Primary hyperaldosteronism

Ergita Nelaj[1], Margarita Gjata[1], Mihal Tase[1]

[1]Service of Internal Medicine and Hypertension, University Hospital Center "Mother Teresa", Tirana, Albania.

Corresponding author: Ergita Nelaj, MD;
Address: Rr. Dibres, No. 371, Tirana, Albania;
Telephone: +355692066148; E-mail: dr_ergi@yahoo

Abstract

Primary aldosteronism (PA) is the most common form of secondary hypertension accounting for approximately 10% of the patients referred to hypertension clinics and as high as 20% of those with refractory hypertension in the industrialized countries.
Patients with PA exhibit hypertension, high plasma aldosterone concentration, low plasma renin activity, and varying degrees of hypokalemia and metabolic alkalosis. PA is usually caused either by aldosterone-producing adenoma (APA), in one adrenal or bilateral hyperplasia of the zona glomerulosa (idiopathic hyperaldosteronism: IHA), also called bilateral zona glomerulosa hyperplasia; but it may also be caused by small hyperplastic lesions of one adrenal gland (unilateral adrenal hyperplasia (UAH), unilateral multiple adrenocortical nodules (UMN)), bilateral APAs, and three familial types of PA or hyperaldosteronism.
For many years, it was thought that primary aldosteronism was a relatively benign cause of hypertension, rare (<1%) and suspected only in patients with severe hypokalemia. We know now that none of this is the case: primary aldosteronism is relatively common (5% to 16% of unselected hypertensive cases), with much higher cardiovascular risk factors (stroke, atrial fibrillation, and nonfatal myocardial infarction) than age-, sex-, and blood pressure-matched essential hypertensives and with hypokalemia only in a minority of cases.
Hence, detection of secondary forms of hypertension is particularly important because it allows for the targeted management of the underlying disease.

Keywords: adrenal gland, aldosterone, hypertension, renin.

Introduction

Primary aldosteronism (PA or Conn's syndrome) is the most common cause of secondary hypertension. Previously thought to be a rare and relatively benign cause of hypertension, primary aldosteronism is currently recognized as the leading cause of secondary hypertension, with a prevalence of 4.6% to 16.6% among unselected hypertensive adults and with an estimated prevalence ranging between 6% and 23% in patients with resistant hypertension (1,2,5).

PA, described by Conn in 1955, is caused by the autonomous secretion of aldosterone from adrenocortical lesions, and is associated with hypertension due to sodium (Na) retention, hypokalemia due to increased potassium (K) excretion, and organ disorders (cerebral hemorrhage, cerebral infarction, myocardial infarction, cardiomegaly, arrhythmia, renal insufficiency, etc.) due to inappropriate aldosterone levels (3,4).

Although aldosterone excess is directly linked to the development of hypertension through renal sodium and water retention, it also induces tissue inflammation and an increased central sympathetic drive, with subsequent fibrosis and remodeling in critical organs such as the kidney, heart and vasculature. As a consequence, PA leads to the development of renal impairment, atrial fibrillation, stroke and myocardial infarction (3-5). A history of stroke, myocardial infarction and atrial fibrillation were 4-fold (12.9% vs. 3.4%), 6-fold (4.0% vs. 0.6%), and 12-fold (7.3% vs. 0.6%) more common in patients with PA than essential hypertension, respectively (6).

Current guidelines of the Endocrine Society recommend the confirmation or exclusion of PA in all groups of patients with an increased risk of the disease. These include patients with Joint National Commission stage 2 (>160–179/100–109 mm Hg), stage 3 (>180/110 mmHg), or drug-resistant hypertension; hypertension and spontaneous or diuretic-induced hypokalemia; hypertension with adrenal incidentaloma; or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 yr) (1).

Thus, the early detection of PA is important to initiate the proper specific treatment by unilateral adrenalectomy or medical treatment.

