis is of utmost importance. This article aims to review the topic of primary hyperaldosteronism, with emphasis on patient evaluation and management.

Keywords: hypertension, hyperaldosteronism, aldosterone/renin ratio, adrenal adenoma, bilateral idiopathic hyperplasia

Introduction

First described in 1953 by Polish internist Michal Litynski and later in 1955 by endocrinologist Jerome W. Conn [1], primary hyperaldosteronism (PH) is the most common cause of endocrine secondary hypertension (HTN) in the general population. The two most common causes of PH are adrenal adenoma (AA - Conn adenoma) and bilateral idiopathic hyperplasia (BIH). This article aims to review this topic, with emphasis on patient evaluation and management.

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Epidemiology

The prevalence of PH varies depending on the criteria used to diagnose this pathology and the population it refers to. Thus, studies report a prevalence of PH ranging from 10% of patients with a BP >180 mmHg and up to 20% of those with resistant HTN [2, 3]. Regarding the two most common causes, when the screening is performed selectively for PH using the aldosterone/renin ratio (ARR), the prevalence of AA exceeds that of BIH (60% versus 35%) [4]. Paradoxically, when broader, non-selective screening is performed, the prevalence of BIH appears to be greater (65% versus 30%) [5]. 5% of PH cases are familial cases [6].

In the evaluation of a patient with resistant HTN, it may take up to ten years for PH to be

investigated, which results in an average age of diagnosis of 50 years [7]. PH affects both sexes in equal proportions, but AA has a higher prevalence among women [8].

Anatomy, physiology and pathology

The adrenal glands are retroperitoneal organs composed of cortex (in which mineralocorticoid, glucocorticoid and sexual hormones are synthetized) and medulla (in which catecholamines are synthetized). From the outer to the inner layer, aldosterone is synthesized in the zona glomerulosa, cortisol is synthesized in the zona fasciculata, and androgens and estrogens are synthesized in the zona reticularis.

PH is caused by an independent and uncontrolled production of aldosterone by the adrenal cortex. Normally, aldosterone production is regulated by the renin-angiotensin-aldosterone system (RAAS), in which the kidney, in response to decreased renal perfusion, produces renin and subsequently angiotensin II, which acts on the cortex and stimulates the production of aldosterone that will restore renal perfusion by reabsorption of water and salt. Other mechanisms regulating aldosterone secretion are serum potassium, adrenocorticotropic hormone (ACTH) synthesis and dopamine. In addition to renal effects, there are aldosterone receptors in cardiomyocytes, smooth muscle vascular cells, macrophages and neurons. At this level, aldosterone induces oxidative stress, endothelial dysfunction, inflammation and vascular, cardiac and renal fibrosis. In addition, aldosterone secretion appears to inhibit NO-synthase, increasing oxidative stress and suppressing NO-dependent vasodilation [9].

In PH, excess aldosterone is produced autonomously by a primary adrenal tumor (AA) or by BIH, without being suppressed by the RAAS. Although the exact causes of AA or BIH development are not clear, there are a number of mutations that appear to be associated with some subtypes of PH (e.g. *KCNJ5, CACNA1D, ATP1A1, ATP2B3* or *CTNNB1*) [10]. These mutations affect the zona glomerulosa by promoting increased expression of *CYP11B2*, the gene responsible for the production of aldosterone synthetase, an important enzyme in aldosterone biosynthesis. Mutations in the *KCNJ5* gene (potassium channels) are the most common and present in approximately half of AA cases [11]. Although the pathogenesis of BIH is even less understood than that of AA, a recent study evaluating anatomical-pathological specimens of a cohort of subjects known to have BIH, suggests that a possible precursor modification of BIH could be represented by cell agglutination caused by a mutation in the *CACNAID* gene [12].

Both frequent and less common causes of PH are detailed in Table 1. Regardless of the primary or secondary cause, increased levels of aldosterone can cause resistant HTN and electrolyte imbalance. Moreover, individuals with PH have an increased risk of long-term cardiovascular complications (stroke, coronary artery disease, atrial fibrillation, and heart failure) compared with those with essential HTN [13].

