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REVIEW

Primary aldosteronism: from bench to bedside

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Abstract Primary aldosteronism is now thought to be the commonest potentially curable and specifically treatable form of hypertension. The detection of primary aldosteronism is of utmost importance not only because it provides an opportunity for a targeted treatment, but also because it has been demonstrated that patients with primary aldosteronism are more prone to cardiovascular events and target organ damage than essential hypertensives. Normalization of blood pressure and hypokalemia should not be the only goal of treatment. Normalization of circulating aldosterone or mineralocorticoid blockade is necessary to prevent aldosterone-induced tissue damage that occurs independent of blood pressure. This review will focus on the current understanding and comprehensive management review of primary aldosteronism, highlighting the new evidence that has become recently available.

Keywords Primary aldosteronism · Aldosterone renin ratio · Adrenal venous sampling · Familial hyperaldosteronism · Bilateral adrenal hyperplasia

Introduction

Primary aldosteronism (PA) was first described by Jerome W. Conn, who was a Professor of Medicine and Head of the Endocrinology Division, University of Michigan, in 1954, the same year Sylvia Simpson and James Tait purified a new steroid hormone with mineralocorticoid action that they named aldosterone [1]. In PA, aldosterone production is excessive to the body's requirements and relatively autonomous [2]. Aldosterone, produced in the zona glomerulosa, is synthesized and released mainly in response to renin-dependent production of angiotensin II. However, adrenocorticotrophin (ACTH) and potassium levels can significantly affect its production and secretion, and many other agents such as dopamine have also been shown to affect aldosterone production, at least in vitro. Aldosterone exerts its effect by binding to the nuclear mineralocorticoid receptor. This ligand-receptor complex attaches to deoxyribonucleic acid (DNA) and promotes gene expression. In the distal nephron of the kidney, mineralocorticoid receptor induction of serum and glucocorticoid-inducible-kinase-1 gene expression triggers a cascade that leads to the absorption of sodium through the epithelial sodium channels causing volume expansion, hypertension and suppression of renin. This is accompanied by urinary loss of potassium and hydrogen ions which, if it is severe and prolonged enough, results in hypokalemia and metabolic alkalosis.

PA comprises a wide spectrum of conditions ranging from a solitary unilateral nodule to bilateral diffuse or nodular hyperplasia, with several intermediate phenotypes. The two major subtypes of PA are: bilateral adrenal hyperplasia (BAH), accounting for 65–70% of cases and aldosterone-producing adenoma (APA), accounting for 30–35% of cases. Other rarer subtypes include unilateral primary hyperplasia, familial varieties and adrenocortical carcinoma.

Within 10 years, Conn described many of the important pathophysiological and clinical features of PA [2]. Among these were the notable observations that patients were normokalemic in the early stages, changes in the relationship between plasma aldosterone and renin were more sensitive in diagnosis than potassium level, and the drop in

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blood pressure (BP) could take many months after unilateral adrenalectomy.

Why is PA important?

The importance of PA lies not only in its high prevalence as a potentially curable and specifically treatable form of hypertension, but also because patients with this condition have higher cardiovascular morbidity and mortality than age- and sex-matched patients with essential hypertension and matched for the degree of BP elevation [3, 4]. Cerebrovascular, renal and metabolic sequelae have also been described in PA. Furthermore, specific treatments ameliorate these outcomes [5]. Hypertensive individuals with APA can be cured or can at least experience significant improvement following unilateral adrenalectomy, and individuals with BAH can benefit from specific medical pharmacotherapy.

What is the cause of PA?

At present, the cause of PA is still unknown. However, evidence accrued over the past decade suggests that genetic factors are likely to be involved with this condition. As of now, three familial varieties have been described, each of which has shown an autosomal-dominant pattern of inheritance.