The most common form of PA are idiopathic bilateral hyperplasia (IHA) and aldosterone-producing adenoma (APA), accounting for 95% of clinical cases. Unilateral adrenal hyperplasia is less commonly identified, but this diagnosis should be considered if lateralization test (*e.g.*, adrenal venous sampling (AVS)) is positive but radiological and histological examination does not detect an adenoma. Approximately 1% of the patients are shown to have aldosterone-producing carcinoma (7) and further 5% of PA are attributed to familial hyperaldosteronism (FH), including three forms. The first is glucocorticoid-remediable aldosteronism (GRA), inherited in an autosomal dominant fashion, caused by the presence of a chimeric gene originating from an unequal cross-over between the *CYP11B1* and *CYP11B2* genes, leading to ACTH-sensitive aldosterone production. Most individuals with familial hyperaldosteronism type I develop severe hypertension early in life (before the age of 20 years) and display high rates of morbidity and mortality from cerebrovascular events, although milder clinical phenotypes have also been reported (8).

FH-II, the most common, responsible for 3% to 5% of cases of primary aldosteronism, is of yet unknown cause though many cases are in linkage with chromosome 7p22 (8). FH-II families can present clinically with APA or IHA, and are not distinguishable from patients with non-familial PA (1,2).

Recently a mutation in KCNJ5 gene, encoding the potassium channel Kir 3.4, has been shown to be associated with FHA III. The mutation occurs near the selectivity filter for potassium resulting in increased sodium conductance and cell depolarization, which, in adrenal glomerulosa cells, produces opening of voltage-activated calcium channels with increased calcium signaling, followed by increased aldosterone production and cell proliferation (8,9).

Histopathology is quite heterogeneous ranging from

micro- or macronodular hyperplasia to adenoma formation, whereas the adjacent adrenal cortex may be atrophic, diffuse hyperplastic or nodular hyperplastic (10). FH-III is a particularly aggressive form of hyperaldosteronism, with medication-resistant hypertension. Clinically, patients present with severe hypertension and variable hypokalemia.

Screening tests

The diagnosis of primary aldosteronism is usually made in patients who are in the third to sixth decade of life (11). Patients with marked hypokalaemia may present with muscle weakness and cramping, headaches, palpitations, polydipsia, polyuria, nocturia, or a combination of these. Polyuria and nocturia are attributed to the hypokalaemia-induced renal concentrating defect (2,11). In recent studies, only a minority of patients with PA (9-37%) had hypokalemia (12). Thus, normokalemic hypertension constitutes the most common presentation of the disease, with hypokalemia probably present in only the more severe cases. Half the patients with an APA and 17% of those with idiopathic hyperaldosteronism (IHA) had serum potassium concentrations less than 3.5 mmol/liter (13,14). Thus, the presence of hypokalemia has low sensitivity and specificity and a low positive predictive value for the diagnosis of PA.

The guidelines recommend screening of patients for PA by simultaneously measuring the plasma aldosterone concentration PAC (pg/mL) and plasma renin activity PRA (ng/mL/hr) and calculating the PAC/PRA ratio (ARR). ARR is currently the most reliable and available means of screening for PA. Many studies have demonstrated that ARR is superior to other laboratory markers (serum potassium, aldosterone concentration or renin alone) owing to its higher sensitivity (15). It should be performed in the morning, with serum potassium level restored to normal level (hypokalemia reduces aldosterone production), and without postural stimuli. If the patient is medicated, since many antihypertensive drugs affect the renin-angiotensin-aldosterone (RAA) system, it is recommended to measure the ARR after changing the anti hypertensive drugs. So, ARB, ACEI, betablockers, Ca-chanel blockers, diuretics and MR must not be used as they interfere with the levels of PRA. It is then prudent to discontinue these medications for 2-4 weeks before starting on the test. For controlling blood pressure during the drug washout period, it is preferable to use effect-neutral antihypertensive drugs, such as verapamil (slow-release form), hydralazine (combined with verapamil to avoid reflex tachycardia) and á1-antagonists (prazosin, doxazosin, and terazosin) (1,2).

Lack of uniformity in diagnostic protocols and assay methods for ARR measurement has been associated with substantial variability in cutoff values used by different groups ranging from 20-100 (8). Therefore, a cut-off value of ARR (according to PRA) of 35 (ng/dL per ng/mL/hr) with highest sensitivity and specificity is recommended for screening purpose (16).

Confirmatory tests

Patients with a positive aldosterone-renin ratio (ARR) measurement undergo testing, by any of four confirmatory tests, to definitively confirm or exclude the diagnosis.