Clinical presentation

Patients referred for evaluation for PH typically have moderate to severe, persistent HTN, resistant

Table 1. Causes of hyperaldosteronism

Primary Hyperaldosteronism		Secondary Hyperaldosteronism
Frequent causes	Rare causes	Causes
Adrenal adenoma (35%) Bilateral (60%) or unilateral (2%) idiopathic hyperplasia	Aldosterone secreting tumors (<0.1%) Adrenocortical adenocarcinoma (<1%) Familial hyperaldosteronism Type 1 – glucocorticoid responsive (<1%) Type 2 (<2%) Type 3	Renal artery stenosis Congestive heart failure Decompensated liver cirrhosis Nephrotic syndrome

to multiple classes of antihypertensive drugs. At baseline, they are often asymptomatic, and when symptoms are present, they are generally nonspecific and may be attributed to hypokalemia and hyperaldosteronism. These include muscle spasms, fatigue, headache, polyuria and polydipsia. Postmortem studies have demonstrated the presence of extensive fibrosis in the heart, kidneys, lungs, pancreas and adrenal glands in subjects with PH. The presence of myocardial fibrosis explains the increased risk of arrhythmogenesis and death and is also confirmed by the data from the RALES and EPHESUS, studies that confirmed the beneficial effects of spironolactone and eplerenone respectively [14, 15].

Hypokalemia is the result of the direct effect on the nephron by increasing excretion in the distal tube, and it is present in only 40% of cases of PH, much rarer in BIH. [16, 17]. When present, it may be associated with other metabolic imbalances such as alkalosis, mild hypernatremia, and hypomagnesemia [17].

Screening in high risk patients

Given the increasing prevalence of PH and the known impact on CV morbidity, early diagnosis is of utmost importance. The populations at risk for PH who should be screened are patients with values of BP >150/100 mmHg on three measurements on different days, those with values >140/90 mmHg under treatment with three classes of antihypertensives, those with values <140/90 mmHg but with a minimum of four antihypertensives, those who associate HTN and hypokalemia/incidentaloma/sleep apnea/family history of early HTN, stroke <40 years or first-degree relatives diagnosed with PH [18].

Screening should be initiated by measuring aldosterone/renin ratio (ARR) - the ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA) or, less frequent, direct renin concentration (DRC). ARR is a sensitive index that integrates the pathophysiological changes in PH - the increase of PAC and the suppression of the renin level. It is superior to the isolated measurement of aldosterone, DRC or potassium. In order to properly measure ARR, it is necessary to stop certain drugs for at least four weeks (mineralocorticoid antagonist - MRA, amiloride, triamterene, loop diuretics or thiazides) and then interpret the ARR in the context of the remaining medication. If ARR results are not diagnostic, the remaining classes (beta blockers, central alpha antagonists, ACE inhibitors, angiotensin receptor blockers, renin inhibitors, dihydropyridine calcium blockers) should be discontinued for two weeks. These drugs may be temporarily replaced with alpha blockers (doxazosin, prazosin, terazosin), non-dihydropyridine calcium blockers or vasodilators (hydralazine, moxonidine), which have minimal effect on serum renin and aldosterone levels. Moreover, in order to correctly interpret the results of the ARR, it is necessary to take into account electrolyte imbalances, kidney disease, sex, age, menstrual cycle phase and pregnancy [19, 20]. The ideal conditions for the determination of ARR are: in the morning, fasting, with the patient awake for at least two hours, in a sitting position for at least five minutes, with all medication stopped for at least two weeks (mineralocorticoid antagonists at least four weeks), with a potassium around 4 mEq/l, under an unrestricted sodium diet [19].

