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Primary Aldosteronism: Current trends and challenges to the diagnosis

*Jahan S[1], Fakhrul-Alam M[2], Monzur-Elahi[3], Farhana-Rahman[4], Fariduddin M[5] , Hasanat MA[6]

[1]Sharmin Jahan, Associate Professor, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh; [2]Mohammad Fakhrul-Alam, Assistant Professor (Endocrinology), Abdul Malek Ukil Medical College, Noakhali, Bangladesh; [3]Monzur-Elahi,, MD phase B resident, Department of Endocrinology, BSMMU, Dhaka, Bangladesh; [4]Farhana-Rahman, MD phase B resident, Department of Endocrinology, BSMMU, Dhaka, Bangladesh; [5]Md. Farid Uddin, Professor, Department of Endocrinology, BSMMU, Dhaka, Bangladesh; [6]Muhammad Abul Hasanat, Professor, Department of Endocrinology, BSMMU, Dhaka, Bangladesh

Abstract

Primary aldosteronism (PA) is the autonomous secretion of aldosterone from the adrenals causing excess salt and water retention from the kidneys. It is now a well-established fact that PA is a widely prevalent disorder affecting one in ten hypertensive patients with early and inappropriate target organ damage. It has got excellent response to targeted therapy namely the mineralocorticoid receptor antagonists (MRAs) or surgery for aldosterone producing adenoma (APA) whereas first-line anti-hypertensives medications are mostly ineffective. However the diagnosis is often missed or delayed because of the absence of typical clinical phenotype or the use of hypokalemia as an obligatory screening pre-requisite. While hypokalaemia was historically considered as a hallmark of PA, near about 40% patients are normokalaemic, leading to missed diagnoses. The current diagnostic pathway is challenging for the physician requiring meticulous patient selection and preparation followed by adoption of the screening and the confirmatory biochemical testing that best corroborate the local expertise. Adrenal venous sampling (AVS), thought to be gold standard procedure for subtype differentiation, is limited by its cost, availability, technical demand and high inter-center variability. It is imperative to create awareness regarding this commonplace disease and establish a center-specific, simplified, convenient and cost-effective diagnostic protocol. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2025; 4 (1):21-30]*

Keywords: Primary aldosteronism, Endocrine hypertension, Diagnostic challenge

***Correspondence:** Dr. Sharmin Jahan, Associate Professor, Department of Endocrinology, BSMMU, Dhaka, Bangladesh. e-mail: sharmindmc@yahoo.com, cell no.: +8801731061056.

Introduction

Primary aldosteronism (PA) is the inappropriate and excessive secretion of aldosterone from the adrenal glands independent of the renin-angiotensin-aldosterone (RAAS) axis. Inappropriate or autonomous secretion of aldosterone leads to excessive salt retention by the kidneys which in turn suppresses the production of renin. It is classically characterized by the triad of hypokalemic hypertension (HTN), suppressed plasma renin activity, and increased aldosterone excretion. Even with similar blood pressure level, PA can cause more severe cardiovascular and end organ damage compared to essential hypertension, if diagnosis is delayed.[1]

Primary aldosteronism is popularly known as "Conn syndrome" after Jerome W. Conn who was one of the first physicians to describe such a case.[2] It is a common yet unsuspected cause of Endocrine HTN demanding timely adequate appraisal. Both the physician and the patient are seemingly unaware of its presence and in most cases the diagnosis is much delayed till there is irreversible end organ damage. So, it is imperative to impart adequate knowledge regarding the widespread prevalence and unfavorable outcome of untreated PA patients and to establish a simple and convenient management protocol for individual center.[1] The following review is a brief discussion highlighting the importance of PA diagnosis and the practical problems that are encountered during the diagnostic procedure.

