High Blood Press Cardiovasc Prev (2016) 23:69–72
DOI 10.1007/s40292-016-0136-5

REVIEW ARTICLE

Hyperaldosteronism: Screening and Diagnostic Tests

Chiara Sabbadin[1] · **Francesco Fallo**[2]

Received: 29 January 2016 / Accepted: 26 February 2016 / Published online: 14 March 2016

Abstract Primary aldosteronism (PA) is the most common secondary cause of hypertension, accounting for 10 % of hypertensives and 20 % of those with drug-resistant hypertension. Aldosterone excess is associated with the development of adverse cardiovascular, renal and metabolic effects that are partly independent of its effect on blood pressure. Guidelines recommended wider screening for PA in an effort to maximize detection of patients who may benefit from optimal, specific management. All patient groups with increased prevalence of PA, including hypertensive patients with type 2 diabetes mellitus and those with obstructive sleep apnea, should be carefully screened for PA. Screening with aldosterone-to-renin ratio (ARR) is the most practical and informative initial test. Subsequent confirmatory tests are: (1) oral salt loading; (2) saline infusion; (3) captopril challenge and (4) fludrocortisone suppression test. Confirmation of PA can avoid that patients with a false positive ARR would inappropriately undergo costly and harmful lateralization procedures. If confirmatory testing is positive, further investigations are directed toward determining the subtype of PA, as the treatment differs for each subtype.

Keywords Hypertension · Aldosterone · Primary aldosteronism

✉ Francesco Fallo
francesco.fallo@unipd.it

[1] Endocrinology, Department of Medicine-DIMED, University of Padova, Padua, Italy

[2] Clinica Medica 3, Department of Medicine-DIMED, University of Padova, Via Giustiniani 2, 35128 Padua, Italy

1 Introduction

Primary aldosteronism (PA) is the most common secondary cause of hypertension, affecting about 10 % of the general hypertensive population and 20 % of drug-resistant hypertension. The diagnosis of PA is critical not only to prevent and correctly treat the complications related to hypertension, but also to prevent the non-epithelial effects related to hyperaldosteronism. Indeed, there is great evidence that PA patients have an increased rate of cardio- and cerebro-vascular events and of metabolic complications compared to essential hypertensives [1, 2]. In fact, PA patients have an increased risk of stroke, myocardial infarction, arrhythmias, heart failure and type 2 diabetes [3]. As a result, the current Endocrine Society (ES) guidelines (a new version is expected to be published in 2016) recommend case detection of PA in patient groups with relatively high prevalence of PA, in an effort to maximize detection of subjects who may benefit from optimal specific management [4].

2 Who Should Be Screened?

Firstly, patients who should be screened include those with Joint National Commission stage 2 (160–179/100–109 mmHg) and stage 3 (>180/110 mmHg) hypertension and/or with hypertension resistant to 3 conventional antihypertensive drugs, including a diuretic. In fact, several studies demonstrated that the probability of having PA increases with the severity of hypertension, reaching a prevalence of about 20 % in resistant hypertensives [5, 6]. Secondly, PA screening is suggested in patients with hypertension and spontaneous or diuretic-induced hypokalemia. Although normokalemic hypertension constitutes

the most common presentation of the disease, hypokalemia is much more frequent in PA patients compared to essential hypertension [7]. Hypertensive patients with adrenal incidentaloma represent another recommended patient subgroup, PA prevalence being about 1.6 % [8]. Finally, PA should be screened in hypertensive patients with a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years) and all hypertensive first-degree relatives of patients with PA: this could indicate in fact familial hyperaldosteronism type 1 (glucocorticoid-remediable aldosteronism) or type 2 [9] or type 3 [10]. However, other subgroups of patients with a potentially increased PA prevalence have subsequently identified. Jerome W. Conn firstly described the association between PA and impaired glucose tolerance in 1965 [11], but some reports did not confirm these results, partially because of the small sample of patients evaluated and the different criteria used to diagnose altered glucose metabolism and PA. A significant increased prevalence of metabolic syndrome, including hyperglycemia, was found in PA patients compared to essential hypertensives patients (41.1 vs 29.6 and 27 vs 15.2 %, respectively) [12], and a more recent study in a large German cohort confirmed a higher prevalence of type 2 diabetes mellitus in PA than in essential hypertensives [13]. Thus, an abnormal glucose metabolism due to insulin resistance appears to be linked to aldosterone overproduction, and appears to be the major contributor to metabolic dysfunction in PA [14, 15]. Many pathogenic mechanisms, both direct (aldosterone excess) and indirect (hypokalemia, oxidative stress) [16], have been suggested to explain this effect. Another interesting association has been described between hyperaldosteronism and severity of obstructive sleep apnea (OSA) in patients with resistant hypertension [17]. Addition of spironolactone to the ongoing antihypertensive therapy reduced the severity of OSA, probably due to its diuretic effect and the consequent reduction in pharyngeal edema and in upper airway resistance [18]. Moreover, a high prevalence of PA has been in fact found in patients with OSA [19]. This suggests to include patients with OSA among those to be investigated for PA. Table 1 reports patient groups indicated by the ES guidelines and those suggested to be screened for PA.

