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Our experience in primary hyperaldosteronism

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SUMMARY

Abstract: *The aim of this paper is to analyze the ways of appearance, clinical characteristics, diagnosis and treatment related to patients suffering from primary hyperaldosteronism (HA1º) in external nephrology consultation since their opening.* ***Methodology:*** *A retrospective study was carried out, checking out all HA1º diagnosed patients of clinical records from 1981-2005.* ***Results:*** *35 patients were diagnosed, with an average age of 50 and a predominance of men (82%). The main reason for starting the HA1º study was persistent hypertension; other reasons were hypertension and hypopotassemia (34%). Sixteen of the cases were adenomas (7 classic adenomas and 9 renin-dependents) and fourteen of them were hyperplasia (10 bilateral hyperplasias and 4 primary adrenals hyperplasia). Five cases were excluded because they were waiting for complementary tests. For location diagnosis, gammagrafía I-131cholesterol was the test showing more agreement with final diagnosis, and then RMN and TAC. In eight of the cases, an adrenal vein sampling was made. Ten of sixteen adenomas suffered a surgery performance. The result showed standardization of tensional levels, without any treatment in 60% of the cases. The rest of them are currently treated with spironolactone under an appropriate tensional control. Gynecomastia was the most usual adverse effect found.* ***Conclusion:*** *Contrary to other published papers, we found out a male predominance in our database. A similar incidence of adenomas e hyperplasias was obtained. The most usual way of appearance was persistent hypertension to treatment. Adenomas surgery does not imply healing results, though it achieves a better tensional levels control, using less drugs and diminishing aldosterone levels. It implies a descent in myocardic and vascular toxicity.*

Key words: ***Primary hyperaldosteronism. Secondary hypertension. Aldosterone.***

NUESTRA EXPERIENCIA EN EL HIPERALDOSTERONISMO PRIMARIO

RESUMEN

Objetivo: *Analizar las formas de presentación, características clínicas, diagnóstico y tratamiento de los pacientes diagnosticados de hiperaldosteronismo primario (HA1º) en la consulta externa de nefrología desde su apertura.* ***Método:*** *Se realizó un estudio retrospectivo revisando todas las historias clínicas de pacientes diagnosticados de HA1º desde 1981-2005.* ***Resultados:*** *Se diagnosticaron un total de 35 pacientes con una edad media de 50 años con predominio de varones (82%). El motivo principal de inicio de estudio de HA1º fue la hipertensión arterial (HTA) rebelde, seguido de hipertensión más hipopotasemia(34%). Dieciséis casos eran adenomas (7 adenomas clásicos y*

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9 renino-dependientes) y 14 hiperplasias (10 hiperplasias bilaterales y 4 hiperplasias adrenales primarias). Cinco casos fueron excluidos del estudio por encontrarse en el momento de realización del estudio pendientes de pruebas complementarias. Para diagnóstico de localización la prueba que mostró más concordancia con el diagnóstico final fue la gammgrafía I-131colesterol seguida de la RMN y la TAC. En 8 casos se realizó muestreo venoso suprarrenal. Fueron intervenidos 10 de los 16 adenomas con resultado de normalización de cifras tensionales sin tratamiento en el 60% de ellos. El resto de los casos se encuentran en tratamiento con espironolactona con adecuado control tensional. El efecto adverso más frecuente fue la ginecomastia. ***Conclusión:*** *En contra de lo publicado en la literatura, en nuestra serie observamos un claro predominio de varones. Obtuvimos una similar incidencia de adenomas e hiperplasias. La forma de presentación más frecuente fue la hipertensión arterial rebelde al tratamiento. La opción quirúrgica de los adenomas no significa un resultado curativo, pero sí un mejor control de las cifras tensionales con menos fármacos y una disminución de los niveles de aldosterona con el consiguiente descenso de la toxicidad miocárdica y vascular.*

Palabras clave: ***Hiperaldosteronismo primario. Hipertensión arterial secundaria. Aldosterona.***