Familial hyperaldosteronism type I (FH-I)

FH-I, also known as glucocorticoid remediable aldosteronism (GRA), is a monogenic form of hypertension and responsible for less than 1% of PA. The condition was originally reported in 1966 by Sutherland et al. [6], who described, in a 41-year-old man and his 16-year-old son, hypertension, hypokalemia, raised aldosterone and suppressed renin, all of which normalized with the administration of 2 mg dexamethasone/day. The father had been hypertensive since the age of 19 years and the son since 13 years, and three of the father's 11 siblings had died prematurely from cerebrovascular accidents. The molecular basis of FH-I has been elucidated by Lifton et al. [7]. FH-I is due to recombination between the genes coding for *CYP11B1* (11-beta-hydroxylase) and *CYP11B2* (aldosterone synthase), diagnosis made by long PCR [8].

Familial hyperaldosteronism type II (FH-II)

In 1991, the Greenslopes Hospital Hypertension Unit first reported on a new familial form of PA [9], which was not glucocorticoid remediable, and indistinguishable from sporadic PA. The molecular basis of FH-II is still unknown, although several analyses have shown a linkage with chromosomal region 7p22 [10, 11]. The diagnosis of FH-II requires PA to be confirmed in two or more family members and exclusion of FH-I. The prevalence of FH-II is unknown but is at least five times more common than FH-I. The search for genetic mutations causing FH-II has involved both candidate gene and genome wide search approaches. Several candidate genes have been excluded as a cause of FH-II such as *PRKAR1B*, *RBaK*, *GNA12* [12, 13], *ZNF 12*, *RPA3* and *GLCCI* (Sukor N, unpublished data, 2009). As of now, no mutations likely to be causative for FH-II have been identified.

Familial hyperaldosteronism type III (FH-III)

In 2008, Geller and colleagues [14] described a father and two daughters with severe childhood-onset hypertension, excess aldosterone with markedly suppressed PRA and severe hypokalemia. Measurement of serum and urinary hybrid steroids were markedly raised. Unlike in FH-I, genetic testing for the hybrid gene was negative and BP and serum aldosterone levels progressively increased (rather than decreased) in response to dexamethasone administration. In all three individuals, hypertension and hypokalemia responded poorly to aldosterone antagonists, but were corrected by bilateral adrenalectomy. Very recently, Lifton's group [15] reported the affected (but not the unaffected) members of this pedigree to harbour a mutation in the potassium channel *KCNJ5*.

Prevalence of PA

PA was previously considered to be a rare cause of hypertension, accounting to less than 1% of cases. However, following the widespread use of plasma aldosterone concentration to plasma renin activity (PAC/PRA) ratio or aldosterone/renin ratio (ARR) as a screening test for PA, as much as 10% of hypertension can be due to PA [16–18]. The policy to screen all (not just hypokalemic and resistant hypertensives) revealed that majority of PA patients are normokalemic and hypokalemia is only present in a minority of patients (9–37%) [17]. The increased in detection rate has led to the recognition of the milder clinical forms of PA, the BAH, which was found to be the most common form of PA rather than APA.

Studies have shown that prevalence of PA rises with increasing severity of hypertension. In one study, the prevalence ranged from 6.6% in patients with grade I to 19% in grade III hypertension [18]. A similar trend was observed by Mosso et al. [19] who found a prevalence of 2.0% in grade I, rising to 13.2% in grade III hypertension [Joint National Committee VI (JNC VI)].

The prevalence of PA is also highly dependent on the studied population. Prevalence of PA has been studied in subgroups including African American patients with resistant hypertension [20], type 2 diabetes mellitus with resistant hypertension [21] and hypertensive patients with adrenal incidentalomas [22]. Black subjects generally have lower plasma renin levels than white subjects. However, in two reported studies, neither PAC/PRA ratio nor the prevalence of PA in black and white patients with resistant hypertension was statistically different (24% in African Americans and 20% in white patients) [20, 23]. In a further group of 100 patients with type 2 diabetes mellitus and poorly controlled hypertension, a 14% prevalence of PA was reported. This was independent of glycemic control [21]. PA prevalence has also been assessed in patients with adrenal incidentaloma. Bernini et al. [22] screened 90 normokalemic subjects with an adrenal incidentaloma with hypertension and 35 subjects without hypertension for the presence of PA. Of the subjects with hypertension, 5.6% had PA, whereas no cases were found in the normotensive subgroup. Recently, the prevalence of PA was studied in patients with obstructive sleep apnoea (OSA) [24]. OSA is an independent risk factor for cardiovascular disease, such as myocardial infarction, stroke, congestive heart failure and resistant hypertension. The prevalence of PA in this population was noted to be high at 22%, and there was a positive correlation observed between PRA and OSA severity.