The tests include oral salt loading (OST) or intravenous salt infusion test (SIT), fludrocortisone stimulation test (FST), captopril or losartan challenge test, each with their proponents. Although these tests may differ in terms of sensitivity, specificity, and reliability, the choice of confirmatory test is commonly determined by considerations of cost, patient compliance, laboratory routine and local expertise. It should be noted that confirmatory tests requiring oral or intravenous sodium loading should be administered with caution in patients with uncontrolled hypertension or congestive heart failure.

- *Oral salt-loading test:* On an inpatient basis, the patient is given a 12 g/day salt diet for 3

days, and 24-hour urine pooling is performed thereafter (If a 12 μg/day salt diet is unavailable at the hospital, the salt intake is adjusted by prescribing additional salt). The 24-hour urinary aldosterone and Na excretion is determined, and PA is definitively diagnosed if the urinary alsosterone excretion is >14 μg /day (Na >170 mEq/day) (Criterion at Mayo Clinic: Urinary aldosterone excretion > 12 μg /day (Na > 200 mEq/day).

• *Saline-loading test:* It is desirable to perform the test under inpatient observation. 1) Blood sampling after 30-minute bed rest. 2) Intravenous infusion of 2 L of saline over 4 hours (Ex.: From 8:00 to 12:00). 3) Blood sampling during bed rest after 4 hours (ambulation for urination is permitted after pre-loading blood sampling until 30 minutes before post-loading blood sampling. 4) Judgment criterion: Post-loading PAC > 60 pg/mL (>10 ng/dL with Dynabot RIA Kit II). It is well known that changes in aldosterone during saline loading test are usually observed because of diurnal rhythm of ACTH. It is sometimes useful to simultaneously determine cortisol for judging the results. 5) During the test, the blood pressure and symptoms must be monitored, with safety the first consideration 6) If renin suppression after loading is insufficient, attention to the possibility of secondary aldosteronism is appropriate. This test must be avoided in patients with reduced cardiac function and those suspected of having heart failure.

• *Captopril-challenge test:* i) Blood sampling after 30-minute bed rest (or rest in the sitting position); ii) Administration of four 12.5 mg captopril tablets, crushed (= 50 mg); iii) Blood sampling after 60 (90)-minute bed rest (or rest in the sitting position). 4) Judgment criterion: Plasma aldosterone is normally suppressed by captopril (> 30%). In patients with PA, it remains elevated and PRA remains suppressed. Differences may be seen between patients with APA and those with IHA, in that some decrease of aldosterone levels is occasionally seen in IHA (13,17). Attention to shock associated with a captopril-induced excessive decrease in the blood pressure is necessary in patients with angioedema or renovascular hypertension.

The losartan challenge test (LST) is an alternative form of the captopril-based test,with the assumption that changes in ARR may be larger if ARB is used instead of ACE inhibitor (18).

• *Fludrocortisone Stimulation Test:* i) Patients receive 0.1 mg oral fludrocortisone every 6 h for 4 days, together with slow-release KCl supplements (every 6 h at doses sufficient to keep plasma K^+, measured four times a day, close to 4.0 mmol/liter), slow-release NaCl supplements (30 mmol three times daily with meals) and sufficient dietary salt to maintain a urinary sodium excretion rate of at least 3 mmol/kg body weight; ii) On day 4, plasma aldosterone and PRA are measured at 1000 h with the patient in the seated posture, and plasma cortisol is measured at 0700 and 1000 h.; iii) Upright plasma aldosterone >6 ng/dl on day 4 at 1000 h confirms PA.

Proponents of the FST argue that: i) it is the most sensitive for confirming PA; ii) it is a less intrusive method of sodium loading than SIT and therefore less likely to provoke non-renin-dependent alterations of aldosterone levels; iii) it allows for the potentially confounding effects of potassium to be controlled and for ACTH (via cortisol) to be monitored and detected; and iv) it is safe when performed by experienced hands.

Imaging studies

Once primary aldosteronism is confirmed biochemically, radiologic investigations provide a preliminary method for localization and subtyping of aldosterone-producing lesions. Adrenal computed tomography (CT) scan is the initial modality of choice (1,7,11). The findings on CT for adrenal hyperplasia are usually nonspecific, showing either enlarged or normal-size adrenal glands (19).

