

## Increasing Incidence of Primary Aldosteronism in Patients Investigated for Resistant Hypertension: An Observational Study from a Nephrology Unit

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### Abstract

**Introduction:** Primary Aldosteronism (PA) is a secondary form of hypertension characterized by an autonomous and inappropriately high production of aldosterone. Its prevalence is 5-12% and the two main subtypes are the Bilateral Adrenal Hyperplasia (BAH) and the Aldosterone-Producing Adenoma (APA). In this study, we report the results of an evaluation of some patients diagnosed with PA in a Nephrology Unit between 1987-2011.

**Patients and methods:** As much as 54 patients were screened for PA by measuring Plasma Aldosterone Concentration (PAC) and Plasma Renin Activity (PRA), and by calculating the aldosterone/renin ratio (ARR). Confirmation tests were performed on 47 patients with PAC  $\geq 15$  ng/dL and ARR  $\geq 40$ . Subtype diagnosing was possible through adrenal CT scan, scintigraphy and adrenal venous sampling.

**Results:** As much as 31 patients were diagnosed with PA. In 17 of them, the concordance of CT, scintigraphy and AVS findings made it possible to determine the subtype diagnosis: BAH in 10 and APA in 7 patients.

**Conclusions:** Our results confirm the increasing frequency of diagnosis of PA among patients investigated for resistant hypertension. Early detection of PA in nephrological settings is important because of the relationship between aldosterone and kidney function.

### Introduction

Primary Aldosteronism (PA) is a condition characterized by an inappropriately high production of aldosterone, which is relatively autonomous from the renin-angiotensin system, and nonsuppressible by sodium loading [1].

First described by Conn in 1955 [2], PA usually, but not invariably, presents the triad of hypertension, hypokalemia and metabolic alkalosis.

The two main forms, or subtypes, of PA are the Bilateral Adrenal Hyperplasia (BAH), or Idiopathic Hyper Aldosteronism (IHA), with a relative frequency of 65%, and the aldosterone-producing adenoma (APA), with a relative frequency of 30%.

Less common forms are the Unilateral Adrenal Hyperplasia (UAH), that is the micro- or macronodular hyperplasia of the zona glomerulosa of the adrenal cortex, mainly involving one of the adrenal glands (3%); and the bilateral adrenal hyperplasia, micro- or macronodular (1%) [3,4]. Even if sporadic, PA may be familial and manifests in at least two forms [5,6]: the Familial Hyperaldosteronism type I (FH-I), or Glucocorticoid-Remediable Aldosteronism (GRA), very rare (< 1%), which has an autosomal dominant mode of transmission and is caused by an adrenocorticotrophic hormone-regulated, hybrid *CYP11B1/CYP11B2* gene [7,8]; and the familial hyperaldosteronism type II (FH-II), which is the familial form of APA or BAH or both. FH-II relative frequency is unknown, but it is considered to be at least 5 times higher than that of FH-I. This form is clinically indistinguishable from apparently non-familial forms of PA, is not glucocorticoid-remediable and is thought to have a variable mode of transmission: autosomal dominant in some families and possibly recessive in others. Regarding FH-II, linkage studies have implicated a locus at chromosome 7p22

in some of the families studied, thus allowing a probable genetic heterogeneity [9,10].

Finally, among the rare forms of PA, there are the pure aldosterone-producing adrenocortical carcinomas (1%) and the ectopic aldosterone-producing tumors, such as some tumors of kidney and ovary (< 1%) [11]. Although the prevalence of PA is still debated and has not been accurately defined yet, it seems to be higher than suggested in the past. Conn himself, who was the first to describe this condition [2], later hypothesized that 20% of the hypertensive subjects could be suffering from PA [12].

However, this hypothesis was not confirmed in the following years because of the lack of reliable methods of assay for plasma renin activity and plasma aldosterone [13].

Therefore, for a long time PA was thought to be a rare and relatively benign form of hypertension, with an estimated prevalence of approximately 1% among non selected hypertensives. On the other hand, among the patients suffering from resistant hypertension, the

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Received March 29, 2012; Accepted April 16, 2012; Published April 18, 2012

**Citation:** Del Giudice A, Di Giorgio C, Di Giorgio G, Grifa R, Lauriola V, et al. (2012) Increasing Incidence of Primary Aldosteronism in Patients Investigated for Resistant Hypertension: An Observational Study from a Nephrology Unit. J Nephrol Therapeutic S3:007. doi:10.4172/2161-0959.S3-007

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prevalence has been estimated 3% to 13%, with some studies reporting figures even up to 20%. As a consequence, an “epidemic” of PA was hypothesized [14,15].