INTRODUCTION

Primary hyperaldosteronism (PHA) is a clinical syndrome produced by increased secretion of aldosterone by the glomerular layer of the suprarenal cortex. Seven subtypes are recognized: classical adenoma, renin-dependent adenoma, bilateral suprarenal hyperplasia, primary adrenal hyperplasia, suprarenal carcinoma, and familial hyperaldosteronism types I and II.[1]

It was first described by in 1950 by Jerome Conn *et al.*,[2] reporting an aldosterone-producing adenoma (classical adenoma). By the end of the 1960s, Davis *et al*.[3] described another form of presentation of PHA associated with hyperplasia of both adrenal glands, and in the 1990s Irony *et al*.[4] described two subtypes, renin-dependent suprarenal adenoma and primary adrenal hyperplasia.

The prevalence of this condition as a secondary cause of arterial hypertension has experienced a marked increase in recent years, from < 1% among patients with arterial hypertension up to 10% in recent studies and 16-32% in refractory AHT.[5, 6, 7, 8] This difference is explained by the different screening methods used and the population selected. In classical studies, hypokalemia was used and currently a more sensitive screening method is used leading to detection of milder forms of PHA: the aldosterone/plasma renin activity ratio (A/R ratio).[5, 7, 9] For this reason and due to the continuous increase of this condition, we decided to broaden our study, already performed in 2001, on the prevalence at our Nephrology Unit.[10]

Aldosterone increase is implicated in vascular, cardiac, and renal toxicity,[11] independently of blood pressure values.[12, 13] It is thus important to early diagnose and establish whether aldosterone secretion is uni- or bilateral to implement a specific therapy: surgery or medical management with diuretics inhibiting aldosterone secretion (spironolactone) or aldosterone receptor antagonists (eplerenone).

The classical presentation of PHA is as moderate-severe AHT WITH hypokalemia, increased urinary potassium excretion, and metabolic alkalosis, although more and more cases with normal serum potassium levels are being diagnosed, likely due to higher sensitivity of diagnostic tests. For localization diagnosis there exist several tools: iodine-cholesterol scintigraphy, axial computerized tomography, (CT scan), and magnetic resonance imaging (MRI). Currently, suprarenal veins sampling (SVS) is gaining relevance because of high sensitivity and specificity.[14, 15]

In this descriptive retrospective study, we have analyzed the clinical and biochemical characteristics, the localization diagnosis, and the response to medical or surgical treatment of patients diagnosed with PHA at the Nephrology Unit of the Hospital of San Pedro de Alcántara (Cáceres), from 1981 to 2005.

PATIENTS AND METHODS

For the purpose of this study, we reviewed the clinical charts of the patients diagnosed with PHA at the monographic clinic of AHT of the Nephrology Unit of our hospital, from 1981 to December of 2005.

The diagnosis of PHA was suspected before: a) a hypertensive patient with sustained hypokalemia not

Table I. Diagnostic algorithm for the most common subtypes of PHA

	Postural test	Scintigraphy I-cholesterol	MRI or CT scan	SVS
Classical adenoma	↑< 30% or ↓	Unilateral	Unilateral or normal	Positive*
Renin-dependent adenoma	↑↑	Unilateral	Unilateral or normal	Positive*
Bilateral hyperplasia	↑↑	Bilateral	Bilateral or normal	Negative
Primary adrenal hyperplasia	↑< 30% or ↓	Uni/bilateral	Uni/bilat/normal	Uni/normal: SVS* positive* Bilat: negative

* Indication for surgery.

justified by the use of diuretics; b) Severe and/or refractory AHT; c) good response to spironolactone in a poorly controlled hypertensive patient with 2-3 drugs;[16] d) young hypertensive patient, not obese, not black, without family history of AHT; and e) adrenal incidentaloma in a hypertensive patient.

