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Is Primary Aldosteronism Still Largely Unrecognized?

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ABSTRACT

Primary aldosteronism (PA) was first reported by Jerome W. Conn in 1954 when it was considered a rare disorder, only suspected in cases of hypertension and spontaneous hypokalemia. Over the last 30 years, with the wide application of the plasma aldosterone to plasma renin activity ratio as screening test, the clinical spectrum of PA has dramatically changed. Different studies displayed significant differences in term of patients investigated, diagnostic criteria and hormonal assays; however, large prospective studies with robust diagnostic criteria indicated that the prevalence of PA is around 6% of the general hypertensive population and 11% of the patients referred to hypertension centers. In light of these epidemiological studies, the Endocrine Society Guideline recommends the screening for PA of around 50% of patients with hypertension, and identifies the categories of patients at high risk for the disease. However, clinical data obtained from “real-life” show that the screening rate is much lower and PA remains an under-diagnosed and under-treated cause of secondary hypertension with an associated increased risk of cardio- and cerebrovascular mortality and morbidity.

Introduction

Primary aldosteronism (PA) is an overlooked but frequent cause of secondary hypertension. A timely diagnosis, followed by a targeted treatment are important to reduce the risk of cardio- and cerebrovascular complications associated with aldosterone excess in affected patients [1–3].

In 2008, the Endocrine Society (ES) Guideline defined categories of patients at high risk for PA, that should undergo a screening test [4]. Later, the updated version of the Guideline [5] further expanded these categories, to include around 50% of the patients with arterial hypertension. In a recent survey, 500 general practitioners (250 in Italy and 250 in Germany) were asked to complete a questionnaire on the management of patients with arterial hypertension and the diagnosis of PA. Disappointingly, the results of the study showed that only 7–8% of patients with hypertension

were screened for PA and, as a consequence, the prevalence of the diagnosis of the disease was in view of the participants only 1% in Italy and 2% in Germany [6], far below the figures reported in primary care studies [7, 8]. Similarly, a recent analysis conducted on information available from the Database of the Emilia-Romagna (Northern Italy) Health Service, showed that in the period 2000–2015, only 1.9% of the expected cases of PA were diagnosed and 1% of the expected adrenalectomies were performed [9]. Taken together, these data clearly indicated that, despite significant advances in its clinical management, PA remains a largely unrecognized and undertreated disease. The PASO (primary aldosteronism surgery outcome) study [10] highlighted the importance of the early diagnosis of PA: patients with a complete clinical outcome (cure of hypertension) had a duration of hypertension that was half that of patients with partial or absent clinical success. Furthermore,

the appropriate subtype diagnosis resulted in a relevant success of adrenalectomy for patients with unilateral PA: normalization or a significant reduction in blood pressure was observed in 84% of the patients and the complete biochemical cure of PA in 94% [10]. Finally, it has been shown that diagnosis and treatment of PA is also cost-effective [11].

Historical Perspectives

PA was reported as a new clinical entity for the first time by Jerome W. Conn during his presidential address to the Central Society for Clinical Research in Chicago, Illinois in 1954 [12]. The index case was a 34-year old woman with a 4-year history of hypertension, muscle spasms, temporary paralysis, and weakness associated with severe hypokalemia, mild hypernatremia, and metabolic alkalosis. A bilateral adrenalectomy was planned, but during the surgical intervention a 13 g adrenal tumor was discovered and resected, sparing the contralateral adrenal. The tumor resection reverted the clinical and metabolic alterations and for the first time a relationship between aldosterone excess and the aforementioned features was established. Conn “temporarily” defined the clinical syndrome primary aldosteronism [12, 13].

A few years after its first description, Conn himself predicted the prevalence of PA to be comprised between 10 and 20% among hypertensive patients [14, 15]. However, several authors refused Conn’s hypothesis and, until the ‘90s, PA was considered to be a rare disorder, accounting for less than 1% of all hypertensives [16–19].

Similarly, PA was believed to be a relatively benign condition [20], always associated with spontaneous hypokalemia [21, 22]. The consideration of PA as a benign condition originated from studies by the group of John Laragh who showed that the occurrence of cardiovascular events in patients with essential hypertension was directly correlated with renin levels [23, 24], that is, patients with low renin displayed a low risk for events.