CT contributed to lateralization in about 50% of cases only, and this number decreased further to lower than 25% if APAs were smaller than 1 cm

in diameter (1). This makes adrenal venous sampling (AVS) a procedure of choice for differentiating unilateral from bilateral forms of PA, despite its being expensive and invasive. The sensitivity and specificity of successful AVS (95% and 100%) for detecting unilateral disease are significantly better than those of adrenal CT (20).

AVS is the reference standard test to differentiate unilateral (APA or UAH) from bilateral (IHA) disease in patients with PA (21). Although AVS can be a difficult procedure, especially in terms of successfully cannulating the right adrenal vein (which is smaller than the left and usually empties directly into the IVC rather than the renal vein), the success rate usually improves quickly as the angiographer becomes more experienced. Patients may be spared AVS if they are younger than 40 years old, with solitary unilateral apparent adenoma on CT, with still high biochemical and clinical cure rates (20).

Treatment

Treatment of PA is targeted to prevent the excess morbidity and mortality associated with hypertension, hypokalemia and aldosterone-associated organ damage. Since treatment for PA differs among disease types, disease typing is important. If aldosterone hypersecretion from one adrenal has been identified as the cause of PA by AVS, the condition is an indication for laparoscopic adrenalectomy. This surgery can be performed by: (1) a transperitoneal approach (transperitoneal anterior or lateral approach), or (2) retroperitoneal approach (retroperitoneal lateral or posterior approach). Patients are recommended to undergo laparoscopic surgery by an appointed specialist at an experienced facility. Unilateral laparoscopic adrenalectomy is used in patients with unilateral PA because blood pressure and serum potassium concentrations improve in nearly 100% of patients postoperatively (22,23). After adrenalectomy, the final diagnosis is made pathologically. Hypertension is cured (defined as blood pressure <140/90 mm Hg without the aid of antihypertensive drugs) in about 50% (range, 35-60%) of patients with APA after unilateral adrenalectomy (23), with a cure rate as high as 56-77% when the cure threshold was blood pressure less than 160/95 mmHg (24,25). Blood pressure typically normalizes or shows maximal improvement in 1-6 months after unilateral adrenalectomy for unilateral APA but can continue to fall for up to 1 year in some patients.

For patients with PA from bilateral adrenal disease, medical treatment with mineralocorticoid receptor (MR) antagonist, which antagonizes aldosterone action, is the first-line treatment of choice. Spironolactone has been the agent of choice. The dosage is 12.5 mg to 25 mg per day initially and titrated upward to 400 mg per day if necessary to achieve normokalemia without potassium supplementation. The response of hypokalemia usually occurs promptly, but blood pressure response may take months to be fully achieved (11).

Eplerenone is a newer, selective MR antagonist without antiandrogen and progesterone agonist effects (26), thus reducing the rate of adverse endocrine side effects. Eplerenone has 60% of the MR antagonist potency of spironolactone. Amiloride and triamterene are also distal sodium epithelial channel antagonists, and amiloride in particular has been studied most extensively in PA patients. Amiloride can ameliorate both hypertension and hypokalemia and is well tolerated, without the notorious side effects of spironolactone. However, the impact of its clinical use is still not elucidated.

Conclusions

It is now widely recognized that the prevalence of PA is substantially higher than previously believed. Considering the high prevalence of hypertension in the general population, reliable, easy to perform and cost-effective diagnostic tests are required for an early diagnosis of PA. This is particularly relevant as the clinical signs and symptoms of PA are not specific, whereas hypokalaemia, which is regarded as the most distinctive biochemical feature of PA, is not always present. Current standard practice for the diagnosis of PA is to initially apply a screening test

using the calculation of basal ARR followed by a confirmatory test to document autonomous from the RAS aldosterone secretion, such as an oral sodium loading test, saline infusion test, fludrocortisone suppression test or captopril challenge test. The use of ARR as a screening test has simplified the diagnosis of PA, as it permits the application of diagnostic tests only to a pre-selected hypertensive population with a high probability of PA.

Thus, early diagnosis is of paramount importance in order to initiate specific treatment by either surgical removal of the hyperfunctioning adrenal lesion(s) or administration of targeted medical treatment, with the promises of reduced morbidity and mortality and improved quality of life.

Conflicts of interest: None declared.

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