In a prospective multicentre study carried out in 2006, Rossi et al. [16] reported a 11.2% prevalence of PA in 1,125 newly diagnosed hypertensive patients referred to hypertension centers.

On the other hand, in a retrospective observational study conducted in 2008, Douma et al. [17] reported a prevalence of PA of 11.3% among 1,616 patients with resistant hypertension who had been evaluated over 20 years. Although the prevalence was so high, it was substantially lower than previously reported. On the basis of this finding, the authors assumed that the prevalence of primary hyperaldosteronism in the general unselected hypertensive population was much lower than that reported until then [17]. Hence, prevalence of PA could currently be estimated at 5-12%, suggesting that PA may be the most common endocrine form of hypertension [18].

Moreover, there is an emerging evidence of association between PA and renal injury [19-23] as well as with cardiovascular events [24,25] and metabolic syndrome [26].

The aim of this study is to report the results of an observational evaluation of patients who were investigated for resistant hypertension in our Nephrology Unit between 1987 and 2011 and were diagnosed with PA.

## Patients and Methods

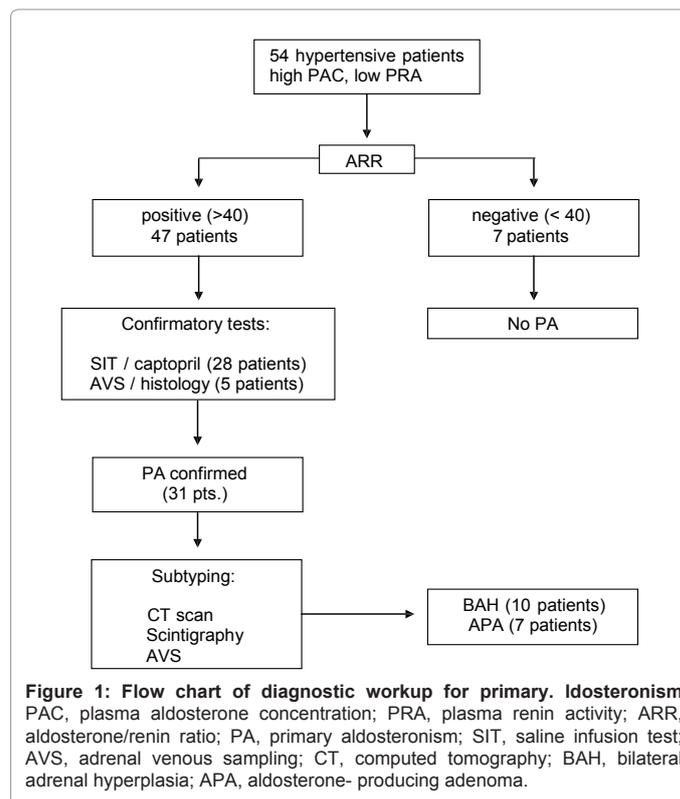
All 54 patients, 35 females and 19 males of a mean age of 47.7 ± 9.3 (range: 30-73), were selected from hospital records and history case forms. All of them had either suspended antihypertensive therapy or were receiving  $\alpha$ -blockers treatment. All of the patients had been screened for PA by measuring serum potassium, Plasma Aldosterone Concentration (PAC) and Plasma Renin Activity (PRA), both after night's sleep in bed and after 3 hours of standing and walking. The PAC/PRA ratio (Aldosterone/Renin Ratio, ARR) was calculated in all cases. For this calculation, lower values of PRA were arbitrarily set to 0.2 ng/mL/h, due to the poor accuracy of assays of PRA at its lower values and the influence of PRA, as denominator, on the ARR [1,16]. In 2003, we introduced confirmation/suppression tests in the diagnostic procedure: the suppression test, which was performed on 34 patients, with infusion of the isotonic saline solution in 4 hours (Saline Infusion Test, SIT) and re-evaluation of PAC; and the captopril administration test, with 50 mg per os, performed on 3 patients, with re-evaluation of ARR after 2 hours. CT of adrenal glands was performed on 43 patients, adrenal scintigraphy with <sup>131</sup>I- cholesterol was performed on 21 patients and adrenal venous sampling (AVS) on 8 patients. Finally, genetic testing for the familial hyperaldosteronism type I (GRA) was performed on 2 patients. For the diagnosis of PA, we adopted the following cut-off values: PAC  $\geq$  15 ng/dL, ARR  $\geq$  40 ng/dL of PAC per ng/mL/h of PRA [27,28]; for confirmation, values of PAC  $\geq$  6 ng/dL after SIT or of ARR  $\geq$  40 after captopril. CT, scintigraphy and AVS - when performed - made the subtype diagnosis possible [1,28]. The statistical comparison between demographic and biochemical characteristics in patients with BAH and APA was made by means of the Mann-Whitney test U for continuous variables and with the Fisher exact test for categorical variables.

