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AN UPDATE OF THE GUIDELINES FOR DIAGNOSIS AND MANAGEMENT OF PRIMARY ALDOSTERONISM

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INTRODUCTION

Primary aldosteronism (PA) involves about 6% of the hypertensives seen by general practitioners,[1] more than 11% of those referred to specialized hypertension centers, [2] and up to 20% of those with difficult-to-treat hypertension [3,4]. Moreover, unilateral adrenal-vein sampling (AVS)-guided adrenalectomy was shown to resolve resistant hypertension in practically all patients [5]. Notwithstanding this, and the fact that PA damages the heart, arterial wall, and kidneys [6], only 1% to 2% of the hypertensive patients [7] are currently screened for PA in Europe.

The poor awareness of the high prevalence of PA, and the lack of hypokalemia, the classical alerting sign of PA, in the majority of the patients, and a diagnostic work-up that is perceived as too complex are major reasons for this under detection.

This newsletter is aimed at providing an updated concise information on a simplified strategy for identification, subtyping, treatment, and follow-up of PA patients. For more details the readers are referred to a state-of-the-art review,[8] the most recent guidelines published, [9] and ESH Consensus document. [10]

CLINICAL FORMS OF PA

Clinically, PA patients should be divided into those with surgically curable and non-surgically correctable forms.[8] A unilateral form of PA can be identified in about two thirds of the cases with systematic use of AVS, a rate two-fold higher than in centers that cannot perform AVS, indicating that surgically curable PA is common, but can be pinpointed only by using AVS. When AVS-guided, adrenalectomy provides cure of the hyperaldosteronism and can resolves or improve arterial hypertension, if the diagnosis is made early [11]. It is, therefore, of paramount importance to implement strategies for the early identification of PA in newly diagnosed hypertensive patients.

WHO SHOULD BE SCREEN FOR PA?

Screening is mandatory in the categories of patients listed in the Table 1. However, PA follows a long natural history, starting with normotension and renin suppression, then progressing into florid PA, and ultimately evolving in stage II-III and/or drug-resistant hypertension [12]. Therefore, it might be reasonable to propose screening of all newly-presenting hypertensive patients, giving priority to those who can benefit more, like those with drug-resistant hypertension, have unbearable side effects with drug treatment, and have a high chance of being cured by adrenalectomy as, for example, young women with a short duration of hypertension.[13] Accumulating evidences suggest that these categories should be further expanded to include hypertensive patients presenting with unexplained atrial fibrillation [14].

DIAGNOSIS

Low or undetectable renin levels along with inappropriately plasma aldosterone concentration (PAC) are the biochemical hallmarks of PA. In most laboratories the direct active renin concentration (DRC) chemiluminescent assay has replaced the plasma renin activity (PRA) because it is cheaper, faster, automatable, and also because it allows handling samples at room temperature.[15] Available automated chemiluminescent assays for the simultaneous rapid measurement of DRC and PAC provide a straightforward assessment of the aldosterone: renin ratio (ARR). [16]

As the ARR is a simple bivariate ratio, its value is overinflated when renin is low even when PAC is normal. It is, therefore, common practice to fix the renin value at a minimum of 2 mIU/L for DRC or calculate the ARR only if PAC exceeds 15 ng/dl. This caveat is important particularly in patients who have low renin values, as the elderly and people of African origin.

The ARR is popular mainly because it is simple and within-patient reproducible when performed under standardized conditions,[17] but its use requires a number of considerations as shown in Table 2. When using it, attention should be paid not only to the actual PAC and renin values, but also to the ARR value itself. Instead, the ARR is commonly interpreted simply as positive or negative, which leads to disregard the important quantitative information that it carries: in a very large study [18], and endorsed by the Endocrine Society Guidelines, a noticeably raised ARR value furnishes a biochemical diagnosis of PA without need for further testing. Applying this strategy translates into a prominent simplification of the work-up, shown in the diagnostic algorithm (**Figure**) and allows saving time and money, while not endangering the accuracy of the diagnosis and the clinical outcome.

With PAC measured in ng/dl and DRC in mUI /L, an ARR cutoff greater than 2.06 (ng/dl/mUI /L, i.e. 20.6 in ng/mU) has a high overall accuracy (sensitivity and specificity) for the identification of aldosterone-producing adenoma (APA).[15] When the ARR values are borderline, referring the patient for AVS can require repeating the ARR under better standardized conditions, including a longer wash-out from potentially interfering drugs, with verification of normokalemia and normal sodium intake (> 6 g NaCl). Multivariate artificial intelligence techniques are valuable alternatives to the ARR,[19]. A freely downloadable (at the Apple Store website) ARR-App, which is for use on tablets and mobile phones, utilizes one such approaches,[20] and allows to circumvent one of the most common problem encountered in clinical practice, i.e. the difficulty of calculating the ARR starting from renin and PAC values that are furnished in different units of measures by different laboratories.