When establishing the limit values for a positive ARR test for PH, it should be taken into account that the sensitivity and specificity differ. Thus, when using an ARR calculated as the PAC/PRA ratio, the values range from 20-40 ng/dl per ng/ml per hour, 20 ng/dl per ng/ml per hour (554 pmol / l per ng / ml per hour) being the most commonly used. In some cases, false positive ARR may be secondary to low levels of both PAC and PRA, as is the case of hypertensive patients with suppressed renin levels, in addition to low aldosterone. Therefore, in the case of low renin hypertensives (30% of hypertensives), some investigators recommend combining a positive ARR with a minimum PAC of 15 ng/dl (416 pmol/l) in order to increase the positive predictive value [21, 22].

Confirmatory tests for PH

In the case of a positive ARR test, clinicians should confirm or deny the diagnosis of PH with one of the confirmatory tests. Their purpose is to determine if aldosterone synthesis can be influenced, because in the case of PH it should be independent,

uncontrolled. However, according to the latest guidelines of the Society of Endocrinology, there is a case in which confirmatory tests are no longer required: spontaneous hypokalemia with undetectable plasma renin and with PAC >20 ng/dl. For all other cases, confirmation is required to limit additional invasive procedures in false-positive cases [18].

Currently, there are four approved confirmatory tests for PH diagnosis: oral sodium loading, saline infusion test (SIT), fludrocortisone suppression test (FST), and captopril challenge test [23]. Although there is no gold-standard, each test offers specific advantages and disadvantages that allow an individualized decision for each case. As with the screening test, it is necessary to stop the medication that interferes with the aldosterone levels and to comply with the test indications mentioned above. A recent meta-analysis of 3686 patients concluded that the SIT and the captopril challenge test had high and comparable accuracy for PH diagnosis, but that the latter would be a more feasible method, being safer and easier to perform [23].

Oral sodium loading implies an increase in sodium intake to >200 mmol/day (> 6g/day) for 3 days, quantified by measuring the urinary sodium. It is important to administer potassium supplements in order to maintain potassium within normal limits. Urinary aldosterone/24h is measured in urine collected from day 3 to day 4. PH is unlikely in the case of urinary aldosterone <10 μg/24 h, in the absence of renal disease, while a value >12-14 μg/24 h makes the diagnosis of PH very likely [18].

The saline infusion test involves the administration of 2 liters of saline in 4 hours, starting at 8 a.m., with continuous monitoring of BP and heart rate. The values of renin, aldosterone, cortisol and potassium are determined before the infusion is administered and at the end. Post-infusion aldosterone <5 ng/dl makes PH diagnosis unlikely, values above 10 ng/dl suggest this diagnosis, while values between 5-10 ng/dl are impossible to interpret [18]. The oral sodium test and SIT should not be used in patients with severe uncontrolled HTN, renal failure, cardiac arrhythmias or severe hypopotassemia.

Fludrocortisone suppression test involves the administration of 0.1 mg fludrocortisone orally every six hours for four days, together with potassium and salt supplements (to maintain urinary sodium excretion of at least 3 mmol/kg). On day 4, PAC, PRA and plasma cortisol are determined. Confirmation of PH diagnosis is made by determining a PAC > 6 ng/dl and a PRA of <1 ng/ml/h [18].

The challenge test with captopril involves the administration of 25-50 mg of captopril after one hour in a sitting or orthostatic position. Subsequently, with the patient sitting, the PAC, PRA and cortisol are determined at time 0, at one hour and at two hours after. Normally, plasma aldosterone is suppressed by the administration of captopril. In patients with PH, PAC remains elevated, with low PRA [18].

Two other methods are under investigation as possible alternatives: dexamethasone-enhanced FST (FDST) and sitting SIT (SSIT). FDST is a modified form of FST in which dexamethasone is administered on the last day of the test to neutralize any endogenous stimulatory effect induced by ACTH on aldosterone synthesis [24]. SSIT is a modified form of SIT, in which the patient receives a saline infusion in a sitting position, but with a raised thorax, based on the fact that the level of aldosterone is dependent on posture (increases in clinostatism).[25].