Table 1 Groups of patients with high prevalence of primary aldosteronism (PA)

Patients groups indicated by Endocrine Society Guidelines to be screened for PA
Patients with hypertension Stage 2–3
Drug-resistant hypertension
Hypertensives with spontaneous or diuretic-induced hypokalemia
Hypertensives with adrenal incidentaloma
Hypertensives with a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)
Hypertensive first-degree relatives of patients with PA
Patient groups suggested to be screened for PA
Hypertensives with metabolic syndrome including type 2 diabetes
Hypertensives with obstructive sleep apnea

3 Which Screening Test Is Recommended?

The ES guidelines recommend the use of aldosterone-to-renin ratio (ARR) as the most reliable test to detect cases of PA. After its introduction, the prevalence of PA has in fact significantly increased, detecting PA in normokalemic cases and/or with normal plasma/urinary aldosterone values. The cutoff level of ARR is usually set between 20 and 40 (using aldosterone units of ng/dL and plasma renin activity as ng/mL/h), considering serum aldosterone levels greater than 15 ng/dL (416 pmol/L). To increase ARR accuracy, conditions of sampling are crucial: blood samples should be collected in the morning, after the patients have been out of bed for at least 2 h and usually after they have been seated for 5–15 min; ideally, patients should have unrestricted dietary salt intake and potassium-repleted before testing. Moreover, antihypertensive drugs (β-blockers, ACE-inhibitors, angiotensin II receptor antagonists, MR-antagonists and diuretics) and some conditions like advancing age and renal impairment, could affect the ARR measurements. Washout of interfering medications is feasible in patients with mild hypertension which can be controlled by α-antagonists and/or non-dihydropyridine calcium antagonists, which do not significantly affect ARR. If this switch is difficult, most investigators suggest to interpret the ARR considering the possible interferences, allowing the patient to proceed to confirmatory/exclusion testing without delay [4]. The measurement of PRA is time consuming and shows poor inter-laboratory variability. Recently, a monoclonal antibody against active renin has been used by several laboratories to measure plasma renin concentration (PRC) instead of PRA. However, more studies are needed to test this method for detection of PA cases [20], and it would be reasonable to consider the PRC only when its value is below the lower limit of detection for the assay.

4 Which Confirmatory Tests Should Be Performed?

The ES guidelines recommend that patients with a positive ARR should undergo confirmatory procedures, in order to avoid costly and potentially harmful lateralization procedures in subjects with false positive ARR. The four confirmatory tests recognized by the ES guidelines are: (1) oral salt loading; (2) saline infusion; (3) captopril challenge and