Meanwhile in 1973, Buhler et al. used for the first time the plasma aldosterone to plasma renin activity ratio (ARR) to identify patients with low renin hypertension [25] and, three years later, Dunn and Espiner applied the ARR for PA diagnosis with and without fludrocortisone suppression [26]. However, the new era for PA began in 1981, when Hiramatsu et al. [27] investigated the role of ARR in 348 hypertensive individuals to identify patients with aldosterone producing adenoma (APA), showing a prevalence of 2.6%. In the following years, PA screening was progressively extended to patients with normokalemic resistant hypertension and later on to relatively unselected populations, leading to a 15-fold increase in prevalence [28–30]. Intriguingly, in the cohort of patients with hypertension investigated by Hiramatsu, 67% of those with a final diagnosis of APA displayed normal potassium levels [27] and over the following years the proportion of patients with normokalemic PA progressively increased to 63–91% [30]. The widespread use of ARR progressively changed the relative reported prevalence of the two main PA subtypes, APA and bilateral adrenal hyperplasia (BAH) [30]. In 1998 aldosteronoma was still considered the most common cause of PA and BAH was thought to account for no more than 20–30% of all cases [19]. On the contrary, recent studies indicate

that the prevalence of APA among patients with PA ranges from 28 to 50% in centers that perform adrenal venous sampling (AVS) for subtype diagnosis [8, 30].

Prevalence of Primary Aldosteronism in Primary Care Units

Prevalence of PA in apparently unselected patients with hypertension was investigated for the first time by Gordon et al. [31] in 1993. Several other studies were subsequently conducted, reporting a wide heterogeneity in the prevalence of PA, ranging between 3.2 and 12.7% (► Fig. 1). The majority of these studies were published before the release of the first edition of the Endocrine Society Guideline for the treatment and diagnosis of PA in 2008 [4], which can partially explain the wide variation reported for the prevalence of PA, due to the different criteria used for patient selection and diagnosis.

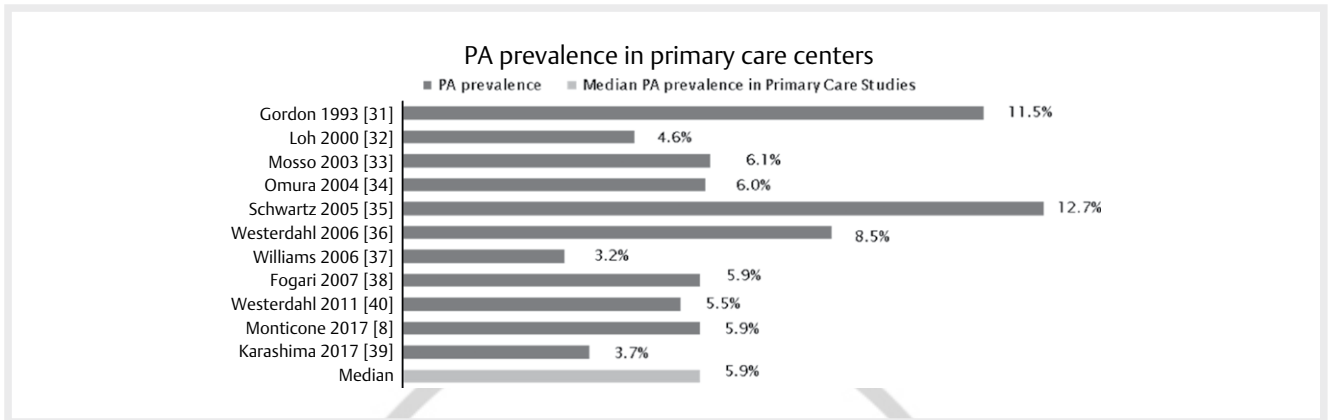
In particular, some studies excluded patients with hypertension and hypokalemia [35–37] or severe hypertension [37] thereby underestimating the prevalence of PA; other studies only investigated newly diagnosed patients with hypertension [34, 40] or included relatively young patients with mild forms of hypertension [8], and one study included patients with normotension [39].