CONDITIONS FOR TESTING

Careful preparation of the patient and standardization of the testing conditions are key steps when screening for PA, since multiple factors affect the ARR (Table 2). Standardization means prior correction of hypokalemia and keeping the patients quiet resting supine, or sitting for 1 hour. Urinary potassium and sodium excretion should be measured in a 24-hours urine collection; the former provides a basis for titrating KCl supplementation to correct hypokalemia, if present, in preparation for AVS; the latter provides an estimate of salt intake, which allows a correct interpretation of the hormonal values.

Withdrawal of anti-hypertensive treatment is never necessary before measuring the ARR. Instead a switch to doxazosin and/or a long-acting calcium channel blocker, which have negligible effects on the ARR,[21,22] can be used to control blood pressure during screening. Diuretics, ACE inhibitors and ARBs raise renin and decrease the ARR and thus the rate of false negative; conversely, beta-blockers blunt renin and therefore raise the ARR thus increasing the false positive rate. These drugs should be withdrawn at least 4 weeks before testing. At variance with common beliefs, mineralocorticoid receptor antagonists (MRA) can be used, because they do not alter the ARR and do not preclude the diagnosis of unilateral PA as shown in the EMIRA study, which used a within-patient prospective design and post-surgical confirmation of the diagnosis.[23] These agents are particularly indicated in patients with drug-resistant hypertension, a common presentation of PA and/or severe hypokalemia, as they are the most effective agents to control high blood pressure [24-26] and hypokalemia during the screening of PA.

In patients with severe and/or drug-resistant hypertension and/or evidence of target organ damage or previous cardiovascular events, knowledge of the effects of interfering agents on renin and aldosterone (Table 3) can allow to make the correct diagnosis as discussed elsewhere.[8]

EXCLUSION OF PRIMARY ALDOSTERONISM

The (relatively) low ARR cutoff values often used to maximize sensitivity during screening, can generate false positive results, which must be identified in order to exclude the patients from useless AVS. Hence, exclusion ("confirmatory") tests are deployed[27,28], under the yet unproven premise that the hyperaldosteronism is autonomous from the renin–angiotensin system. However, aldosterone-producing adenomas express the angiotensin II type 1 receptor and respond to angiotensin II [29]; moreover, one such tests - the captopril challenge - provided no diagnostic gain over a carefully performed and interpreted ARR in a very large study.[18] Besides, relying on these tests increase costs and complexity of the work-up and can lead to missing several patients with surgically curable PA, who suppress PAC in response to blunting angiotensin II.[30] Hence, the last Endocrine Society Guidelines wisely suggested skipping these tests in patients with a florid PA phenotype,[22] and to proceed directly to AVS, provided that the patient is willing to pursue a surgical cure and has a markedly raised ARR (**Figure**).

IMAGING

Imaging by CT or MR is recommended in all PA patients to exclude an aldosterone-producing carcinoma, and to identify adrenal venous drainage,[22] but is inadequate to refer the patients to surgery, because it does not identify the culprit adrenal. In AVIS-2, a recent large multiethnic international study of PA patients submitted to AVS imaging was negative in one third of the patients [31]. Moreover, the assessment of adrenal micro-adenomas is the main limitation of adrenal imaging, which explains why imaging has a poor accuracy in predicting unilateral disease: one fifth of the PA patients would have been denied curative adrenalectomy, and others would have undergone unnecessary or inappropriate adrenalectomy by relying solely on CT.[32,33]

SUBTYPING OF PRIMARY ALDOSTERONISM

AVS is key to identify candidate for unilateral adrenalectomy [34], and therefore should be proposed only to patients with PA, who are reasonable candidates for general anesthesia and surgery, wish to achieve long-term cure of PA with adrenalectomy, and do not have any surgically-incurable forms of mineralocorticoid excess. Given its limited availability and its invasive nature, noninvasive alternatives to AVS have been explored, albeit with inconsistent results.[35-37]

Functional imaging by positron emission tomography with C11methomidate seems to be a promising approach to identifying lateralized aldosterone excess,[38] but due to the low selectivity of C11-metomidate for CYP11B2 versus CYP11B1, and the need of a cyclotron facility on site it was feasible in only few centers. An in-depth discussion of when and how to perform AVS and how to interpret its results is provided elsewhere [39].

GENETIC TESTING

The discovery of somatic mutations in the Kir3.4 gene encoding the KCNJ5 potassium channel in a subset of APA [40] and in very rare families hypertension and bilateral adrenal hyperplasia paved the way to the discovery of mutations also in other genes,[41-43] and to a novel classification of familial hyperaldosteronism (FH) and to genetic tests [44]. Currently, indication for genetic testing for familial forms of PA (familial hyperaldosteronism, FH) is limited to patients with PA diagnosed before age 30 years, particularly if they have a family history of PA and/or stroke at young age .[44]