Why it is important to diagnose PA?

a. *The most common etiology of secondary HTN*

Previously, primary aldosteronism was thought to be a rare disorder occurring only in a subset of hypertensive patients with hypokalemia. The prevalence of PA in earlier literature was reported to be as low as 0.5%-1% using hypokalemia as an obligatory screening criterion. However, recent studies showed only a minority of patients with PA (9% to 37%) have hypokalemia. Thus, normokalemic hypertension constitutes the most common presentation of the disease, with hypokalemia probably present in only the more severe cases.[3] Currently, the availability and use of sensitive screening methods like plasma aldosterone to renin ratio (ARR) in both normokalemic and hypokalemic hypertensive patients have dramatically increased the case detection rate for PA. Primary aldosteronism (PA) is now considered the most common endocrine cause of secondary HTN affecting one in ten hypertensive patients. It is also the single most important disorder causing treatment-resistant hypertension (TRH) that is referred to tertiary hypertension centers. The prevalence of PA is reported to be between 4.6% to 13.0% in uncomplicated HTN and up to 30% in patients with treatment-resistant HTN.[3-5]

b. *Tissue specific toxicity leading to early inappropriate end organ damage in PA*

PA occurs due to autonomous production of aldosterone from zona glomerulosa of the adrenals that leads to inappropriate salt and water retention on one hand with continued potassium loss on the other hand by the renal tubules causing hypokalemic HTN. In addition to the distal nephron, the aldosterone receptor has also been identified in the colon, salivary glands, vasculature, heart, adipose tissue, and hippocampus,[6] where both genomic and nongenomic effects occur.[7] Specifically, aldosterone-mediated oxidative stress has been demonstrated in the vasculature by inducing endothelial dysfunction and increasing arterial stiffness and intima to media thickness by promoting the deposition of collagen within arterial walls.[8] These cellular changes are