Who should be screened?

In view of the significant prevalence rate, the excess rate of cardiovascular, cerebrovascular, renal and metabolic complications which can be prevented by early diagnosis, and the fact that hypertension may be cured or at least improved by adrenalectomy and responds well to specific medical therapy, it could be and has been proposed that PA should be excluded systematically in all hypertensive patients [25]. However, this remains a controversial issue [26, 27].

The Endocrine Society Clinical Practice Guideline [28] recommends that case detection should be done in the following groups:

- Stage 2 hypertension (>160–179/100–109 mmHg)
- Stage 3 hypertension (>180/110 mmHg)
- Drug resistant hypertension
- Hypertension and spontaneous or diuretic-induced hypokalemia
- Hypertension with adrenal incidentaloma
- Hypertension with a family history of early onset hypertension or cerebrovascular accident at a young age (<40 year)
- Hypertensive first-degree relatives of patients with PA

Diagnosis of PA

Screening test

Measurement of ARR is widely regarded as being the most reliable means of screening for PA. However, several factors can affect the ARR and compromise its sensitivity or specificity [29]. The most common confounders are antihypertensive medications. β-blockers, α-methyldopa and clonidine are known to cause false positive ratios, while false negatives may be encountered in patients taking diuretics (including spironolactone and amiloride), dihydropyridine calcium channel antagonists, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers [29–31]. Therefore, diuretics are ceased for at least 4 weeks, and β-blocker, α-methyldopa, clonidine, dihydropyridine calcium channel antagonists, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blocker are ceased for at least 2 weeks prior to ARR testing [30, 32]. Other agents that have lesser effect on the ratio [31] such as slow release verapamil (with or without hydralazine) or prazosin are used to control the BP during this period. Hypokalemia must be corrected prior to the testing as potassium influences aldosterone secretion and low potassium levels may be associated with false negative ratios in patients with PA.

Other medications that have potential to affect ARR include the recently introduced renin inhibitors, contraceptive agents and antidepressants. These agents are able to raise or lower ARR depending on whether renin is measured as PRA or direct active renin (DAR). Renin inhibitors are likely to raise ARR if renin is measured as PRA, and lower it if measured as DAR [33]. Contraceptive agents and other oestrogen-containing preparations causes falsely elevated ratio when DAR are used rather than PRA [34]. Increase hepatic production of angiotensinogen induced by oestrogen, resulted in higher angiotensin I concentrations (if renin remained constant) leading to increased negative feedback by angiotensin-suppressing active renin production [35, 36], hence, prevents PRA from rising significantly. However, it would be expected to lead to suppressed renin concentration and raised ARR if measured using DAR. The selective serotonin reuptake inhibitor antidepressants [37], on the other hand, can significantly reduce ARR, leading to false-negative screening for PA. Therefore, it is essential that during the work-up for PA, ARR is measured without any interfering medications.

An ARR greater than 100 (plasma aldosterone in pmol/l, direct renin in mU/l) or 30 (plasma aldosterone in ng/dl, direct renin in ng/ml/h) is considered highly suggestive of PA. Different centres use different cut-off values. Some centers use the ARR alone [38] while others use a combination of the ARR with absolute PAC levels [17, 39–42].

