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ABSTRACT

Context: the clinical spectrum and knowledge of the molecular mechanisms underlying primary aldosteronism (PA), the most frequent form of endocrine hypertension, has evolved over the past years. In accordance with the Endocrine Society guideline and in light of the growing evidence showing adverse cardiovascular outcomes, it is expected that a progressively wider population of patients affected by hypertension will be screened for PA, including the elderly.

Evidence Acquisition: a systematic search of PubMed was undertaken for studies related to renin-angiotensin-aldosterone system (RAAS), primary aldosteronism and adrenal histopathology in the elderly population.

Evidence synthesis: several studies showed an age-dependent decrease in the activity of RAAS, together with a progressive decrease of the aldosterone response to sodium intake, particularly after the sixth decade of life. The positive correlation between age and serum aldosterone during liberal sodium intake over serum aldosterone during sodium restriction is paralleled by histological changes in adrenal aldosterone synthase (CYP11B2) expression patterns. Immunohistochemical studies showed a progressive loss of the continuous expression of CYP11B2 in adrenal zona glomerulosa with ageing and a concomitant increase of aldosterone-producing cell clusters, which might be responsible for a relatively autonomous aldosterone production. Additionally, following PA confirmation and subtype diagnosis, older age is correlated with a lower benefit after adrenalectomy for unilateral PA.

Conclusions: accumulating evidence suggests that RAAS physiology and regulation show age-related changes. Further studies may investigate to what extent these variations might affect the diagnostic work-up of patients affected by PA.

Introduction

Primary aldosteronism (PA) is a condition of inappropriate aldosterone production for renin levels and sodium status (1). Over the last two decades, clinical studies have provided evidence that PA is the most frequent cause of secondary hypertension (2-4) and is associated with a higher occurrence of cardiovascular and renal damage and metabolic complications compared with essential hypertension (5,6). The Endocrine Society (ES) guideline recommends screening of patients with hypertension and other risk conditions, resulting in the potential screening of at least 50% of patients with hypertension (1). Despite the low application of the Guideline, even in developed countries (7), it is expected that a progressively wider population of patients with hypertension will be screened. The Guideline does not give specific indications for a different strategy for screening patients according to age. However, many physicians tend to study the younger rather than older patients more extensively.

In this manuscript we review the available data on variations of aldosterone production with age, the pathophysiological changes in aldosterone regulation and in adrenal pathology. We will also discuss the appropriate strategies for diagnosis and management of PA in elderly patients.

Genetic alterations in sporadic and familial PA

PA is more frequently a sporadic condition, comprising unilateral and bilateral forms. Unilateral forms comprise aldosterone-producing adenoma (APA) and unilateral diffuse hyperplasia or hyperplasia with multiple nodules and account for 30-40% of cases of PA. Bilateral PA also known as idiopathic hyperaldosteronism or bilateral adrenal hyperplasia, is the most frequent form accounting for the remaining sporadic cases. Familial hyperaldosteronism (FH) is relatively rare accounting for less than 5% of cases (8). After the demonstration in 1992 that FH type 1 (also known as glucocorticoid-remediable aldosteronism) was due to a recombination between *CYP11B1* and *CYP11B2* genes resulting in a chimeric gene regulated by adrenocorticotrophic hormone (ACTH) encoding a hybrid enzyme able to produce aldosterone (9), it wasn’t until after 2011 that

CLCN2 (10), KCNJ5 (11), and CACNA1H (12), were demonstrated to be the genes involved in the pathogenesis of FH2-4. A further gene, *CACNA1D* (13), was shown to be responsible for a genetic but not familial condition named PASNA (primary aldosteronism, seizures and neurological abnormalities). In FH2-4 and in the PASNA syndrome, aldosterone hyperproduction is due to an alteration of the function of ion channels, resulting in an increase of intracellular calcium in zona glomerulosa cells of the adrenal cortex, that activate CYP11B2 transcription and aldosterone production (14,15). Somatic mutations in these genes and in the *ATP1A1* and *ATP2B3* were shown to be responsible for the dysregulated aldosterone production in sporadic APAs (14-18).

