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PRIMARY ALDOSTERONISM

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Primary aldosteronism (PA) is a common form of endocrine hypertension in which aldosterone production is inappropriate and at least partially autonomous of the renin–angiotensin system. The inappropriate production of aldosterone results in sodium retention and suppression of renin. PA is commonly caused by an adrenal adenoma or bilateral hyperplasia of the adrenocortical zona glomerulosa, and in very rare cases by the inherited condition of glucocorticoid-remediable aldosteronism (GRA) also known as Familial Hyperaldosteronism type 1 (FH1).

Some misconceptions concerning PA must be addressed. PA was held to account for less than 1% of hypertensive patients and, moreover, hypokalaemia was considered a prerequisite for pursuing the diagnostic tests for PA [1] However, recent studies carried out by applying the plasma aldosterone/plasma renin activity (PRA) ratio (ARR) as a screening test in hypertensive patients, regardless of the presence or absence of hypokalaemia, have found a much higher prevalence of this disease, with PA accounting for up to 12% of hypertensive patients. In recent studies, only a minority of patients with PA (9 to 37%) had hypokalaemia [2]. Thus, normokalaemic hypertension constitutes the most common presentation of the disease, with hypokalaemia probably being present only in the more severe cases [3]. An early diagnosis of PA is crucially important not just because PA is common and if overlooked exposes the patient to the need for long-life treatment, but even more so because if undiagnosed and not properly treated these patients have higher cardiovascular morbidity and mortality than age-, sex, blood-, and pressure-matched patients with essential hypertension, including a greater incidence of left ventricular hypertrophy, fibrosis, atrial fibrillation, myocardial infarction, and stroke [4]. In fact, aldosterone has been shown to induce endothelial dysfunction, norepinephrine release, cardiovascular fibrosis, and proteinuria, independently from increase of blood pressure. Furthermore, specific treatments are available that ameliorate the impact of this condition on patient-important outcomes (Figure 1).

Diagnosis

The growing recognition of PA as a common and important contributor to hypertension development and cardiovascular disease has led to a "Renaissance" in interest regarding the detection and diagnostic workup of this disorder by clinicians involved in the treatment of hypertensive patients. The Clinical Guidelines Committee of The Endocrine Society [5] has developed clinical practice guidelines for the diagnosis and treatment of patients with PA. Diagnosis of PA is divided into different steps including: case detection, case confirmation, and subtype classification.

Case detection

Case detection of PA is recommended in patient groups with relatively high prevalences of PA. These include patients with: stage 2 (>160–179/100–109 mm Hg), stage 3 (>180/110 mm Hg), or drug-resistant hypertension; hypertension and spontaneous or diuretic-induced hypokalaemia; hypertension with adrenal incidentaloma; or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (< 40 yr).

The Aldosterone-Renin Ratio (ARR) is currently the most reliable means available for screening for PA. It is recommended that hypokalaemia be corrected and that those drugs which could cause false-positive or false-negative results be removed for at least 2–3 weeks, before measuring the ARR. Like all biochemical case detection tests, the ARR is not without false positives and false negatives and can be affected by numerous conditions (see Table 1) [3, 6]. The ARR should therefore be regarded as a detection test only and should be repeated if the initial results are inconclusive or difficult to interpret because of suboptimal sampling conditions. It should also be appreciated that the ARR conveys quantitative information: in other words a markedly elevated value should be taken as a strong indication for the presence of PA, which can warrant adrenal vein sampling without any further confirmation, while borderline elevated values should be repeated and perhaps followed by an exclusion test.

In recent years it has become more common to use the direct active renin assay instead of the plasma renin activity (PRA) to evaluate the renin–angiotensin system. A major problem is that there are important and confounding differences across laboratories regarding the methods and units used to report values of renin and aldosterone; this, together with the lack of uniformity in diagnostic protocols, has been associated with substantial variability in cut-off values used by different groups, ranging from 20 to 100 as ng/dl Aldo over ng/dl/hr (or 68 to 338 as pMol/L over mU/L) [7]. Most groups, however, use cut-offs of 20–40 (for Aldo in ng/dl over PRA in ng/ml/h) (68–135) when testing is performed in the morning on a seated ambulatory patient. In the largest available study in which the ARR was used to identify the only PA subtype that could be conclusively diagnosed based on the "four corners" criteria, the optimal cut-off for the ARR (PAC in ng/dl, PRA in ng/ml/h) was 25.86 [3].