In these patients with suspected PHA we carried out initial screening tests by measuring baseline aldosterone and renin (12-hour rest) and after stimulation (2-hour walking). Before these analyses were carried out, the patients were on free diet without salt restriction in order to assure urinary sodium excretion > 150-200 mEq/24 hours. Besides, 2 weeks before hormone determination antihypertensive drugs capable of interfering with renin-angiotensin system were withdrawn: diuretics, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists (ARA-II), and beta-blockers, incorporating therapy with alpha-blockers, calcium-channel blockers or a combination of both.

PHA was diagnosed in those patients presenting baseline aldosterone levels > 16 ng/dL, low/suppressed renin but no lower than 0.3 ng/mL/min (in that case, aldosterone level ought to be > 20 ng/dL), and A/R ratio > 30 (probable diagnosis) or > 50 (high diagnostic value for PHA).

We carried out the tilt test, valued by the increase in aldosterone level after two-hour walking, which allowed dividing adenomas into classical adenomas when the increase percentage of aldosterone after stimulation was < 30%, and renin-dependent adenomas when that increase was greater than 30%. Besides, hyperplasias were categorized as bilateral idiopathic hyperplasia when the aldosterone increase after stimulation was > 30% and primary adrenal hyperplasia when that increase was < 30%.

For lesion localization we used: a) The morphofunctional test: scintigraphy with ^{131}I-6E-iodomethyl-19-norcholesterol (^{131}iodocholesterol) after adrenal suppression protocol with dexamethasone during the week before and thyroid uptake block with 5% lugol; b) Imaging tests: CT scan done with 5-mm collimation and 5-mm cross-section; MRI done with turbo, DP, SPIR, and FLAIR sequences, T1- and T2-enhanced by axial, sagittal, and coronal cuts.

According the these results, we classified PHA into four groups: renin-dependent adenoma, classical adenoma, bilateral hyperplasia, and primary adrenal hyperplasia (See Table I). In our series there were no cases of adrenal carcinoma or type I and II familial hyperaldosteronism.

AHT was considered to be refractory when BP values were ≥ 140 or 90 mmHg while on three hypotensive drugs (not requiring one of them being diuretic).[17]

RESULTS

We obtained a total of 35 patients diagnosed with PHA, which accounts for a prevalence of approximately 1.3% of the whole population of not selected hypertensive patients. Five of them were not included because additional tests were pending for the etiologic diagnosis.

There were 29 males and 6 women, mean age 50 ± 8.4 years.

Of the 30 patients diagnosed, 16 were adenomas (7 classical adenomas and 9 renin-dependent adenomas) and 14 hyperplasias (10 bilateral hyperplasias and 4 primary adrenal hyperplasias) (see Tables I and II).

The reason for PHA study was refractory hypertension in 18 patients; AHT and unjustified hypokalemia in 12 patients; excellent management of blood pressure values after incorporating spironolactone in 2; incidentaloma in another 2 patients, and referral from another department due to renin-angiotensin system impairment in 1 case.

Table II. Demographical and clinidal characteristics of the patients diagnosed with primary hyperaldosteronism (PHA)

Variable	ADN-C (n = 7)	ADN-RD (n = 9)	HPB (n = 10)	HP Adrenal (n = 4)
Mean age (years)	49.4	52.8	48.5	52.3
Gender (% males)	85.7%	77.7%	90%	75%
Mean BP (mm Hg)	155.7/93.5	180/104	174/103.3	160/101.2
Hypokalemia (%)	28.6%	22.2%	30%	100%
Refractory AHT (%)	43%	55.5%	60%	0%

The results are expressed as mean, except for gender, hypokalemia prevalence, and refractory arterial hypertension at diagnosis. ADN-C: classical adenoma; ADN-RD: renin-dependent adenoma; HPB: bilateral suprarenal hyperplasia; HP Adrenal: adrenal hyperplasia.

The demographical characteristics, clinical and analytical data, the blood pressure value at the beginning of PHA study, percentage of hypokalemia (< 3.5 mEq/L) and difficult to treat arterial hypertension at the beginning of PHA screening are shown in Tables II and III.