The choice of the screening test varied widely: in some studies, the ARR was used alone, in others the plasma aldosterone concentration was taken into account and in other studies a screening test was not performed, evaluating PA prevalence directly with a confirmatory test [7, 35]. The choice of the confirmatory test also varied: fludrocortisone suppression tests and intravenous saline load tests (SLT) were the most frequently used, while oral SLT and captopril tests were used less frequently [7]. In the PATO (primary aldosteronism in Torino) study, the choice between intravenous SLT and captopril test was made individually for each patient, based on clinical characteristics and comorbidities [8]. Finally, only two studies performed AVS systematically for subtype diagnosis [8, 40].

Excluding studies in which only normokalemic hypertensives were selected [35, 37] or a screening test was not performed [35], the variability in PA prevalence is reduced to 3.7–11.5%. The prevalence range is further reduced to 4.6–8.5%, if studies with a small sample size are not considered [31, 39]. This prevalence is similar to that reported by the recent PATO study (5.9%) that included 1672 patients prospectively recruited from primary care in Torino, Italy [8].

Hypokalemia was detected in 24.6–37.5% of patients with confirmed PA [8, 34, 38], with the exception of the study by Mosso et al., which reported significantly lower figures (2.7%) [33].

Prevalence of PA according to the severity of hypertension was evaluated in two studies reporting a PA prevalence of 2.0–3.9% in stage 1, 8.0–9.7% in stage 2, and 11.8–13.2% in stage 3 [8, 33]. Finally, when AVS was systematically performed, prevalence of APA was 27% and BAH 65–73% [8, 40]. It should be underlined that, even in patients with PA from primary care, the prevalence of target organ damage and cardiovascular events was significantly higher than for patients with essential hypertension [8].



► **Fig. 1** Prevalence of PA in studies including patients with hypertension selected in Primary Care and the median prevalence rate of PA.

Prevalence of Primary Aldosteronism in Referral Centers

In a recent meta-analysis of 30 studies that included 36 614 patients, Käyser et al. [7] reported a wide heterogeneity in PA prevalence among selected patients with hypertension from referral centers, ranging from 0.7 % to 29.8 % (► **Fig. 2**). Many differences in terms of patient selection, study design, screening test and confirmatory testing for PA were identified across studies as expected. A meta-regression analysis identified a higher prevalence of PA in studies published after 2000, in studies with consecutive patient inclusion, when no screening test was performed and when the study objective was to assess the prevalence of secondary hypertension [7].

A retrospective analysis, evaluating PA diagnosis before and after ARR application in 5 referral centers worldwide, demonstrated that hypokalemia affects from 9 % to 37 % of patients with PA and BAH is the most common subtype. In fact, in centers that systematically performed AVS, APA is diagnosed in 28–50 % of patients with confirmed PA [30].

In referral centers PA prevalence also progressively increases with the severity of arterial hypertension, from 6.6 % in stage 1, to 19 % in stage 3 [52]. Patients with resistant hypertension demonstrated the highest prevalence of PA, up to 20 % in some centers [66]. Hypokalemia is more frequent in this subgroup of patients, ranging from 45.6 % to 72 % [66], in agreement with a more severe phenotype.

Calhoun et al. evaluated PA prevalence among African American and Caucasian patients with resistant hypertension in North America, and confirmed that plasma renin activity (PRA) and aldosterone are lower in African Americans; however, this finding does not reflect significant differences in PA prevalence [66]. A high prevalence of PA among patients with resistant hypertension was also found in Chinese (7.1 %) [62], European (11.3–15.2 %) [53, 63], and South American (5.9 %) populations [58]. Differences in reported prevalence among these populations could be due to ethnic variability or to differences in patient selection and diagnostic workup.