Changes in the adrenal *zona glomerulosa* with aging

The availability of specific monoclonal CYP11B2 and CYP11B1 antibodies allowed the understanding of the histological structures involved in aldosterone production (19) and the study of its changes during aging and in different pathological states (20,21). The use of these specific CYP11B2 antibodies allowed the identification of small, mainly subcapsular, nodules of CYP11B2 expression, usually referred to as aldosterone-producing cell clusters (APCC) (22). APCC are present in both normal and pathologic adrenals (22-24); their presence in the adjacent cortex to an APA indicates that aldosterone production in these cells is not suppressed by the excessive aldosterone produced by the APA and therefore they could represent a source of potentially inappropriate or dysregulate aldosterone production in the adrenals (20). The exact role and function of these structures is unknown: for example, they are associated with a lower lateralisation index at adrenal vein sampling (AVS) and lower prevalence of contralateral suppression of aldosterone production, indicating that their presence may be bilateral in these patients operated for unilateral PA (25). Furthermore, APCC may also affect the results of ACTH stimulation during AVS (26). However, the presence of APCC was not associated with absent biochemical success, that is persistence of PA, after adrenalectomy (24). It was also demonstrated that in APCC from normal adrenals from kidney donors may carry somatic mutations in aldosterone driver genes such

as *CACNA1D, ATP1A1* and *ATP2B3* (27), genes that are also found mutated in sporadic APAs (16). In APAs the most frequently mutated gene is usually reported as KCNJ5 (which is very rarely mutated in APCC) in contrast to APCC which show the highest incidence of mutations in CACNA1D (28). In patients with bilateral PA, APCC are more often present and increased in number and are more frequently mutated (29). Putative transitional structures with similarities to both APCC and APA have also been shown (30) and these transitional lesions, as well as APCC, are able to produce and accumulate both aldosterone and 18-oxocortisol, whose secretion is increased in many APAs (31). Further clues on the potential role of APCC as precursor lesions of APAs have been provided by the *in situ* metabolic phenotypes of APCC and APA in adrenals removed for unilateral PA (32): the authors identified 2 subgroups of APCC, one with specific distribution patterns of metabolites closely resembling those in APA and a different subgroup with a metabolic phenotype highly distinct from APA (32). Interestingly, all APCC within an adrenal displayed the same metabolite pattern (32).

Overall, these findings suggest that APCC could be involved in the pathogenesis of both unilateral PA, as precursors of APAs, and of bilateral PA as contributors of the dysregulated aldosterone production. The reason for the absence of mutations in KCNJ5 in APCC may be related to the high expression of KCNJ5 in APCC which may be incompatible with the presence of KCNJ5 mutations which are associated with high cell toxicity (33). This is in contrast to the relatively lower expression levels of KCNJ5 in APA with KCNJ5 mutations compared with APA (33) carrying other mutations and the adjacent zona glomerulosa layer (33,34).

In young subjects, CYP11B2 is expressed as a continuous pattern in the *zona glomerulosa* (23). With aging there is a progressive loss of the continuous expression of CYP11B2 and a concomitant increase of APCC in the outer layer of the adrenal cortex (20,27) (Figure 1). The result of these age-related changes is that in older people, CYP11B2 expression is mainly localized in the APCC structures whereas in the young, CYP11B2 is expressed in a continuous layer in the *zona glomerulosa* under the capsule (20,27). These changes in the pattern of CYP11B2 expression with

aging could explain in part the different production and regulation of aldosterone both under basal and stimulated conditions.

Changes of aldosterone secretion with aging

An age-dependent decrease in the activity of the renin-angiotensin-aldosterone system (RAAS) has been observed in normal subjects (35,36), independent from the status of sodium repletion. The reduction of basal and sodium depletion-stimulated renin production becomes evident after the sixth decade of life (35) (Figure 1). The concomitant decrease of aldosterone levels appears to reflect a decline of the angiotensin II stimulus rather than an alteration of *zona glomerulosa* function, because the response of aldosterone to ACTH stimulus is unchanged with aging (35). The lower RAAS activity is attributed to the reduction of renin, which in turn diminishes plasma renin activity, rather than angiotensinogen production (37). The decrease of renin levels with age is probably due to a deterioration of kidney function and has been used by many clinicians as the basis for the choice of anti-hypertensive therapy. For example, the NICE guideline 2019 for diagnosis and management of hypertension in adults (38) suggests the treatment of patients with hypertension aged more than 55 years with calcium channel blockers or thiazide diuretics, two classes of drugs that are more efficient in patients with hypertension and a low-renin profile (39,40). Aldosterone levels remain unchanged (23) or tend to decrease with aging (41) but less than renin levels. This is probably attributable to the reduced potassium secretion which parallels the decline in kidney function with aging and the subsequent stimulatory effects of potassium on aldosterone secretion. Between the fourth and the eighth decade of life there is a progressive lowering of the glomerular filtration rate (around 1 ml/min/year) and of the renal blood flow (42). Also, distal tubular function progressively declines and concomitantly, the ability to eliminate potassium, resulting in susceptibility to hyperkalaemia in the elderly (43). The potassium retention stimulates aldosterone production to maintain normokalemia: this results in an increase of the aldosterone-renin ratio (ARR) with age (23,41). This pattern of increased ARR with aging results in a progressively higher

number of patients with essential hypertension but with a high ARR in older patients (44), in a study from 0% in patients with hypertension aged less than 30 years to 21% in patients of 60 years or older (44). These observations may have an impact on the interpretation of screening and confirmatory/exclusion tests in older patients (41,44,45) (Figure 1).