7. PH subtyping

So far, this article has outlined the initial steps in PH diagnostics. Once the biological diagnosis is established, the next step is to evaluate the differentiation between HP subtypes (AA or BIH), as the treatment is different. Classification is performed by imaging methods of the adrenal glands and adrenal vein sampling (AVS).

Imaging the adrenal glands

High-resolution computed tomography (CT) is a useful and noninvasive method for PH subtyping. A protocol focused on the adrenal glands where thin sections (<3 mm) are obtained, has a good sensitivity and specificity for identifying an AA (80-85% and 70-75% respectively). Performing an MRI does not offer additional benefits [26]. CT findings can be interpreted as one of the following: (1) normal adrenal glands; (2) unilateral macroadenoma (>1 cm); (3) bilateral micro/macroadenomas; (4) minimum unilateral thickening. Although some features of a unilateral mass >1 cm on CT examination support the diagnosis of AA, there are important overlaps

in CT quantitative analyzes between BIH and AA, making it very difficult to differentiate between AA and nodular hyperplasia, for example. In addition, unilateral adenomas diagnosed with CT may be non-secreting, but they are radiologically impossible to differentiate from secreting AA [27].

Adrenal vein sampling (AVS)

AVS is an invasive procedure that involves the catheterization of bilateral adrenal veins and the determination of aldosterone and cortisol levels uni/bilaterally, as well as from a peripheral vein. Proper cannulation of adrenal veins is defined as an adrenal/peripheral (inferior vena cava) cortisol ratio of at least 2 (or >3 after ACTH administration). Thereafter, the ratio of adrenal/peripheral cortisol to each adrenal vein is determined - a ratio> 3 (or > 5 after ACTH administration) is suggestive for a vein that serves an AS and thus allows the exact location of the incriminated adrenal gland. ACTH administration during AVS may allow to increase the selectivity, since ACTH controls the variations of aldosterone and cortisol [28, 29]. Although it is a laborious technique, especially in catheterizing the right adrenal vein, AVS has a success rate of over 95% in experienced centers. Therefore, due to the high specificity and sensitivity (100% and 95% respectively), AVS is considered to be the gold standard for differentiating an AA from BIH [30, 31].

Due to the low availability and the lack of standardization between different centers, there is an ongoing concern for the discovery of new methods of diagnosing an AA, such as PET-CT or steroid profiling [32].

Management

Adrenalectomy for unilateral AA

In theory, adrenalectomy for unilateral AA should reduce excess aldosterone, normalizing the values of potassium and BP. However, the evolution of patients after adrenalectomy varies widely in the literature data. In 2008, Zarnegar et al. developed a predictive model for selecting patients that may benefit from adrenalectomy at one year, identifying four predictive factors: the use of less than two antihypertensives, a BMI <25 kg/m^2, duration of HTN <6 years and female sex. Based on this, the probability of a favorable response is low (27% in case of 0-1 characteristic), moderate (46% in case of 2-3 characteristics) and high (75% in case of 4 characteristics) [33].

In 2017, an international commission of experts (The Primary Aldosteronism Surgery Outcome group) published a consensus for defining clinical and biochemical outcomes for patients undergoing unilateral adrenalectomy (Table 2) [34]. In the cohort they used for the analysis, biochemical success was observed in 94% of the cases, but the clinical success was obtained only in 37% of the subjects. It should be noted that post-adrenalectomy results depend on the duration of disease and aldosterone-induced HTN, as well as the effects on the CV and renal apparatus. Younger female seem to have better outcomes after surgery, while obese patients have poorer outcomes [35].

Adrenalectomy with open trans peritoneal approach has been the gold standard for many years, but lately the latero-posterior laparoscopic approach has been gaining more and more popularity, being an effective and safe treatment, with fewer postoperative complications. In addition, the small incision, low postoperative pain, and shorter hospitalization are other benefits. A recent meta-analysis comparing classical trans peritoneal adrenalectomy and laparoscopic retroperitoneal approach, showed that the retroperitoneal approach is superior in the short term to the classical one, while another meta-analysis showed the equivalence of the two methods. [36, 37].