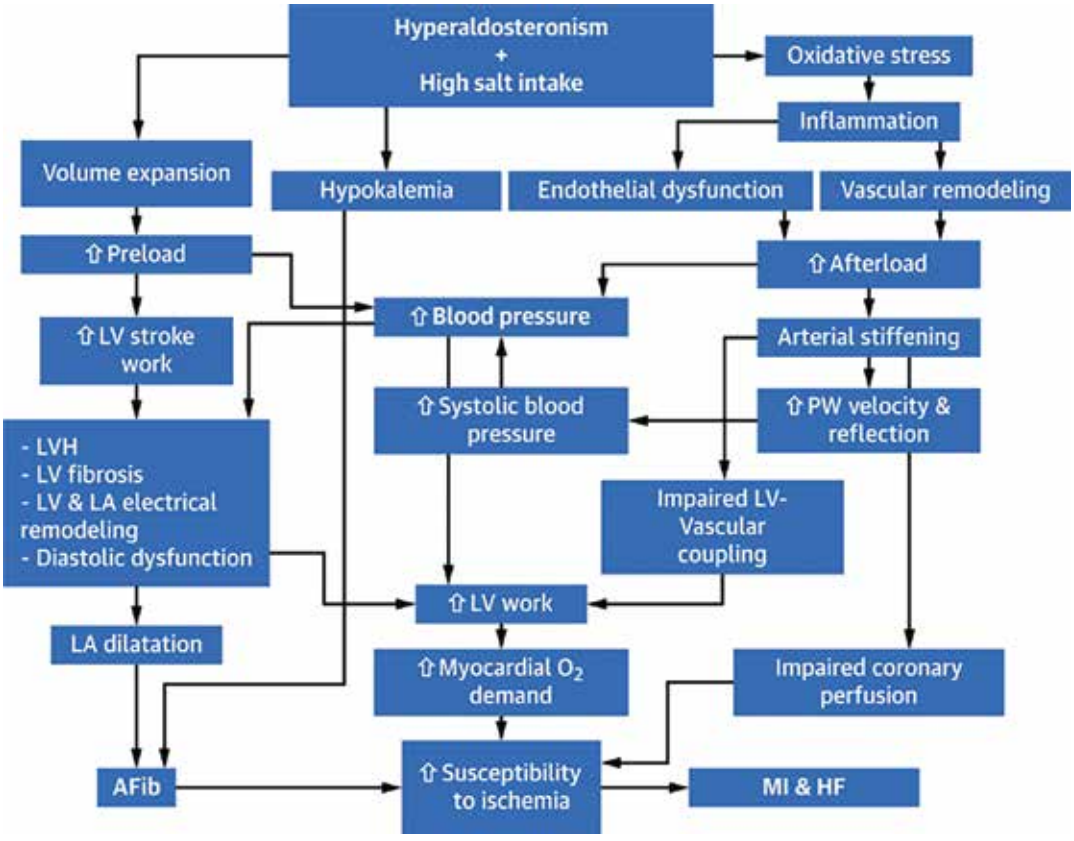

Figure-1: Sequence of events leading to increased risk of MI, heart failure, and atrial fibrillation in PA.[34]

translated clinically by the mounting evidence that continues to support the multisystem sequelae of aldosterone excess that are both independent of blood pressure control as well as out of proportion to the degree of hypertension (Figure-1)

c. The excellent response to specific treatment

HTN in PA is mostly due to inappropriate activation of the mineralocorticoid receptor(MR) by excess aldosterone without the direct involvement of other pathways promoting HTN. As a result, the first-line medications for hypertension have not been shown to effectively treat the excess mineralocorticoid receptor (MR) activation characteristic of PA. When PA goes undetected, patients may not receive effective treatment for excess MR activation and will not be offered surgery, which can cure PA (and sometimes hypertension) in patients with aldosterone-producing adenomas (APA).[2] The response to either medical or surgical management is excellent in PA with either normalization of BP and hypokalemia or dramatic reduction for need of anti-hypertensive medication and preventing/delaying the progression of target organ damage. Early diagnosis and appropriate treatment of PA reduce the long term burden on healthcare system.

What are the obstacles to diagnosis?

a. ***The variable or atypical clinical feature***

Primary aldosteronism, though the commonest cause of secondary HTN, yet it remains an underdiagnosed disorder to date. The misconception of the rarity of the disease, the presence of hypokalemia as a screening prerequisite, the absence of typical clinical phenotype, and the seemingly complicated diagnostic procedure all are responsible for this. The classic presentation of hypokalemic HTN occurs only in a minority of patients whereas the majority are asymptomatic and presents like patients with essential hypertension (EH).

i. The classic presentation

Primary aldosteronism is usually diagnosed between 20 and 60 years of age.[9] The patient may present with either new-onset or long-standing HTN and related end-organ damage. The HTN is commonly moderate to severe and is often resistant to conventional anti-hypertensive medications. The disorder might be brought into notice because of repeated episodes of periodic paralysis resulting from hypokalemic HTN even necessitating hospitalization of the patient several times.

A hypokalemia-induced renal-concentrating defect can result in polyuria and nocturia; this presentation is frequently mistaken for prostatism in men.[10]

However, hypokalemia is not a constant in PA. Only a minority of patients with HTN induced by PA present hypokalemia, with a prevalence ranging from 9% to 37% according to a review by Gruber and Beuschlein.[3] Normokalemia should not be used to rule out PA and patients with resistant hypertension should undergo aldosterone-to-renin ratio (ARR) testing, regardless of potassium levels.[11]

ii. Cardiovascular complications

PA is associated with a higher risk of stroke, nonfatal myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation compared to blood pressure (BP) matched essential hypertension.[12,13] A recent large study by Ohno et al. on Japanese patients showed that those with PA have adverse cardiovascular risk profiles, such as higher body mass index (BMI), more prominent proteinuria, and a higher diabetes mellitus rate. The prevalence of cardiovascular disease was 11% versus 3.4% in the matched hypertensive group in his study.[14] Indeed, the Endocrine Society has referred to PA as a "major public health issue" that needs adequate appraisal.[15]

iii. Quality of life

Several studies have demonstrated the negative impact of PA on quality of life (QoL).[10-13] A recent systematic review found that untreated patients with PA (APA and IHA) had impaired physical and mental QoL compared to the general population. Symptoms of anxiety, demoralization, stress, depression, and nervousness were more frequently reported in untreated patients with PA than in the general population and in patients with hypertension.[16] Adrenalectomy improved QoL and the symptoms of psychopathology.