The imaging tests performed were: CT scan in 16/30 patients, MRI in 12/26, and scintigraphy with I-cholesterol in 26. The results from these tests were in agreement with the final diagnosis in 25% of the cases (4 cases), 41.6% (5 cases), and 92.3% (24 cases), respectively.

Ten patients diagnosed with adenoma (5 classical adenomas and 5 renin-dependent adenomas) were submitted to surgery, being normotensive with no need for antihypertensive medication in 6 out of 10. Four remain normotensive with pharmacological therapy.

The reasons why the remaining 6 adenomas have not been surgical removed were either because the patient refused this option or either because they kept an excellent blood pressure control with low doses of spironolactone. These 6 patients are kept under medication with a mean spironolactone dose of 70 mg, in addition with an average number of other antihypertensive drugs of 1.4.

The 14 patients with hyperplasia are under medical therapy with a mean spironolactone dose of 125 mg and 1.2 antihypertensive drugs.

The adverse events described were: gynecomastia in 7 patients (2 patients diagnosed with adenomas and 5 with hyperplasia), libido and sexual potency deterioration in 1 case (hyperplasia), creatinine increase in one case (adenoma). In one gynecomastia case spironolactone therapy was switched to eplerenone, this side effect vanishing and with good blood pressure control.

DISCUSSION

We describe 30 patients with PHA, 16 adenomas, (7 classical) and 14 hyperplasias, (10 bilateral idiopathic hyperplasia). The most common reason for the study was refractory AHT, previously defined.

Until the inclusion of the aldosterone/renin ratio, the most common presentation form of PHA was AHT with hypokalemia; with the introduction in the clinical practice of the A/R ratio as a detection method, the prevalence has gone up to 10-32%, depending on the study population.[5, 6, 7, 9, 18]

In recent years, the diagnostic value of this ratio has been a matter of important debate. There is an unanimous thinking that the higher the ratio the more likely the diagnosis of PHA.[1, 6, 12, 19] Once the syndromic diagnosis has been performed, it is necessary to confirm the diagnosis by means of confirmatory tests: 1) saline overload, 2) oral salt overload for three days before to assure a sodium urinary excretion > 150-200 mEq/24h, and 3) suppression with fludrocortisone.

We chose the option of free diet without salt restriction for three days because we thought it was more convenient for the patient (confirmed by urinary sodium > 150-200 mEq/24 h).

Given the higher use of the A/R ratio as a screening method, there are more diagnoses of mild forms of PHA. Thus, the adenomas/hyperplasias ratio has reversed and may be around 40:55; in fact, as Pérez Pérez AJ indicates,[1] a proportion of adenoma:hyperplasia of 1:1 is quite reasonable nowadays. Our series is in agreement with this datum (16 *vs* 14).

In our series there is a clear male preponderance (29), by contrast to what has been observed in other series.[20, 21]

The most common reason for studying PHA was refractory AHT, possibly due to the fact that our Unit is

Table III. Analytical data and imaging tests of PHA patients

Variable	ADN-C (n = 7)	ADN-RD (n = 9)	HPB (n = 10)	HP Adrenal (n = 4)
Baseline PRA (ng/mL/h))	0.27	0.12	0.21	1.2
Baseline ALD (ng/dL)	37.9	29.2	24.4	35.5
Baseline A/PRA	230.3	406.5	161	429.7
Na (mEq/L)	141.5	141.5	141.6	139.7
K (mEq/L)	3.7	3.4	3.7	3.2
Urinary Na/24 h	178	173	171.3	246.5
Urinary K/24 h	64.7	61.8	62.6	106.2
Scintigraphy	5/7	7/9	10/10	4/4
CT scan	4/7	5/9	7/10	2/4
MRI	3/7	7/9	2/10	0/4