## Results

In all of the 54 patients evaluated, PAC was found to be  $>$  15 ng/dL and PRA  $<$  1 ng/mL/h. During re-examination of cases, using the cut-

off values indicated above, ARR was found to be  $<$  40 ng/dL of PAC per ng/mL/h of PRA in 7 patients; the diagnosis of PA was consequently excluded in these patients. In 47 patients, ARR was found to be  $\geq$  40 ng/dL of PAC per ng/mL/h of PRA. The diagnosis of PA was confirmed in 31 of them: in 25 patients, PAC was  $\geq$  6 ng/dL after SIT; in 1 patient, ARR was  $\geq$  40 ng/dL of PAC per ng/mL/h of PRA after captopril; in another patient, who was found with a negative SIT, PA was confirmed by AVS; in 4 patients, who did not undergo confirmation/suppression tests, PA was confirmed subsequently by the histologic examination of the adenoma removed with surgery. In the remaining 16 patients with PAC  $>$  15 ng/dL, PRA  $<$  1 ng/mL/h and ARR  $\geq$  40 ng/dL of PAC per ng/mL/h of PRA, diagnosis of PA was not confirmed: in 12 of them the tests had not been performed; in 2 of them, PAC after SIT was found to be  $<$  6 ng/dL; in other 2, ARR after captopril was  $<$  40 ng/dL of PAC per ng/mL/h of PRA. Genetic testing for the familial form of GRA was performed on 2 patients; in both cases it was negative. The concordance of CT scans, scintigraphy and AVS findings made it possible to determine the diagnosis of the subtype in 17 cases: Bilateral Adrenal Hyperplasia (BAH) in 10 patients and Aldosterone-Producing Adenoma (APA) in 7 patients (Figure 1, Table 1 and Table 2).

In particular, through AVS, which was performed in 8 patients, it was possible to confirm the diagnosis of aldosterone-producing adenoma (APA) in 1 patient, and to make a diagnosis of bilateral adrenal hyperplasia (BAH) in 3 patients; in 4 cases, AVS was not possible because the right adrenal vein was difficult to catheterize. However, in one of these four last cases, clinical data (less than 40 years of age and resistant hypertension), laboratory data (serum potassium  $<$  3.0 mEq/L, PAC  $>$  25 ng/L) and instrumental data (CT showed the presence of a lump of  $>$  10mm in one of the adrenal glands) were considered “suspicious” criteria, meaning criteria with a high probability of APA [4,28].



**Figure 1: Flow chart of diagnostic workup for primary aldosteronism** PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone/renin ratio; PA, primary aldosteronism; SIT, saline infusion test; AVS, adrenal venous sampling; CT, computed tomography; BAH, bilateral adrenal hyperplasia; APA, aldosterone-producing adenoma.

Variable	Category	PA patients (n=31)
Age (years)	--	49.77 ± 9.85 (range 31 - 73)
Sex (M/F)	M	10 (32.26%)
	F	21 (67.74%)
Serum potassium (mEq/L)	--	3.71 ± 0.74
PAC recumbent (ng/dL)	--	27.30 ± 17.45
PAC upright (ng/dL)	--	45.29 ± 26.07
PRA recumbent (ng/mL/h)	--	0.27 ± 0.17
PRA upright (ng/mL/h)	--	0.41 ± 0.38
ARR recumbent (ng/dL)	--	118.75 ± 91.17
ARR upright (ng/dL)	--	164.86 ± 125.13
PAC after saline (ng/dL)	--	12.91 ± 7.25

**Table 1: Demographic and biochemical characteristics of patients with primary aldosteronism.** Data were reported as means ± SD or frequencies and percentages for continuous and categorical variables, respectively. PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone/renin ratio.