Confirmatory testing

It is important to note that a raised ARR by itself is not diagnostic of PA. A confirmatory test should be performed to demonstrate that the level of aldosterone secretion is inappropriate for a high salt diet and is not normally suppressible. It has been reported that up to 30–50% of individuals with a positive ARR will have aldosterone levels that are suppressed normally after confirmatory testing [19]. The Endocrine Society Guideline recommends any four confirmatory tests commonly used which include fludrocortisone suppression test (FST), saline loading test (SLT) oral salt loading test (OLT) and captopril challenge test (CCT). The procedure and interpretation is as shown in Table 1. Different centers use different tests and cut-off values. It should be emphasized that all of the confirmatory tests have risks and should be used with care in patients with compromised left ventricular cardiac function. The captopril challenge test has the advantage of being relatively inexpensive, well tolerated, safe and easy to perform, however, it has been associated with a high rate of false positive diagnoses [43, 44] compared with other tests and therefore should only be used in patients at high risk of volume expansion. The FST is regarded by some investigators as the most reliable means of confirming or excluding the diagnosis of PA [45]. The choice of test remains a matter of debate as currently there is insufficient direct evidence to recommend one over the other.

Subtype differentiation

CT/MRI adrenals

If the confirmatory test is positive, a high-resolution computed tomography (CT) scan with fine (2–3 mm) cuts of the adrenal glands should be performed as an initial study in subtype testing and to exclude large masses that may represent adrenocortical carcinoma. However, adrenal CT lacks reliability as it fails to detect many (at least half in some series [46, 47]) APAs, and yet may demonstrate non-functioning nodules in the contralateral gland and apparently unilateral lesions in patients with BAH. Half of APAs are <20 mm in diameter and up to 42% are <6 mm in diameter, which means, most patients with PA due to APA have a small tumour [48, 49]. In a systematic review of 38 studies in a total of 950 patients with PA, adrenal CT/magnetic resonance imaging (MRI) results were discordant with results of adrenal venous sampling (AVS) in 359 of 950 patients (38%). 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% [50].

Adrenal venous sampling

Since adrenal CT scan lack sensitivity and specificity, AVS remains the gold standard test in differentiating between APAs and BAHs. It has been reported that AVS distinguishes unilateral APA from bilateral hyperplasia with 90–100% accuracy [51], with substantial superiority over that of adrenal CT (sensitivity 78% and specificity 75%) [46, 47]. AVS is technically challenging, especially in catheterization of the right adrenal vein. The right adrenal vein usually enters the inferior vena cava posteriorly several centimetres above the right renal vein. It is more difficult to catheterize than the left adrenal vein because of its smaller calibre and shorter length (5–8 mm). As a result, the success rate for cannulating the right adrenal vein is usually less than that for the left. Recent clinical practice guideline recommends that AVS be performed in all patients with confirmed PA who wish to pursue and are suitable candidates for surgical management [28]. With the advance of technology, recently, Plank et al. [52]

Table 1 Different confirmatory tests used to diagnose primary aldosteronism

Type of tests	Method	Confirmation of primary aldosteronism
Fludrocortisone suppression test	Fludrocortisone acetate (0.1 mg every 6 h), Slow Na (30 mmol thrice daily) and sufficient dietary salt to maintain a urinary excretion rate of at least 3 mmol sodium/kg/day, with sufficient potassium supplementation (given every 6 h) to maintain normokalemia	Upright PA > 6 ng/dl (166 pmol/l) at 1000 on day 4, provided upright PRA < 1.0 ng/ml/h, lower cortisol level at 1000 than 0700, and normal plasma potassium
IV saline loading test	IV infusion of 2 l of 0.9% sodium chloride over 4 h (500 ml/h)	Post-infusion PA > 5 or >10 ng/dl (139 or 277 pmol/l)
Oral sodium load	Oral sodium chloride supplementation (300 mmol of sodium per day for 3 days) and potassium supplementation (if required) to maintain normokalemia	Urinary aldosterone on the third day >12 or >14 ug (33 or 39 nmol)/24 h, and urinary sodium >200 mmol in 24 h
Captopril challenge test	Measurement of ARR 2 h after oral 25–50 mg captopril	Post-captopril ARR > 12 (ng/dl)/(ng/ml/h) or 40 (pmol/l)/(mU/l) and PA > 12 ng/dL (330 pmol/l)

PA Plasma aldosterone, *PRA* plasma renin activity, *ARR* aldosterone/renin ratio, *IV* intravenous

demonstrated the additional use of Dyna-CT in AVS. This improves the accuracy of AVS as correct catheter position is reliably shown on multiplanar reformations, thus facilitate the challenging procedure.