iv. Renal cyst

Deep-seated renal cysts are found in up to 60% of patients with PA who have chronic hypokalemia.[17] Because of a reset osmostat, the serum high sodium concentration tends to be-normal or slightly above the upper limit of normal.[18] This clinical sign is very useful in the initial assessment for potential PA, especially in patients treated with thiazide diuretics (where the serum sodium concentration tends to be rather normal than low).

v. Subclinical PA/ normotensive PA

PA is not only confined to patients with moderate to severe and/or resistant HTN, but can also be found in patients with mild HTN, and even in those with normotension.[19]

Several lines of evidence indicated that autonomous aldosterone production that meets the PA confirmatory criteria can be detected in 1.8-14.0% of the normotensive population.[20-24] such normotensive PA cases have been also reported to be more likely to develop hypertension within 5 years compared to those without biochemical PA.20 The clinical significance of asymptomatic PA remains largely unclear, but the subclinical phenotype enables us to consider a continuum model of PA development.[21]

vi. Other manifestations:

There is also mounting evidence for the development of type 2 diabetes, insulin resistance, and metabolic syndrome, obstructive sleep apnea, renal diseases, psychiatric diseases, and bone loss in patients with untreated aldosterone excess.[25-29] Interestingly, PA has been associated with both primary and secondary hyperparathyroidism and it has been proposed that hyperparathyroidism can be a useful identification criterion of patients with PA caused by an APA according to Rossi et al.[30]

b. The difficult diagnostic pathway of PA

The diagnostic pathway of PA comprises three sequential steps: screening test, confirmatory test, and subtype localization (Figure-2).