Prevalence of Primary Aldosteronism in Special Population

Obstructive sleep apnoea

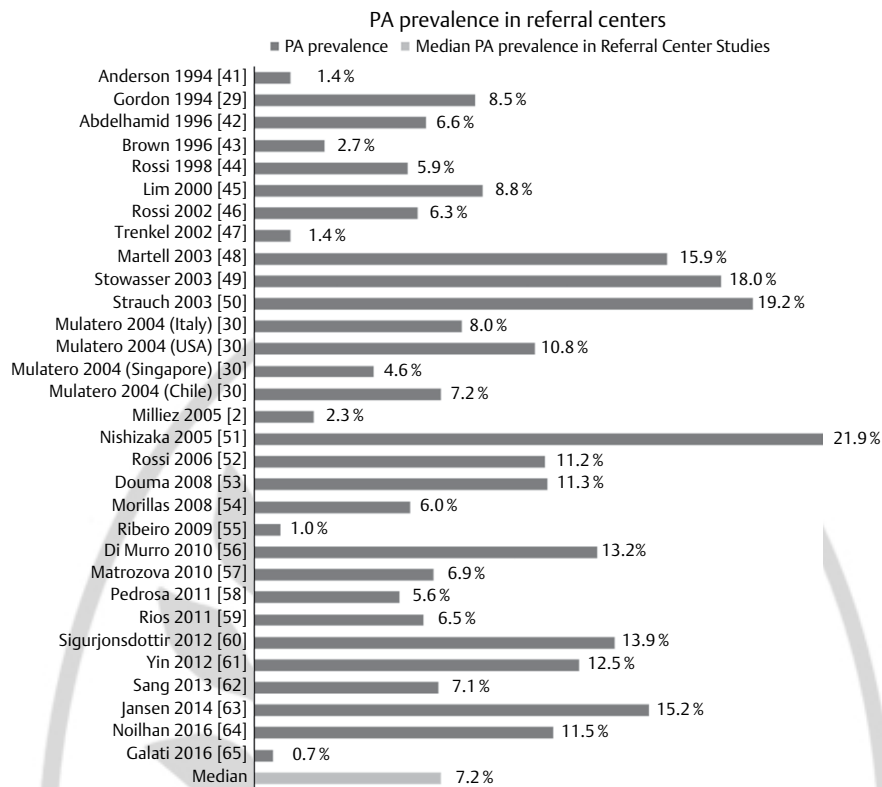
Other than the traditional categories at high risk for the disease, the 2016 ES Guideline recommends the screening of patients with hypertension with obstructive sleep apnoea (OSA) for PA [5].

Patients with OSA display high levels of serum aldosterone [67] and there is a correlation between aldosterone levels and worsening of apnoea-hypopnea index (AHI) [68, 69]. Aldosterone excess may play a pivotal role in the pathophysiology of OSA and, on the other hand, OSA seems to increase aldosterone levels by activation of the renin-angiotensin-aldosterone system; this excess appears to be partially reversible with continuous positive airway pressure in patients with high aldosterone level at baseline [69]. PA and OSA also share obesity as a common underlying condition: obesity is common in OSA patients and increased adipokines such as leptin, which have been shown to increase aldosterone secretion [70], could be responsible for the augmented aldosterone production independent from the renin-angiotensin system activation.

Sim et al. demonstrated a higher prevalence of OSA in hypertensive patients with an elevated ARR compared to patients with a low ARR [71]. However, only one study has directly compared the prevalence of PA in patients with hypertension with and without OSA [56]. The study was performed in a tertiary referral center and a PA prevalence of 34 % was observed in patients with arterial hypertension with OSA (18 of 53 patients), compared with a prevalence of 10 % among patients with hypertension without sleep disorders. All patients with PA underwent computed tomography (CT) imaging and AVS for subtype testing; 28 % of them displayed a unilateral form and 72 % a bilateral form [56].

Diabetes

The association between PA and impaired carbohydrate tolerance was first described by Conn in 1965 [72]. Subsequently it was shown that patients with PA present a higher rate of metabolic syndrome [8, 73, 74], higher levels of plasma fasting glucose, and a



► **Fig. 2** Prevalence of PA in studies including patients with hypertension selected in Referral Centers and the median prevalence rate of PA.

higher probability of developing type 2 diabetes compared with patients with essential hypertension [1, 74]. This is consistent with the experimental findings showing that aldosterone affects glucose metabolism and promotes insulin resistance [75, 76].