During AVS, both plasma aldosterone and plasma cortisol are measured in blood collected from each adrenal vein in turns and simultaneously from a peripheral vein or inferior vena cava well below the adrenal veins. Success of cannulation can be judged by examining the ratio between adrenal and peripheral venous cortisol levels. However, there is lack of agreement on which criteria should be used for defining successful cannulation. In our center, ratios of at least three are taken to indicate adequate sampling. Calculation of the aldosterone/cortisol ratio for each adrenal and peripheral venous sample serves to correct for any differences in 'dilution' of adrenal with non-adrenal venous blood and permits the only meaningful comparison of sample levels. AVS is considered to show lateralization, providing an indication for adrenalectomy, when the average aldosterone/cortisol ratio on one side is significantly (usually two times or more) higher than the simultaneous peripheral venous ratio, with a ratio no higher than peripheral on the other side, which importantly, indicates contralateral suppression. The use of ACTH stimulation during AVS is still debatable. However, recent studies found that ACTH infusion did not aid in the final diagnosis [53, 54].

(11) C-metomidate positron emission tomography

Recently, Hennings et al. [55] evaluated the use of (11) C-metomidate positron emission tomography (MTO-PET) in the detection of small adrenocortical adenomas in PA and whether MTO-PET can be a non-invasive alternative to AVS for lateralisation studies in PA. Metomidate specifically binds to enzymes in the CYP11B cytochrome 450 family in the adrenal cortex. Adrenal glands which hypersecrete aldosterone have been described as having higher standardised uptake value (SUV) than non-functional tumours. The limitation of this technique is that it requires a facility for the preparation of a radioactive tracer and therefore could only be developed at a large tertiary centers. Whether MTO-PET could identify the majority of APAs (which tend to be small) remains to be proven.

Management

Aldosterone exerts major deleterious effects when plasma concentrations are inappropriately high for salt status. Normalization of BP should not be the only goal in managing patient with PA as some of these effects appear to be at least partially independent of BP elevation. The goal of treatment is to prevent the morbidity and mortality associated with hypertension, hypokalemia and cardiovascular damage [56]. The aetiology of PA in each patient helps to determine the appropriate treatment.

Both surgical and medical treatment has been reported to abrogate the excess in cardiovascular and renal morbidity [57]. Appropriate and specific treatment had positive impact not only on clinical and biochemical parameters but also on quality of life of these patients and this can be achieved as early as 3 months following adrenalectomy [58, 59]. Apart from cardiovascular, renal and metabolic sequelae, patients with PA were also noted to have some psychological disturbances. Recent study has demonstrated that about half of patients with PA suffered from an anxiety disorder, and these patients are at a higher level of stress or psychological distress and lower levels of well-being than controls [60]. Therefore, early identification of the condition is important in managing all the associated complications related to PA.

Surgical treatment

Patients who lateralize on AVS are candidates for unilateral adrenalectomy, which results in cure of hypertension in 50–60% and significant improvement in the remainder [61, 62]. Laparoscopic adrenalectomy, as compared to open adrenalectomy, is associated with shorter hospital stays, fewer complications and faster recovery [63–65]. To decrease the surgical risk, hypokalemia should be corrected with potassium supplements and/or a mineralocorticoid receptor antagonist pre-operatively. The potassium supplements and mineralocorticoid receptor antagonist should be discontinued immediately before adrenalectomy. The BP response to aldosterone receptor blockade pre-operatively may in some instances predict the BP response to unilateral adrenalectomy in patients with APA [66–68] but this will depend on the duration of drug therapy.

Post-operatively, sometimes, antihypertensives can be ceased immediately after surgery, but more commonly gradual withdrawal of antihypertensive medications are possible over the ensuing 3–12 months. Surgery almost invariably results in correction of hypokalemia.

Several predictors for hypertension cure have been reported which include lower pre-operative left ventricular mass index [69, 70], lower serum creatinine [70, 71] and absence of co-existing macronodules in the removed adrenal gland [71] while risk factors for persistent hypertension have included advanced age [68, 72, 73], duration of hypertension [68, 69, 72, 74, 75] and use of more than one or two antihypertensive agents [76].