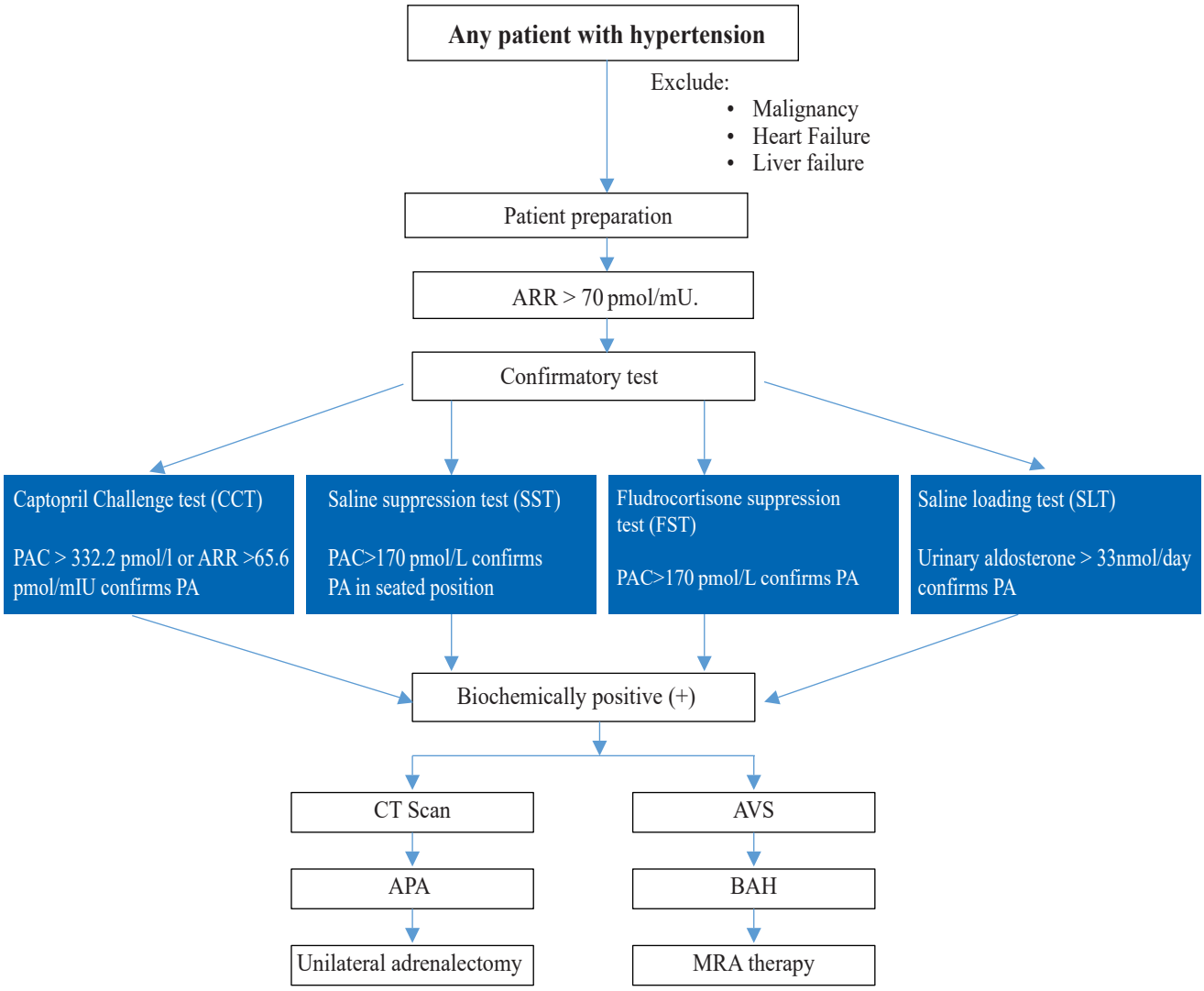

Figure-2: The diagnostic pathway of primary aldosteronism

At present, the plasma aldosterone to renin ratio or ARR derived from the measurement of plasma aldosterone concentrations (PACs) and plasma renin activity (PRA) or the direct renin concentration (DRC) is considered to be the most reliable method of screening for PA. There are multiple difficulties that need to be overcome if a successful diagnosis of PA is to be made. These include appropriate patient selection, drug withdrawal/substitution, maintenance of optimum serum and urinary electrolyte concentration, choice of assay procedure and it's interpretation, determining a population specific diagnostic cut-off etc.

i. Selective or non-selective screening of PA?

The Endocrine Society (ES) Clinical Practice Guideline recommends screening patients with an increased likelihood of PA (Table-I) It has been suggested that all patients with hypertension should be screened for PA, based on the findings of the prospective PATO study, which reported a 5.9% prevalence of PA in 1672 unselected patients with hypertension in primary care.[31] Considering the high prevalence and early target organ damage in untreated PA patients, it is now advisable to screen any hypertensive patient for the disorder at least once in lifetime.

Table-I: Categories of hypertensive patients recommended for screening of PA

1.	Sustained BP > 150/100mm Hg on each of three measurements obtained on different days
2.	Hypertension (BP>140/90mmHg) resistant to three conventional antihypertensive drugs (including a diuretic), or controlled BP (<140/90 mm Hg) on four or more antihypertensive drugs
3.	Hypertension and spontaneous or diuretic-induced hypokalemia
4.	Hypertension and adrenal incidentaloma
5.	Hypertension and sleep apnea Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)
6.	First-degree relatives of patients with PA

ii. Cumbersome patient preparation before testing

The screening as well as other biochemical diagnostic tests should ideally be performed on medications not interfering with the result of ARR. Unless the hormonal tests are performed under an ideal condition with maintenance of optimum blood and urinary electrolyte level and following the discontinuation of interfering medication, the results are likely to be unreliable. For reliable biochemical testing following preparation is mandatory:

a. The major interfering anti-hypertensive drugs are the mineralocorticoid receptor antagonist (MRA) (spironolactone, amiloride) and diuretics that need to be stopped for 6 weeks before testing.