Recently, a new modern technique, robotic adrenalectomy has become an attractive alternative to laparoscopic adrenalectomy. Studies show that it is a feasible and safe method. In a study comparing the classical approach with robotic surgery, the latter was shown to be more cost-effective and safer. [38].

Preoperatively, it is necessary to control the BP and hypopotassemia. This can be obtained by treatment with spironolactone, which has proven useful in preventing the risk of postoperative hypoaldosteronism (absence of chronic inhibition of aldosterone synthesis in the contralateral gland). Postoperatively, treatment with spironolactone should be discontinued [39]. Serum potassium level should be monitored for at least four weeks. Also, due to a possible chronic inhibition in the contralateral gland, there is a risk of hypoaldosteronism

Table 2 Definition of complete or partial remission and failure after unilateral adrenalectomy

	Clinical features	Biochemical features
Complete remission	Normal BP without drug treatment	1. Correction of hypokalemia And 2. ARR normalization Or 3. Suppression of aldosterone in confirmatory tests if ARR remains elevated postoperatively
Partial remission	Stable BP with fewer antihypertensive drugs or lower BP under the same amount of antihypertensive drugs	1. Correction of hypokalemia but increased ARR And 2. A >50% decrease in aldosterone level Or 3. Abnormal but low postoperative aldosterone
Failure	Unchanged or higher BP under the same amount of antihypertensive medication	1. Persistent hypokalemia Or 2. ARR persistently increased And 3. Failure to suppress aldosterone in confirmatory tests

that must be counteracted by administering a high sodium diet [40].

MRA treatment for bilateral PH

Numerous studies have examined the effects of MRA treatment for PH. Although the dose of MRA is usually titrated until normokalemia is achieved, there is no method to quantify the number of antagonized receptors. The guidelines recommend spironolactone to be the drug of choice, keeping in mind the adverse effects such as gynecomastia (6.9% among men who received 50 mg/day and up to 52% among those who received 150 mg/day), erectile dysfunction in men and menstrual disorders in women. In the event of these effects, it is recommended to switch to eplerenone [40].

A study that looked at a cohort of 602 patients with PH treated with MRA compared with a control group with essential HTN over a 15-year period found a 1.9-fold increased risk for CV events (myocardial infarction, coronary revascularization, IC or stroke hospitalization) and a 1.3-fold higher risk of death among patients with PH [41].

The effect of adrenalectomy versus MRA treatment on left ventricular hypertrophy (LVH) was studied in a meta-analysis that included 4 prospective studies with 355 patients. The prevalence of LVH was similar (56% versus 52%) and after four years of follow-up, both drug treatment and adrenalectomy reduced LV mass in a similar manner. It is important to note that most of those who underwent adrenalectomy had an AA, while BIH patients received drug treatment. [42].

Conclusions

PH is a common cause of secondary HTN, caused by autonomic aldosterone secretion by one (AA) or both adrenal glands (BIH). The initial screening test is the ARR, the results of which must be interpreted in the context of the medication administered. Performing the test requires stopping certain classes of drugs and harvesting under special conditions. A positive screening test requires confirmation by additional tests most of the time. After diagnosis, it is recommended to perform an abdominal CT scan, followed by AVS for the exact lateralization of the tumor. Those with a certain unilateral tumor benefit from unilateral adrenalectomy, while those with bilateral involvement predominantly undergo drug treatment. Most patients have post-adrenalectomy

benefits. Recognition and diagnosis of this disease is important, as PH is associated with an increased risk of arrhythmias, coronary heart disease, heart failure, stroke, proteinuria and chronic kidney disease, compared with essential HTN. [43].

Conflict of interest

The authors confirm that there are no conflicts of interest.

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