TREATMENT

Unilateral laparoscopic adrenalectomy is the best available treatment for patients with unilateral PA, who wish to achieve long-term cure and are candidates for general anesthesia. To achieve cure and avoid cardiovascular damage, the sooner the diagnosis is made and surgery is performed, the better the outcome. Adrenalectomy implies a short hospital stay, a very low operative risk in experienced centers.[45,46]When AVS-guided, adrenalectomy usually corrects the hyperaldosteronism and cures arterial hypertension in about 45% of the patients. Arterial hypertension is also ameliorated in an additional 40% of the patients,[11,47] but even when antihypertensive treatment remains necessary, the number and/or the doses of antihypertensive drugs can be markedly decreased. Importantly, AVS-guided adrenalectomy was also shown to resolve resistant hypertension in a proof-of-concept study, sometimes leading to complete cure in these very high-risk patients.[48]

Common reasons of failure to surgically cure PA are inaccurate diagnoses, i.e. non AVS-guided adrenalectomy, and/or, more frequently, the concurrence of chronic kidney disease, and/or primary (essential) hypertension,[49] which involves up to 30% of the PA patients and cannot be expected to be cured by adrenalectomy.

Mineralocorticoid receptor antagonists (MRAs), alone or in combination with other agents, are indicated in preparation of adrenalectomy and are key drugs to control hypokalemia and high blood pressure values in patients, who are not eligible for surgery or do not show unilateral PA on AVS. Spironolactone, canrenone, potassium canrenoate, are the recommended MRAs. Eplerenone, yet not approved by FDA and EMA for the treatment of PA, is less likely to exert off-target effects, but is weaker and shorter acting than the others.

As a guide to up-titration of MRAs treatment, renin levels should be measured, because the persistence of low values can point to inadequate dosing, which may results in uncontrolled disease and excess cardiovascular risk.[50,51] For example, MRAs should be up-titrated to the highest tolerable daily dose (starting from 12.5 and up, but usually 25-100 mg) that permits to control of blood pressure values and warrants normokalemia, but up-titration has to be weighed against the common side effects in men, mainly gynecomastia and impotence, which, being dose-dependent, can be avoided with reduced doses and/or combination with other agents. Inhibitors of the epithelial sodium channel, as amiloride and triamterene, are reasonable options to spare MRAs to the patients with side effects. Aldosterone synthase inhibitors are also promising agents (for rev. [52]), but some of them have revealed poor selectivity in that they also blunted cortisol synthesis.[53]

FOLLOW-UP

Regular follow-up visits with biochemical retesting are advised, at least in the first 6 months, because confirmation of the diagnosis of unilateral PA requires demonstration of biochemical cure of PA after surgery [54]. In the PA patients assigned to long-term medical treatment, attention should be paid to development of blood pressure resistance to treatment. The rise of plasma renin can serve as a guide to MRA titration, as it would indicate adequate correction of salt retention and volume expansion.55 If resistance to treatment develops, reinvestigation to detect a unilateral form of PA by AVS, which is feasible during treatment, and can lead to long-term cure, is advised.

CONCLUSIONS

PA can be identified in a cost-effective manner (**Figure**) and should be considered in all hypertensive patients. When a unilateral cause of PA is discovered, hyperaldosteronism and hypokalemia are curable with adrenalectomy in almost all patients. High blood pressure can also be normalized, or considerably reduced, in a substantial proportion of them. Diagnosing PA is particularly beneficial when hypertension is severe and/or resistant to treatment, because adrenalectomy brings high blood pressure values under control, permits withdrawal, or a prominent reduction in the number and dosage, of antihypertensive medications, and prevents cardiovascular events and renal damage.[48]

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HIGHLIGHTS

BULLETS POINTS
• PA is a common curable cause of hypertension and implies excess cardiovascular damage and events.
• A wide range of hypertensive patients, particularly those with drug-resistant hypertension, should be tested for PA.
• Simplified strategies can allow to identify those who can be long-term cured with surgery.
• Case detection testing for PA should be performed by measuring the aldosterone-renin ratio
• Follow-up is recommended in both the surgically and the medically treated PA patients.

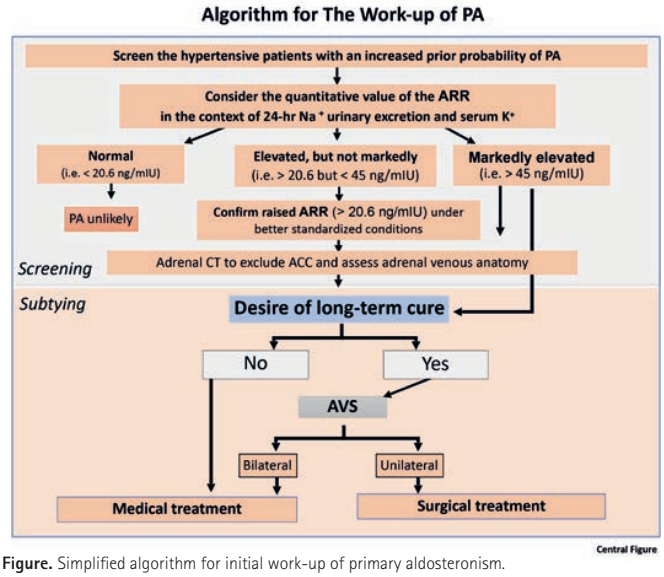

Figure. Simplified algorithm for initial work-up of primary aldosteronism.

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