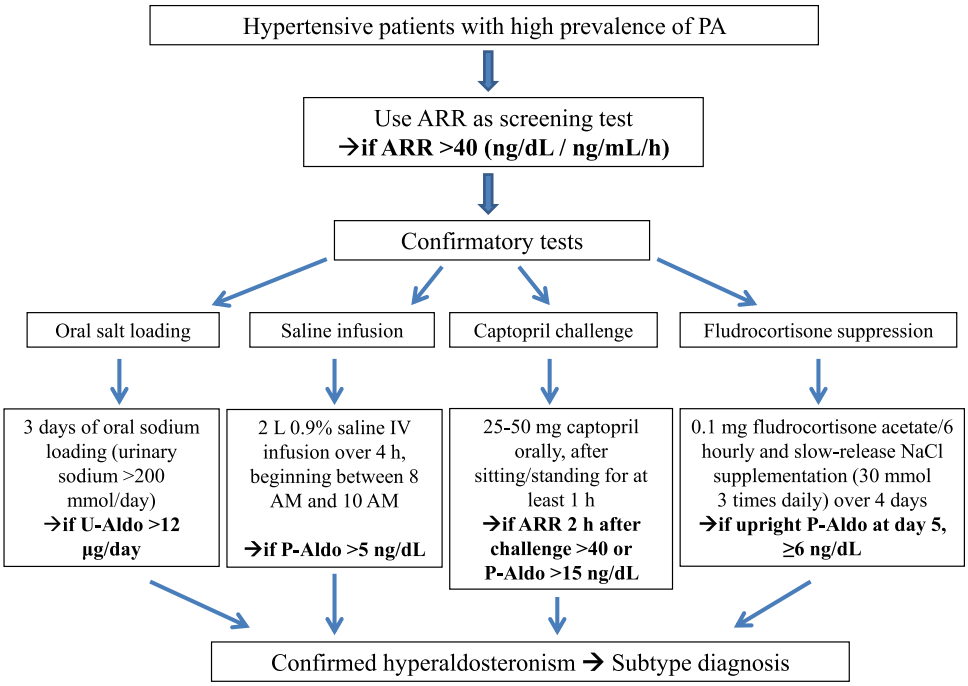

Fig. 1 Flow-chart for confirmatory diagnosis of primary aldosteronism, including test protocols and cut-offs. *PA* primary aldosteronism, *ARR* aldosterone-to-renin ratio, *U-Aldo* urinary aldosterone, *P-Aldo* plasma aldosterone

(4) fludrocortisone suppression (see test protocols and diagnostic cut-offs in Fig. 1). None of these has been identified as a gold standard procedure to confirm PA. The oral salt loading test, after hypertension and hypokalemia are controlled, is quite inexpensive and does not require patient hospitalization: it is however associated with a risk of hypokalemia and its reliability depends on the accuracy of urine collection by the patient. The intravenous saline loading test is safe and relatively inexpensive, but it must be performed monitoring blood pressure and heart rate, being potentially harmful. The captopril challenge is associated with a significant rate of false positive and negative PA diagnosis, but it is the only test without risk of volume expansion and therefore suggested for patients with reduced cardiac or renal function or uncontrolled hypertension. The fludrocortisone suppression test is considered the most physiologic test for PA, but it is also the most expensive and requires a brief hospitalization due to the risk of severe hypokalemia. The use of interfering antihypertensive drugs (it is impossible to interpret data obtained from patients receiving MR-antagonists or direct renin inhibitors) must be always considered, and the optimal cutoff value for these tests depends on the assay used to measure aldosterone and PRA or PRC.

5 Conclusions

All patient groups with increased prevalence of PA, including hypertensive patients with type 2 diabetes mellitus and those with OSA, should be carefully screened, using the ARR as the most practical and initial test. Subsequent confirmatory tests are required to confirm the diagnosis and to avoid that patients with a false positive ARR (for example with low-renin hypertension) would inappropriately undergo costly and harmful lateralization procedures [21]. If confirmatory testing is positive, further investigations are directed toward determining the subtype of PA, as the treatment differs for each subtype.

Compliance with Ethical Standards

Conflict of interest disclosure There are no conflict of interest and no financial disclosure to disclose.

References

1. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence of an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol. 2005;45(8):1243–8.
2. Fallo F, Federspil G, Veglio F, Mulatero P. The metabolic syndrome in primary aldosteronism. Curr Hypertens Rep. 2007;9(2):106–11.
3. Mulatero P, Monticone S, Bertello C, Viola A, Tiziani D, Iannaccone A, Crudo V, Burrello J, Milan A, Rabbia F, Veglio F. Long-term cardio- and cerebrovascular events in patients with primary aldosteronism. J Clin Endocrinol Metab. 2013;98(12):4826–33.
4. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM, Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(9):3266–81.
5. Mosso L, Carvajal C, Gonzàlez A, Barraza A, Avila F, Montero J, Huete A, Gederlini A, Fardella CE. Primary aldosteronism and hypertensive disease. Hypertension. 2003;42(2):161–5.

6. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension. 2002;40(6):892–6.
7. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, Mallamaci F, Mannelli M, Mattarello MJ, Moretti A, Palumbo G, Parenti G, Porteri E, Semplicini A, Rizzoni D, Rossi E, Boscaro M, Pessina AC, Mantero F, PAPY Study Investigators. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol. 2006;48(11):2293–300.
8. Mantero F, Terzolo M, Arnaldi G, Osella G, Masini AM, Giovagnetti M, Opocher G, Angeli A. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. J Clin Endocrinol Metab. 2000;85(2):637–44.
9. Stowasser M, Fallo F, So A, Jeske Y, Kelemen L, Pilon C, Gordon R. Genetic forms of primary aldosteronism. High Blood Press Cardiovasc Prev. 2007;14(2):75–81.
10. Monticone S, Else T, Mulatero P, Williams TA, Rainey WR. Understanding primary aldosteronism: impact of next generation sequencing and expression profiling. Mol Cell Endocrinol. 2015;399:311–20.
11. Conn JW. Hypertension, the potassium ion and impaired carbohydrate tolerance. N Engl J Med. 1965;273(21):1135–43.
12. Fallo F, Veglio F, Bertello C, Sonino N, Della Mea P, Ermani M, Rabbia F, Federspil G, Mulatero P. Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. J Clin Endocrinol Metab. 2006;91(2):454–9.
13. Hanslik G, Wallaschofski H, Dietz A, Riester A, Reincke M, Allolio B, Lang K, Quack I, Rump LC, Willenberg HS, Beuschlein F, Quinkler M, Hannemann A, Participants of the German Conn's Registry. Increased prevalence of diabetes mellitus and the metabolic syndrome in patients with primary aldosteronism of the German Conn's Registry. Eur J Endocrinol. 2015;173(5):665–75.
14. Iacobellis G, Petramala L, Cotesta D, Pergolini M, Zinnamosca L, Cianci R, De Toma G, Sciomer S, Letizia C. Adipokines and cardiometabolic profile in primary hypealdosteronism. J Clin Endocrinol Metab. 2010;95(5):2391–8.
15. Fallo F, Pilon C, Urbanet R. Primary aldosteronism and metabolic syndrome. Horm Metab Res. 2012;44(3):208–14.
16. Petramala L, Pignatelli P, Carnevale R, Zinnamosca L, Marinelli C, Settevendemmie A, Concistrè A, Tonnarini G, De Toma G, Violi F, Letizia C. Oxidative stress in patients affected by primary aldosteronism. J Hypertens. 2014;32(10):2022–9.
17. Pratt-Ubunama M, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. Chest. 2007;131(2):453–9.
18. Gaddam K, Pimenta E, Thomas SJ, Cofield SS, Oparil S, Harding SM, Calhoun DA. Spironolactone reduces severity of obstructive sleep apnea in patients with resistant hypertension: a preliminary report. J Hum Hypertens. 2010;24(8):532–7.
19. Di Murro A, Petramala L, Cotesta D, Zinnamosca L, Crescenzi E, Marinelli C, Saponara M, Letizia C. Renin–angiotensin–aldosterone system in patients with sleep apnoea: prevalence of primary aldosteronism. J Renin Angiotensin Aldosterone Syst. 2010;11(3):165–72.
20. Manolopoulou J, Fischer E, Dietz A, Diederich S, Holmes D, Junnila R, Grimminger P, Reincke M, Morganti A, Bidlingmaier M. Clinical validation for the aldosterone-to-renin ratio and aldosterone suppression testing using simultaneous fully automated chemiluminescence immunoassays. J Hypertens. 2015;33(12):2500–11.
21. Mulatero P, Monticone S, Bertello C, Mengozzi G, Tizzani D, Iannaccone A, Crudo V, Veglio F. Confirmatory tests in the diagnosis of primary aldosteronism. Horm Metab Res. 2010;42(6):406–10.