b. Other anti-HTN drugs like β-blocker, ACE inhibitor, ARB, clonidine, α-methyl dopa, and dihydropyridine calcium channel blocker (CCB) should be discontinued for 2-4 weeks before testing. Meanwhile, other non-interfering anti-HTN drugs including non-dihydropyridine CCB, prazosin/ doxazosin, or moxonidine could be advised temporarily for BP control during the testing procedure.

c. Products containing licorice and non-steroidal anti-inflammatory drugs should also be withdrawn at least 3 weeks before the test, and estrogen-progestin compounds should ideally be withdrawn for 6 weeks.

d. It is recommended that during the 3 days preceding the confirmatory test, patients consume a normal sodium diet which would be reflected by urinary sodium levels of 100–200 mmol/L

e. Patient should receive potassium supplementation to correct prior hypokalemia and to thus ensure a potassium ≥4 mmol/l.

iii. Maintenance of ideal conditions for blood collection

a. Blood should be collected in the mid-morning after the patient has been up (sitting, standing, or walking) for at least 2 hours and seated for 5-15 minutes.

b. Blood should be collected carefully, avoiding stasis and hemolysis

c. Sample should be maintained at room temperature (and not on the ice, as this will promote the conversion of inactive to active renin) during delivery to the laboratory and before centrifugation and rapid freezing of plasma component pending assay.[15]

iv. The fallacy of ARR as a screening test

Although regarded as the most reliable method for screening for PA currently available, the ARR (like any biochemical screening test) is not without false positives and negatives.[32] This partly occurs because renin is not the sole regulator of aldosterone production and plasma levels. The fact that other important regulators such as potassium and adrenocorticotrophin (ACTH) and changes in

hepatic blood flow will also influence levels helps to explain why renin and aldosterone do not always move strictly in parallel in response to physiological maneuvers and certain medications. Furthermore, because some stimuli have differential effects on plasma renin activity (PRA) and the concentration of direct active renin enzyme (DRC), the method used to measure renin may also impact the ARR (Table-II).[32] PRA has been traditionally used for ARR, but DRC is increasingly preferred due to its stability and accuracy. However, standardized ARR cutoffs for DRC are still evolving.[33] There is no precise conversion factor between the two different methods. 1 ng/mL/hr of plasma renin activity approximately equals 7.6 pg/mL of direct renin concentration (range 5.5 to 9.7). Another approximate relationship is [PRA (ng/ml/h) ≈ DRC (mU/L)/12 - 15]. So one will see higher "renin" values with DRC.[34] Threshold values vary by institution but, in general, an ARR greater than 20 ng/dL per ng/mL/h and PAC greater than 10 ng/dL with a suppressed renin are accepted values for a positive screening test.[35] Despite having various pros and cons, still ARR is the crucial first step in diagnosing PA, guiding further testing and treatment.

v. No universal consensus on the choice of confirmatory tests

These assay results of ARR are effective in screening for PA with a sensitivity of 68-94%.[36] However, retrospective analyses suggest that 30–50% of patients with an elevated ARR at screening may indeed correspond to false-positive PA. Such lack of specificity in the screening step for PA diagnosis has led expert centers to perform dynamic testing for confirmation of the PA.[37] Confirmatory tests have been developed to demonstrate a non-suppressible aldosterone secretion using maneuvers that are designed to bring about suppression of circulating renin (Table-III). Such confirmatory tests should principally exhibit a high negative predictive value