Another aspect that should be considered is the progressive change of the aldosterone response to sodium intake with aging. To explore this parameter, researchers used the ratio between the serum aldosterone during liberal sodium intake and the serum aldosterone during sodium restriction (SASSI, Sodium-modulated Aldosterone Suppression-to-Stimulation Index) (46): higher values of SASSI indicate abnormal aldosterone regulation. A higher SASSI is associated with a reduced glomerular filtration rate and decreased renal plasma flow and therefore with the decline of kidney function (47) and is also associated with the severity of metabolic syndrome (46). Furthermore, a higher SASSI was associated with a higher Framingham risk score (47). In patients with hypertension a sharp decrease of the aldosterone response to angiotensin II was observed with aging in females but not in males (48). In another study a blunted renal plasma flow response to angiotensin II was observed with aging independent of sex and this response was inversely correlated with SASSI (47).

A subsequent study by Nanba et al., provided a potential pathophysiological link between the adrenal histopathological changes of CYP11B2 expression with aging and the progressive dysregulation of the aldosterone secretion (23). They observed a negative correlation of the area expressing CYP11B2 with increasing age but a positive correlation of APCC area with aging (23). These findings suggest a switch from a prevalent CYP11B2 expression in the whole *zona glomerulosa* to a prevalent CYP11B2 expression in APCC with aging (23) (Figure 1). In the same study the authors investigated the plasma renin activity and aldosterone levels in a group of 677 subjects with normal blood pressure or hypertension stage I (49), under different conditions and correlated these parameters with age. In this large cohort, plasma renin activity progressively declined with age, whereas plasma and urinary aldosterone levels remained unchanged (23).

Therefore, ARR was significantly correlated with age, even after correction for confounding factors, including sodium excretion (23). Finally, SASSI was also positively correlated with age, indicating that the accumulation of APCC with age may cause an increased non-suppressible aldosterone secretion but in turn, the suppression of the normal *zona glomerulosa* is associated with an impaired aldosterone production under physiological stimuli such as sodium restriction (23).

Diagnosis of primary aldosteronism in the elderly

The ES guideline recommends a three-step procedure for the diagnosis of PA (1). This comprises screening, confirmation and subtype diagnosis (1). Subgroups of patients with a high prevalence of PA should be tested using the ARR: groups of patients with hypertension and at high risk for PA comprise patients with blood pressure higher than 150/100 mmHg including resistant hypertension, patients with spontaneous or diuretic induced hypokalemia, or with an adrenal mass (1). However, there are no specific recommendations for elderly patients and if the ARR cut-offs should be modified in this subgroup. It should be noted that hypertension is a highly prevalent condition in the elderly, with a prevalence of 50-70% in Western countries (50). It is expected that more than 30% of these patients would display an increased ARR, thus requiring a very high number of confirmatory/exclusion tests and potentially a high number of AVS if surgery is considered feasible for these patients. Therefore, it could be reasonable to restrict the screening with ARR to patients with a particularly florid phenotype (and therefore with an expected higher benefit from the diagnosis), such as resistant hypertension and or marked hypokalemia, or to consider the ARR just as a potential indication for the therapy and restrict the continuation of the diagnostic work-up only to those with the florid phenotype. Whatever is the choice, some specific features of the diagnosis of PA in elderly patients with hypertension should be acknowledged.

In older patients the ARR increases and thus the number of false positive results for screening can be high. In fact, children display a relatively low ARR cut-off compared with adults (51), and in adults, the ideal cut-off progressively increases (41). For example, the cut-off that has a specificity

of 0.82 in patients aged less than 40, displays a specificity of only 0.42 in patients older than 60 years (41).

Patients with a positive ARR could be empirically treated with a mineralocorticoid receptor antagonist (MRA) or proceed to confirmatory/exclusion testing. If clinicians choose this option, they should take into account the risks of volume expansion under sodium loading in elderly patients in whom renal and cardiac function is more often impaired. In risk patients, the captopril challenge test may be the test of choice. In this case, clinicians should be aware that a recent study challenged the cut-off suggested by the Endocrine Society guideline and suggested that absolute aldosterone levels, rather than the percentage reduction, should be used to confirm/exclude the diagnosis of PA (52).