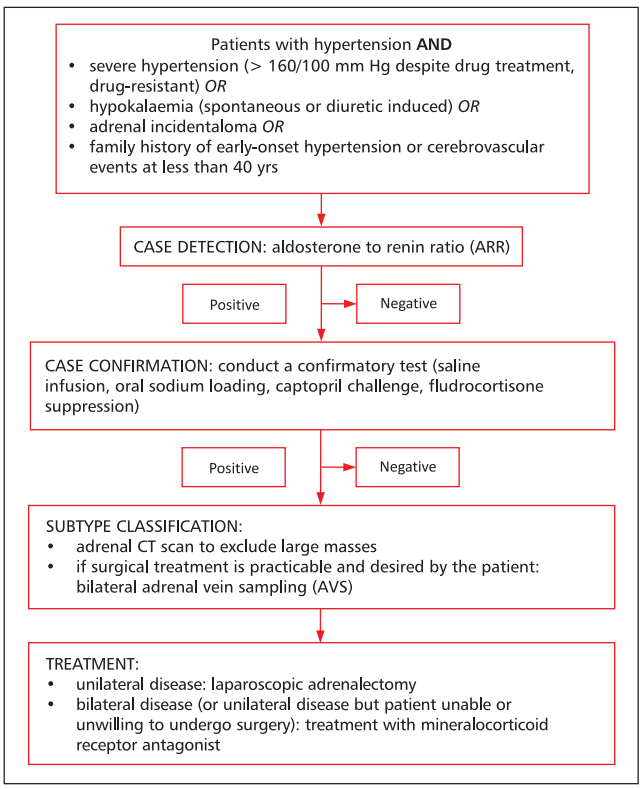

Figure 1. Flowchart outlining the suggested work-up of patients with hypertension and increased risk of hyperaldosteronism [5]

Table 1. Factors that may affect the aldosterone–renin ratio and thus lead to false positive or false negative results [5]

FACTOR	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
Medications			
Beta-adrenergic blockers	↓	↓↓	↑(FP)
Central α-2 agonists	↓	↓↓	↑(FP)
NSAIDs	↓	↓↓	↑(FP)
K^+ wasting diuretics	→↑	↑↑	↓(FN)
K^+ sparing diuretics	↑	↑↑	↓(FN)
ACE inhibitors	↓	↑↑	↓(FN)
ARBs	↓	↑↑	↓(FN)
Ca^{2+} blockers (DHPs)	→↑		↓(FN)
Renin inhibitors	↓	↓↑*	↓(FN)* ↑(FP)*
Potassium status			
Hypokalaemia	↓	→↑	↓(FN)
Potassium loading	↑	→↑	↑(FP)
Dietary sodium			
Sodium restricted	↑	↑↑	↓(FN)
Sodium loaded	↓	↓↓	↑(FP)
Advancing age	↓	↓↓	↑(FP)
Other conditions			
Renal impairment	→	↓	↑(FP)
PHA-2	→	↓	↑(FP)
Pregnancy	↑	↑↑	↓(FN)
Renovascular HT	↑	↑↑	↓(FN)
Malignant HT	↑	↑↑	↓(FN)

*Renin inhibitors lower PRA but raise DRC. This would be expected to result in false-positive ARR levels for renin measured as PRA and false negatives for renin measured as DRC; PHA-2 — pseudohypoaldosteronism type 2 (familial hypertension and hyperkalemia with normal glomerular filtration rate)

Case confirmation

Once a high ARR has been determined confirmatory tests should be performed to definitively confirm or exclude PA [5]. At present, four confirmatory tests to definitively confirm or exclude the diagnosis are used: oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge. These four tests are in common use even though their usefulness is supported at best by a level of evidence C by the AHA criteria, and therefore the level of recommendation for their use is only Iib. Moreover, there is currently insufficient direct evidence to recommend any one of these above the others. These tests may differ in terms of sensitivity, specificity, and reliability, but the choice of a confirmatory test is usually determined by considerations of cost, patient compliance, laboratory facilities, and local expertise. The most commonly used test is the saline infusion test (2 L over 4 hrs) with a temptative cut-off for post infusion plasma aldosterone above 7 ng/dl [8]. It should be noted that confirmatory tests requiring oral or IV sodium loading should be administered with caution in patients with uncontrolled hypertension or congestive heart failure. As all these tests rely on the presumed autonomy of the aldosterone production from angiotensin II, which apparently is not the case in all aldosterone-producing adenoma, these tests are fraught with a large number of false negative and false positive results, and therefore some experts support the view that they should not be used as they can lead to curative adrenalectomy not being given to many patients.