Over the last 10 years many studies investigated the prevalence of PA in patients with type 2 diabetes. Two studies, performed in different ethnic populations, showed similar prevalence data: 14% in a population composed predominantly of patients of African-American descent and 13% among patients with hypertension from Asia [77, 78]. Hypokalemia was present in 46% of the patients and, when AVS was performed systematically, a unilateral form of PA was demonstrated in 61.5% of cases [78].

Murase et al. [79] demonstrated a PA prevalence of 11.3% in a diabetic population of 124 hospitalized patients. Of note, PA patients displayed a shorter history of diabetes, compared to patients with essential hypertension, and most of them were diagnosed with hypertension before than with diabetes [79]. This sequence of events strengthens the hypothesis of a causal role for PA in the development of diabetes.

In contrast with previous studies, Tancredi et al. [80] recently reported a low prevalence of PA among patients with type 2 diabetes (0.93%). However, the study included both patients who were normotensive and those who were hypertensive (the mean systolic and diastolic arterial pressure were 137 mmHg and 77 mmHg respectively); patients treated with MRA or potassium-sparing diuretics (4.7% of the total cohort) were excluded and many patients

with a positive screening test for PA did not undergo further evaluation because of severe comorbidities or old age without clinical signs of PA [80]. These limitations probably affected the final results and underestimated the real prevalence of PA.

Atrial fibrillation

Patients with PA display a risk of atrial flutter or fibrillation 7–12-fold higher than patients with EH [2, 81], and generally display an increased risk of sustained arrhythmias (including sustained ventricular tachycardia and ventricular fibrillation) [1].

Compelling evidence suggests that aldosterone exerts a crucial role in the pathophysiology of atrial fibrillation (AF), promoting cardiac hypertrophy, fibrosis, and inflammation with consequent diastolic dysfunction and left atrium dilatation. These cardiac alterations have been clearly associated with the development of AF in the Framingham Heart Study [82] and several other studies over the following years [83]. In an animal model, aldosterone plays a pro-arrhythmogenic role at the atrial level by altering the cardiac electric properties [84].

Despite evidence of a strict link between AF and PA, no prospective studies, evaluating prevalence of PA in patients affected by AF are currently available. Nevertheless, the demonstration of a high prevalence of PA in patients with AF it is important to address these patients to a systematic screening for PA. The ongoing PAPPHY (prospective appraisal of the prevalence of primary aldosteronism in hypertensive patients presenting with atrial flutter or fibrillation)

study, evaluating PA prevalence in patients with AF diagnosis, will provide further information about this issue [85].

Patients with Arterial Hypertension and Adrenal Incidentaloma

Adrenal incidentalomas are present in 0.5–2.0% of patients undergoing an abdominal CT scan with a prevalence that progressively increases with age up to 7% by 70 years. Conversely, the prevalence of incidentalomas is very low in children, adolescents, and young adults (less than 1%) [86]. In clinical studies, the major part of adrenal incidentalomas are non-functioning adrenal adenomas (almost 75%), 12% are cortisol-secreting adenomas, 7% pheochromocytomas, 8% adrenal carcinomas (almost all with a diameter ≥ 4 cm), 5% metastasis, and only 2.5% are aldosterone producing adenomas (APA) [87]. The Endocrine Society guideline recommends that PA should be considered in all patients with an incidentally discovered adrenal mass and arterial hypertension [4, 5].

Conclusions

Although over the last 20 years many efforts were made to identify the actual prevalence of PA among the general population with hypertension or among patients referred to hypertension units, knowledge is still lacking on the prevalence of PA in selected populations. It is therefore desirable that future studies are addressed to specific populations to further expand the categories of patients with hypertension at high risk of PA to thus reduce the possibility of missing or delaying a diagnosis.

In conclusion, the lessons from the recent PATO and PASO studies, together with increasing evidence from the preceding decade of clinical studies, clearly indicate that most if not all patients with hypertension should be screened for PA and should be screened early, before the occurrence of the detrimental effects of aldosterone on kidney, heart, and vessels.

Conflict of Interest

The authors declare that they have no conflict of interest.

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