In patients with a positive confirmatory test, the subsequent subtype diagnosis should be considered case-by-case. Computed tomography (CT) scanning is used also to rule out the rare but potentially fatal aldosterone-producing carcinoma. By contrast, AVS should be considered in carefully selected patients. It should be performed only in patients not at risk of contrast-induced nephropathy that are potentially candidate for surgery, which can be contraindicated in many cases for concomitant illnesses. Furthermore, clinicians should consider that the proportion of patients with unilateral disease in the elderly may be lower than in the young and that age, duration of hypertension and reduced kidney function are correlated with a lower benefit after adrenalectomy as shown by the PASO study (53). Older age was also a negative predictor of clinical success in patients with PA adrenalectomized on the basis of the CT scanning findings alone, without undergoing AVS (54). Therefore, it is unlikely that an elderly patient with PA can achieve complete clinical cure with adrenalectomy. It seems reasonable to restrict AVS only to patients with a florid phenotype, otherwise healthy, with a short duration of hypertension and motivated for surgery or to patients with resistant hypertension in which MRAs are contraindicated or not tolerated. A particular subgroup is that of patients with hypertension and incidentally-discovered adrenal mass, which tend to increase in prevalence in the elderly. In these patients, when ARR is elevated, if adrenal surgery

is considered feasible by the clinician and desired by the patient, the complete diagnostic workup, including AVS, could be considered. In an area in which there is lack of studies investigating specifically the cost/benefit of diagnosis and treatment of PA, it is not possible to define a specific age cut-off to suggest a change in the diagnostic strategy: usually 65 years is the threshold to define elderly patients. However, different approaches should be considered in a 66 y.o. otherwise healthy female with a newly diagnosis of hypertension and hypokalemia and an 83 y.o. male with a long duration of hypertension and several cardiovascular comorbidities. It is reasonable to perform a personalized choice taking into account pro and cons of the different diagnostic steps and the expected benefit.

Therapy of primary aldosteronism in the elderly

Patients with PA that undergo AVS and show lateralisation of aldosterone secretion (lateralisation index ≥ 4) should be adrenalectomized (1). Patients in whom surgery is contra-indicated or not desired by the patient should be treated with MRA (1). In the large Japanese registry of the JPAS study group showed that elderly patients with PA (≥ 65 years) display worse kidney function and a higher rate of cardiovascular complications and diabetes (55). Furthermore, in agreement with the PASO study (53), complete clinical success was less common in elderly patients, despite a similar rate of complete biochemical cure (55). In these patients, the only independent predictor of complete clinical success was a lateralisation index higher than 4, a cut-off that is usually considered ideal to distinguish unilateral from bilateral PA (56). They also observed a higher rate of renal impairment, a more prominent deterioration of glomerular filtration rate and a higher rate of hyperkalemia in the elderly compared with non-elderly patients with PA after adrenalectomy (55). This is consistent with the reported worsening of kidney function after adrenalectomy in patients with PA (6), to which elderly patients may be particularly susceptible.

Patients with PA who are not candidates for surgery or do not display lateralisation at AVS should be treated with MRAs (1); when spironolactone is not tolerated and eplerenone not available,

treatment with amiloride should be considered. With the decline of kidney function in the elderly and with the reduction of plasma volume with MRA therapy (6), special care should be given to monitoring potassium levels, which can rapidly rise for concomitant deterioration of distal renal tubular function with aging and the consequent reduced ability to eliminate potassium (43). Since potassium is not the ideal indicator of MRA therapy efficacy and compliance, MRA-treated patients should periodically measure plasma renin activity or renin concentrations, since the increase of these parameters, indicating that renin is not suppressed anymore by the excess of aldosterone action, was associated with a lower rate of cardiovascular and renal complications in patients with PA during long-term follow-up (57,58).

Conclusions

Over the last years the clinical spectrum and the knowledge of the molecular mechanisms involved in the development of both sporadic and familial PA have substantially evolved. Accumulating evidence indicates that age-related modifications in RAAS pathophysiology might be more relevant than previously thought. In particular, recent studies have focused on the functional implications of APCCs, which carry somatic mutations in aldosterone-driver genes and might play an important role in both the development of bilateral PA and in the relatively autonomous aldosterone secretion in the elderly population. Further studies should be addressed at investigating whether these changes might influence the diagnostic work-up and the clinical management of patients affected by PA.

Figure legend. Simplified overview of RAAS pathophysiology in the elderly population. APCC, aldosterone producing cell clusters; ARR, aldosterone to renin ratio; CYP11B2, aldosterone synthase; PA, primary aldosteronism RAAS, renin-angiotensin-aldosterone system; SASSI, sodium-modulated aldosterone suppression-to-stimulation index; ZG, *zona glomerulosa*

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