Subtype classification

All patients with primary aldosteronism should undergo *adrenal computed tomography (CT)* as the initial subtype study, to exclude large masses that may represent adrenocortical carcinoma and to ascertain the right adrenal vein anatomy, which is useful for planning and adrenal vein sampling. Of these indications, adrenal CT has no place for differentiation of PA subtypes. In fact, small APAs may be overlooked, and/or non-functioning adenoma ("incidentaloma") on one side can be considered the "culprit" for PA while instead the latter is due to a small CT-undetectable APA or unilateral hyperplasia on the contralateral side. Moreover, apparent adrenal microadenomas may actually represent areas of hyperplasia, and unilateral adrenalectomy would be inappropriate. In addition, non-functioning unilateral adrenal macroadenomas are not uncommon, especially in older patients (> 40 years old) and are indistinguishable from APAs on CT. Unilateral UAH (unilateral adrenal hyperplasia) may be visible, but also invisible on CT. *Magnetic resonance imaging* has no advantage over CT in subtype evaluation of PA, being more expensive and more prone to motion artefacts than CT.

Lateralization of the source of excessive aldosterone secretion is critical to guide the management of PA. Imaging cannot reliably visualize microadenomas or distinguish incidentalomas from APAs with confidence [9], making *Adrenal Vein Sampling (AVS)* the most accurate way of differentiating unilateral from bilateral forms of PA.

It must be understood that AVS should be offered to the patients only if surgical treatment is possible and desired by the patient. The sensitivity and specificity of AVS (95 and 100%, respectively) for detecting unilateral aldosterone excess are superior to those of adrenal CT (78 and 75%, respectively) [10].

Although AVS can be a difficult procedure, especially on 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 [9]. Currently, three protocols for AVS are used: 1) unstimulated sequential or simultaneous bilateral AVS, 2) unstimulated sequential or simultaneous bilateral AVS followed by bolus cosyntropin-stimulated sequential or simultaneous bilateral AVS, and 3) continuous cosyntropin infusion with sequential bilateral AVS. There are actually no clear guidelines which recommend any particular protocol and data are lacking on the impact of AVS on clinical outcomes [11]. Some form of patient stratification is required, possibly firstly identifying which patients should proceed to surgery set against those who can be managed on effective medical therapy with Mineralocorticoid Receptor antagonists. The use of AVS must be justified on a case-by-case basis, asking how it will improve patient care and outcome, and be undertaken in centres of excellence to achieve optimal sensitivity [12].

Other screening tests

- *Posture stimulation test*. In patients with unsuccessful AVS and with a CT scan showing a unilateral adrenal mass, some experts use the posture stimulation test. This test, developed in the 1970s, was based on the finding that the PAC in patients with APA showed diurnal variation and was relatively unaffected by changes in angiotensin II levels, whereas IHA was characterized by enhanced sensitivity to small changes in angiotensin II that occur with standing. Recent reviews showed an accuracy of 85% of this test. The lack of accuracy is explained by the fact that some APAs are sensitive to angiotensin II and some patients with IHA have diurnal variation in aldosterone secretion. Thus, the posture stimulation test may have an ancillary role, for example, in those patients for whom AVS was unsuccessful and CT shows a unilateral adrenal mass [13].
- *Iodocholesterol scintigraphy*. [131I]19-Iodocholesterol scintigraphy was first used in the early 1970s, and an improved agent, [6b-131I]iodomethyl-19--norcholesterol (NP-59), was introduced in 1977. The NP-59 scan, performed with dexamethasone suppression, had the putative advantage of correlating function with anatomical abnormalities. However, the sensitivity of this test depends heavily on the size of the adenoma; consequently, this method is useless in interpreting micronodular findings obtained with high-resolution CT and has no major role in subtype evaluation [14] in most centres. Moreover, the shortage of the radiotracer currently makes this test unfeasible for most centres.
- *18-Hydroxycorticosterone levels*. 18-Hydroxycorticosterone is formed by 18-hydroxylation of corticosterone. Patients with APA generally have recumbent plasma 18-hydroxycorticosterone levels greater than 100 ng/dl at 0800 h, whereas patients with IHA have levels that are usually less than 100 ng/dl. However, this test lacks the accuracy needed to guide the clinician in the subtype evaluation of PA [5].
- *Testing for familiar forms of PA[FH-I (GRA)]*. FH-1 syndrome is responsible for less than 1% of cases of PA and it is inherited in an autosomal dominant fashion. It may be diagnosed in patients with onset of PA earlier than at 20 years of age and in those who have a family history of PA or of strokes at young age. Genetic testing by either Southern blot [15] or long PCR techniques is sensitive and specific for GRA. FH-II syndrome us clinically indistinguishable from non-familiar PA. It is an autosomal dominant disorder. GRA mutation testing is negative. Its prevalence has not been established. An association with chromosomal region 7p22 has been shown [16].
- A further approach that is being tested to identify lateralizedaldosterone excess entails C^{11}methomidate positrone emissiontomography. However, it remains to be demonstrated if it couldidentify the majority of APAs that, as mentioned above, are small.