On the whole, the diagnosis of PA was made for 31 patients. For 5 patients the diagnosis was made over 15 years between 1987 and 2002, with an incidence of 0.33 cases per year; and for 26 patients, it was made over 9 years between 2003 and 2011, with an incidence of 2.88 cases/year.

## Discussion

For a long time PA has been thought to be a relatively benign and rare form of hypertension that could only be detected in the presence of hypokalemia. Although the prevalence of PA is still debated and has not been accurately defined yet, it is currently considered to be higher than suggested in the past, and it is estimated about 5-12% of hypertensive patients [16,17,27]. Recent changes in the perceived epidemiology of PA appear related to an increased investigation and detection in normokalemic patients too [29]. Some authors hypothesize

that such a prevalence could be even higher (up to 15-20%) in selected groups of patients, such as those suffering from resistant hypertension, type 2 diabetes mellitus and sleep apnea syndrome [29].

The use of ARR as screening test for PA, also in primary care settings [30], and of suppression tests, which were meant to confirm or to exclude nonsuppressable high plasma aldosterone levels, could explain the higher prevalence rate of PA recently reported. In our study, the use of ARR as screening test for PA and of confirmation tests made it possible to make the conclusive diagnosis with an increasing frequency during the recent years. However, today the usefulness of ARR is still debated because there are some doubts on its reliability, in terms of reproducibility, sensitivity and specificity. Moreover, several factors could influence ARR, like the posture, the time of the day of blood sampling and the possible use of antihypertensive drugs [1,31-33]. Also, there is a lack of consensus on the types of patients' populations in which the ARR should be used as screening test for PA and on clear cut-off values to adopt. For example, Montori and Young, in a systematic review of 16 studies (for a total of 3,136 patients), reported that the thresholds for the ARR used varied between 7.2 and 100.0 ng/dL per ng/mL per hour [34,35].

In the screening for PA, we tried to comply with the criteria adopted by other authors [27,28] and to follow the suggestions of the guidelines of the Endocrine Society [1]. In fact, for ARR, we decided to use cut-off levels of ≥ 40 ng/dL of PA per ng/mL/h of PRA, in addition to PAC ≥ 15 ng/mL [4]. Independently from the underlying pathologic condition, the overproduction of aldosterone in PA causes sodium and water retention, hypertension, cardiovascular damage, suppression of plasma renin, and potassium excretion that, if prolonged, can lead to hypokalemia [1]. However, contrary to what was initially believed, both spontaneous and diuretic-induced hypokalemia (i.e. serum potassium < 3.5 mEq/L) are now considered not necessary for diagnostic screening for PA. This was noted by Conn in 1965 [36] and also confirmed by later studies in which most of the patients diagnosed with PA resulted to be normokalemic, while hypokalemia in different cases and geographical areas has been detected in less than half of cases and in variable percentages: from 9-37%, as reported by Mulatero et al. in a

Variable	Category	BAH	APA	p-value
n		10	7	--
Age (years)		52.00 ± 8.43 (range 42-70)	49.14 ± 8.97 (range 31-61)	0,961
Sex (M/F)	M	4 (40.0%)	1 (14.29%)	0,338
	F	6 (60.0%)	6 (85.71%)	
Serum potassium (mEq/L)		3.91 ± 0.34	2.62 ± 0.38	0,004
PAC recumbent (ng/dL)		20.26 ± 7.97	49.23 ± 24.68	0,009
PAC upright (ng/dL)		32.79 ± 9.18	63.60 ± 41.25	0,072
PRA recumbent (ng/mL/h)		0.28 ± 0.12	0.31 ± 0.27	0,562
PRA upright (ng/mL/h)		0.48 ± 0.29	0.22 ± 0.03	0,057
ARR recumbent (ng/dL)		84.07 ± 38.18	217.25 ± 147.06	0,034
ARR upright (ng/dL)		88.51 ± 44.41	283.50 ± 137.58	0,015
PAC after saline (ng/dL)		10.75 ± 4.63	23.12 ± 9.09	0,113

**Table 2: Comparison between BAH and APA subtypes.** Data were reported as means ± SD or frequencies and percentages for continuous and categorical variables, respectively.