Table-II: Factors leading to the fallacy of ARR interpretation

Factors	Effect on Aldosterone Levels	Effect on Renin Levels	Effect on ARR
Medications			
β-blocker	↓	↓↓	↑ **(FP)**
Central agonist	↓	↓↓	↑ (FP)
NSAID	↓	↓↓	↑ (FP)
K wasting diuretics	→↑	↑↑	↓**(FN)**
K_-sparing diuretics	↑	↑↑	↓**(FN)**
ACE inhibitor	↓	↑↑	↓**(FN)**
ARBs	↓	↑↑	↓**(FN)**
Ca channel blocker	→↓	↑	↓**(FN)**
Renin inhibitor	↓	↓↑	↑**(FP)**, ↓(FN)
Potassium status			
Hypokalemia	↓	→↑	↓**(FN)**
Potassium loading	↑	→↓	↑
Dietary sodium			
Sodium restriction	↑	↑↑	↑**(FN)**
Sodium loading	↓	↓↓	↑ **(FP)**
Advancing age	↓	↓↓	↑ **(FP)**
Premenopausal	→↑	↓	↑ **(FP)**
Other conditions			
Renal impairment	→	↓	↑ **(FP)**
PHA-2	→	↓	↑ **(FP)**
Pregnancy	↑	↑↑	↓**(FN)**
Renovascular HTN	↑	↑↑	↓**(FN)**
Malignant HTN	↑	↑↑	↓**(FN)**

***Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society, Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93: 3266–3281 (3), with permission. © Endocrine Society.

Table-III: Interpretation of confirmatory tests

Test	Procedure	Interpretation	Concerns
Fludrocortisone suppression test (FST)	• Oral Intake of 0.1 mg/6 h fludrocortisone during 4 days, potassium chloride and sodium chloride (6 g/day) • Blood sampling for plasma potassium/6-h (serum K^+ >4mmol/L) and 24-h urinary sodium from day 3 to day 4 (>200 mEq/24 h) • On day 4, plasma cortisol at 07:00 h and PAC, PRA and plasma cortisol are at 10:00 h	• PAC >6 ng/dL (170 pmol/L) confirms • PA Test validity if PRA < cortisol 07:00 h	4-day hospitalization, monitoring of serum K^+ /6 h
Saline infusion test (SIT)	• Performed between 08:00 and 09:00 h, in supine* position for at least 1 h before and during the test. • Infusion of 2 L of 0.9% saline over 4 h. Blood sampling for PAC and PRA or DRC at T0 and T4 h • Alternatively in seated position for at least 30 min before and during the test	• At T + 4 h, PAC 10 ng/dL (280 pmol/L) confirms PA, 5 ng/dL < PAC < 10 ng/dL is a 'gray zone' (3, 16) PAC >6.8 ng/dL (190 pmol/L) proposed as the most accurate threshold • In the seated test, PAC >6 ng/dL (170 pmol/L) confirms PA	Hourly BP monitoring is recommended, Less reliable in older patients or in kidney failure, can cause volume overload, making it risky for heart failure
Oral sodium loading test (OSLT)	• Non-invasive and convenient for outpatient setting • Oral intake of 6 g/day sodium chloride for 3 days and potassium chloride to correct hypokalemia • 24-h urinary sodium (urinary sodium >200 mEq/24 h) and urinary aldosterone sampling from day 3 at 08:00 h until day 4 at 08:00 h	• Urinary aldosterone concentration >12 or 14 µg/24 h (33 or 39 nmol/24 h) confirms PA, urinary aldosterone concentration	Contraindicated if severe hypertension, kidney failure, cardiac arrhythmia, severe hypokalemia
Furosemide upright test (FUT)	• After 30 min in supine position, intravenous injection of 40 mg furosemide in upright position maintained for 2-h • Blood sampling for PRA at T0, T + 1 h and T + 2 h	PRA below 2 ng/mL/hour after 2 hours of an intravenous dose of furosemid	Contraindicated if advanced atherosclerosis, at risk for cerebrovascular events, or arrhythmia
Dexamethasone-Captopril-Valsartan test (DCVT)	• Simple, fast and can be done in outpatient setting • Oral intake of 2 mg dexamethasone plus 50 mg captopril plus 320 mg valsartan at 12:00h, and 50mg captopril the next morning at 07:30h • Blood sampling for PAC, DRC and cortisol the next morning at 08:30 h	• ARR >0.3 ng/dL/µU/mL (9 pmol/IU) and PAC >3.1ng/dL (85 pmol/L) confirms PA	Monitor plasma potassium level Contraindicated if severe kidney failure (Cl. creatinine <30 ml/min)