Treatment

Treatment of choice in documented unilateral PA (APA or UHA) is unilateral laparoscopic adrenalectomy, whereas medical treatment with mineralocorticoid receptor antagonists is indicated in patients with bilateral adrenal disease (idiopathic adrenal hyperplasia, bilateral APA, GRA).

Surgical treatment in patients with unilateral PA shows improvement of serum potassium concentrations in nearly 100% of patients postoperatively [5] when the diagnosis and the indication of adrenalectomy are made based on AVS. 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, with a cure rate as high as 56–77% when the cure threshold is blood pressure less than 160/95 mm Hg [5].

Factors associated with resolution of hypertension in the postoperative period include having no more than one first-degree relative with hypertension, preoperative use of one or two antihypertensive drugs [17], known duration of hypertension, and the presence of vascular remodelling [18]. As compared with open adrenalectomy, laparoscopic adrenalectomy is associated with shorter hospital stays and fewer complications [19].

In patients who do not undergo surgery and in those presenting bilateral adrenal disease, medical treatment is indicated as follows:

- *MR antagonists* appear to be effective in the control of blood pressure and providing target organ protection.
- *Spironolactone* has been the agent of choice in the medical treatment of PA for more than four decades. Several observational studies in patients with IHA have reported a mean reduction in systolic blood pressure of 25% and diastolic blood pressure of 22% in response to spironolactone 50––400 mg/d for 1–96 months [5]. The incidence of gynaecomastia with spironolactone therapy is dose related, whereas the exact incidence of menstrual disturbances in premenopausal women with spironolactone therapy is unknown. Where available, canrenone (an active metabolite of spironolactone) or potassium canrenoate, might be considered because they possibly have fewer sex steroid-related side effects. In addition, a small dose of a thiazide diuretic, triamterene, or amiloride can be added to avoid a higher dose of spironolactone which may cause side effects. The starting dose for spironolactone should be 12.5–25 mg daily in a single dose. The lowest effective dose should be found by very gradually titrating upward to a maximum dose of 100 mg/d.
- *Eplerenone* is a newer, selective MR antagonist without antiandrogen and progesterone agonist effects, thus reducing the rate of adverse endocrine side effects. Eplerenone has 60% of the MR antagonist potency of spironolactone; its better tolerability profile needs to be balanced against its higher cost, shorter duration of action requiring multiple daily dosing, and the lack of current clinical trial evidence for its use in PA [20]. The starting dose for eplerenone is 25 mg once or twice daily.

Other agents

Up-regulation of distal tubular sodium epithelial channel activity is a major mechanism whereby aldosterone exerts its actions on sodium and potassium handling. Of the available epithelial sodium channel antagonists, amiloride has been the most studied as a mode of treatment for PA. Although less efficacious than spironolactone, amiloride may be useful. Being a potassium--sparing diuretic, amiloride can ameliorate both hypertension and hypokalaemia in patients with PA and is generally well tolerated, lacking the sex steroid-related side effects of spironolactone, but without the beneficial effects on endothelial function [21]. Calcium channel blockers, angiotensin--converting enzyme inhibitors, and angiotensin receptor blockers have been evaluated in very few patients with PA, and in general they are antihypertensive drugs without a major effect on aldosterone excess. Supportive studies are small and methodologically weak and have not measured patient-important outcomes. Aldosterone synthase inhibitors may play a role in the future.

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