Two sided p-values for continuous variables refer to Mann-Whitney test U.

Two sided p-values for categorical variables refer to Fisher exact test.

study conducted in centers from 5 continents [27], to 18%, in Japanese reports [37,38], to 9.6%, in the Italian prospective study of prevalence (the PAPY study) [16], to 45.5%, in the Greek retrospective study of Douma et al. [17]. This suggests that the presence of hypokalemia has low sensitivity and specificity, and has a low predictive value for the diagnosis of PA [1]. As a consequence, excluding normokalemic hypertensives from screening can imply the risk of underestimation of the true incidence of PA [9]. However, it must be said that in the PAPY study spontaneous hypokalemia was observed in 48% of the patients with APA and in only 16.9% of those with IHA [16]. In our study, we observed hypokalemia in 23.4% of all the patients diagnosed with and affected by PA and, moreover, in 1 of 10 patients with BAH and in the 7 patients with APA (data not shown).

In this regard, the two main subtypes of PA, i.e. APA and HIA (or BAH), can be diagnosed on the basis of four modified “corners score criteria” [16,39]. More exactly, APA can be established when all of the following criteria are met: 1) evidence of autonomous excess aldosterone production based on an ARR > 30; 2) lateralization of aldosterone secretion at AVS or during dexamethasone suppression adrenocortical scintigraphy; 3) evidence of a nodule on CT scan; and 4) postsaline loading (PAC > 10 ng/dl) and/or a pathologically proved adenoma after adrenalectomy and cure of hypertension without antihypertensive agents or improved hypertension, potassium, PAC, and PRA. On the other hand, IHA (or BAH) can be diagnosed with the following criteria:

- 1) Evidence of autonomous excess aldosterone production based on ARR > 30;
- 2) non-lateralization of aldosterone secretion at AVS or dexamethasone suppression adrenocortical scintigraphy; 3) evidence of bilateral diffuse enlargement on CT scan, and/or 4) postsaline loading (PAC > 10 ng/dl) and/or evidence of diffuse hyperplasia of cells on pathologic findings [39].

Apart from the suppression test with infusion of the saline solution (SIT), tests with captopril and losartan are also considered useful to discriminate between APA and IHA. To this purpose, Rossi et al. suggested that cut-off values for PAC of 6.75 ng/dL after saline and of 13.9 ng/dL after captopril may be optimal aldosterone cut-off values for discriminating between APA and IHA [40].

Other authors suggest that a post-losartan ARR > 60 with a PAC > 10 ng/dL could be more accurate than the captopril test for the diagnosis of PA and for adequately differentiating APA from IHA [39].

Partially diverting from the criteria and the suggestions mentioned above and trying to comply with the criteria indicated by other authors [4,28], we decided to adopt different cut-off values for the confirmation of PA, in particular PA values  $\geq 6$  ng/dL after SIT or of ARR  $\geq 40$  after captopril.

To a larger extent, we decided to use the approach of a “composite reference standard”, in other words to adopt combined criteria (clinical, laboratory and imaging) in the diagnostic work-up of primary aldosteronism [41].

## Conclusion

Results of our observation of a small population of patients investigated for resistant hypertension confirm the increasing frequency of diagnosis of PA, a secondary and potentially correctable form of hypertension.

Furthermore, early detection and treatment of PA in nephrological settings are very important because of the relationship between aldosterone and kidney function. In fact, recent clinical and experimental evidence induces to consider that the excess of aldosterone not only through the production of blood hypertension, but also by itself alone can lead, in the long term, to a higher rate of cardiovascular events and to structural renal damage disproportionate to blood pressure levels [25]. In particular, it is well known that at renal level the prolonged exposition to vasculotoxic effects of aldosterone excess may cause a relative glomerular hyperfiltration, which not only should be considered as an adaptive response to hypertension, but also as a part of a process that, starting from the production of structural abnormalities (of glomerular podocytes, intrarenal vasculature and interstitium) can lead to progressive kidney injury, with proteinuria and declining glomerular filtration rate [22].

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