Failure to cure hypertension can be attributed to an inaccurate diagnosis of unilateral (as opposed to bilateral) PA due to incorrect performance of AVS or of

interpretation of AVS results, development of PA in the contralateral gland over time, or more commonly, the concurrence of other contributors to ongoing hypertension.

Medical pharmacotherapy

Patients with BAH and those with unilateral PA who are not candidates for or who decline surgery can be treated medically with medications that antagonize aldosterone action. These include the mineralocorticoid receptor (MR) antagonists spironolactone and eplerenone, and epithelial sodium channel inhibitors such as amiloride.

Spironolactone

Spironolactone has been the agent of choice in the medical treatment of PA for more than four decades. However, spironolactone is not completely selective for the mineralocorticoid receptor. Side effects are typically related to androgen receptor blockade and are dose dependent. Antagonism at the androgen receptor may result in painful gynaecomastia, erectile dysfunction and decreased libido in men; and a pro-oestrogen effect combined with agonist activity at the progesterone receptor results in painful breast enlargement with aggravation of fibrocystic disease in women and also menstrual irregularity. The incidence of gynaecomastia in 699 patients treated with spironolactone was 6.9% at doses <50 mg/day and 52% at doses >150 mg/day [77].

Eplerenone

Eplerenone is a steroid-based anti-mineralocorticoid that acts as a competitive and selective aldosterone receptor antagonist. The critical feature of the eplerenone molecule conferring selectivity for the MR is the presence of the 9,11-epoxy moiety in the lactone ring. Compared with spironolactone, eplerenone has up to a 500-fold lower affinity for androgen and progestin receptors, thus greatly reducing the adverse effects associated with androgen antagonism and progesterone agonism observed with spironolactone. Eplerenone is thought to have approximately 60% of the MR antagonist potency of spironolactone [78]. Potency studies showed equal or 25–50% less milligram per milligram potency when compared with spironolactone [79]. Eplerenone is available in 25- and 50-mg tablets. In view of its shorter half-life, it should be given twice daily for optimal control. The maximum dose is 100 mg daily. Recently, the safety and efficacy of eplerenone was compared with spironolactone in a small, prospective, randomised, open-label study in 34 patients with bilateral PA [80]. Eplerenone was shown to be as effective as spironolactone in controlling BP. However, more recently, in a double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of PA [81], the antihypertensive effect of spironolactone was significantly greater than that of eplerenone.

Other agents

Amiloride, an epithelial sodium channel antagonist, has been used for the treatment of PA. Although may not be as powerful as spironolactone, amiloride can be very useful, lacking the sex steroid-related side effects. Amiloride can correct or improve both hypertension and hypokalemia. Amiloride administered for between 6 weeks to 6 months resulted in 20–30 mmHg fall in systolic and 10–15 mmHg diastolic blood pressure [82, 83]. Unlike spironolactone where nearly 50% of patients can be maintained on monotherapy, about 75% of patients on amiloride needed additional antihypertensive agents to control blood pressure. It is generally very well tolerated.

Anti-hypertensive agents such as angiotensin-converting enzyme inhibitors [84], angiotensin receptor blockers [85] and calcium channel blockers [86] have been evaluated in few patients with PA without major effect on aldosterone excess. Aldosterone synthase inhibitors may play a role in future.

Conclusion

The field of PA has undergone rapid evolution. From a relatively rare curiosity it is clear that PA is not an uncommon condition amongst hypertensive populations. Patients with PA are at higher risk of cardiovascular, renal and metabolic diseases than patients with "essential" hypertension and comparable BP levels, due to non-BP dependent adverse effects of aldosterone excess. The fact that PA is a specifically treatable and curable cause of hypertension, and the complexities in screening and confirming the diagnosis, both emphasizes the importance of finding a simple genetic testing method for detecting and diagnosing the condition. The diagnosis of PA permits institution of specific surgical or medical treatments which are usually highly effective in terms of controlling hypertension. Conversely, missing the diagnosis could have significant negative consequences [87].

Conflict of interest None

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