so that false positives selected by ARR screening can be eliminated.[38] However there is universal choice of a confirmatory test and none is regarded as the gold standard. There is also considerable variability regarding the diagnostic thresholds of these tests depending on the age, gender, ethnicity, anti-hypertensive drugs, assay procedure and techniques (immunoassay/LC-MS) used.

Confirmatory testing is considered mandatory by the ES guideline for a definitive diagnosis of PA. An exception is in evident cases of PA with spontaneous hypokalemia and a PAC > 20 ng/dL (550 pmol/L) with PRA (or DRC) below assay detection limits.[15] The gold standard is often considered fludrocortisone suppression test (FST), but saline infusion test (SIT) is commonly used due to practicality. FST mimics physiological mineralocorticoid activity, providing a clear distinction between PA and other causes. But it requires hospitalization or close monitoring (four-day duration), there is risk of severe hypokalemia and hypertension and it is expensive and logistically difficult.[39] On other hand, SIT is widely used and standardized.[40] Things to be concerned while performing different confirmatory test are discussed in Table-3.

vi. Difficulty with subtype localization

Following biochemical confirmation of PA either CT adrenal and/or AVS should be performed for subtyping into unilateral adrenal adenoma or bilateral adrenal hyperplasia that will guide towards surgical or medical management accordingly. Adrenal CT is the initial study in subtype testing as it is a less expensive, non-invasive and readily available technique than AVS. However, adrenal CT lack's reliability having a poor concordance rate of only 62% with adrenal venous sampling (AVS). A systematic review showed if only CT/MRI results had been used to determine lateralization, inappropriate exclusion from surgery would have occurred in 19%, inappropriate surgery would have been done in 15% and surgery on the wrong side would have been performed in 4%.[41] On the other hand AVS is proposed as the gold standard method for localization though it is both technically difficult to perform and lacks procedural standardization, which can interpret the results challenging for the physician.[42,43] 8F-FDG PET-CT (fluorodeoxyglucose positron emission tomography-computed tomography) is not a standard tool for PA diagnosis, as most aldosterone-producing adenomas (APAs) have low FDG uptake, making FDG PET-CT less effective for PA diagnosis. However, it can sometimes be useful in differentiating between adrenal adenomas and adrenocortical carcinomas (ACC), as ACCs usually show high FDG uptake and evaluating incidental adrenal masses with indeterminate CT features. Recently, 11C-Metomidate PET-CT is found to be more promising than FDG PET-CT, as metomidate binds to adrenal cortical enzymes and helps localize APAs.[44]

Finally the limited availability of resources including the assay techniques, the expensive nature of the hormonal tests, absence of local expertise in adrenal CT or AVS are the other important barriers to timely diagnosis of PA specially in resource constraint areas or in low-medium income countries.

Conclusions

There has been a paradigm shift in the management of PA in the recent years. From being a very rare disorder affecting only a subset of hypertensive subjects with hypokalemia, it has now been recognized as a widely prevalent disease involving any hypertensive subjects with adverse CVD outcome. The myths surrounding PA prevalence and the diagnostic challenges leading to its under diagnosis are to be addressed appropriately so that, timely intervention can be offered.

Conflict of interest

The authors have no conflicts of interest to disclose.

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