The results are expressed as mean with the exception of imaging tests (scintigraphy, CT scan, MRI), wich are expressed as a proportion. PRA: plasma renin activity; ALD: aldosterone; A/PRA: aldosterone/plasma renin activity ratio; CT scan: computerized axial tomography; MRI: magnetic resonance imaging.

a referral center for AHT that systematically uses spironolactone in refractory AHT with 2 or 3 drugs. The second most frequent reason for staring a PHA study was arterial hypertension and hypokalemia, unjustified by the use of diuretics, being present in 12 out of 30 patients, which accounts for 40%, maybe a high value comparing it with recent studies that point towards a higher percentage of cases with normokalemia.[22,23]

Two patients started PHA screening even after good BP control when incorporating spironolactone.[16] For some authors, this a suspicion criterion for PHA that should be followed by confirmatory studies. [6] Finally, in 2 patients the screening study was started because of incidental finding of a suprarenal mass.[24]

Mean blood pressure (BP) values at the beginning of PHA study were 167/100. We did not find blood pressure differences between the different subtypes.

In a recent study by Mosso L *et al.*,[25] it was shown that PHA prevalence increased with more severe arterial hypertension; thus, in grade 1, grade 2, and grade 3 hypertension the PHA prevalence was 2%, 8%, and 13%, respectively.

Mean spironolactone dose used was 70 mg in adenomas and 125 mg in hyperplasias, a surprising fact since we expected the opposite results, because theoretically hyperplasia patients, with lower Ald/PRA ratio, would need lower spironolactone doses. This may be due to the fact that the Ald/PRA ratio in hyperplasias of our series is not lower than that of adenomas, with the exception of bilateral hyperplasias.

In spite of nor surpassing the recommended spironolactone dose, above which the adverse effects are increased (150 mg/day),[6,26] seven of our patients have presented some of the effects described in the literature, vanishing when the dose was reduced or when switched to eplerenone.

The characterization of the different subtypes is important, although what is important from a therapeutic perspective is establishing the site of hormone hyperproduction. Imaging tests (CT scan and MRI) are put into question today and several works have lowered their reliability with a specificity and positive predictive value of only 58% and 72%, respectively. The lack of sensitivity is attributed to the fact that most of adenomas are not bigger than 2 cm, and such small nodules are not detected by CT scan or MRI.

scintigraphy, a morphofunctional test, is a non-invasive and simple technique. It is done after suppression with dexamethasone for 7 days and thyroid blocking with lugol during 2 days, in order to increase its reliability. It has, however, false positive and false negative results, with poor resolution with those adenomas measuring less than 1.5 cm.[18]

Combined assessment with both imaging tests and scintigraphy and with a congruent postural test has a synergistic value. In our series, the test showing the best agreement with final diagnostic was scintigraphy, followed by MRI and CT scan.

Venous sampling is for some authors the gold standard test for diagnosing uni- or bilateral hormone hyperproduction. Since it carries some risks, it is not recommended to routinely perform it and should be reserved for those cases in which there is a discrepancy between the postural test and imaging test/scintigraphy or before the surgical option to assure unilateral secretion.[6,14,15]

Of 16 diagnosed adenomas, 10 have been surgically removed, 6/10 maintaining normal BP values without medication, and 4/10 well controlled hypertensive patients with lower antihypertensive medication than before surgery. Although surgical therapy represents the cure for most of adenomas, persistence of AHT after adrenalectomy is not infrequent since the arterial wall changes (remodeling) taking place

depending on the time course of AHT. Thus, in a study done at the Mayo Clinic, in which AHT normalization was assessed after adrenalectomy in 97 patients, the authors concluded that this phenomenon depended on lower patient's age, absence of a family history of AHT, shorter course of AHT, and preoperative use of 2 or more antihypertensive medications.[27]

In spite of the fact of persisting AHT after adrenalectomy (it usually is a milder form easily controlled), the surgical procedure is worth undertaking it since high aldosterone levels have vascular, cardiac, and renal toxicity independently of BP values control, predisposing to premature events such as cerebrovascular disease or cardiac fibrosis.[12]

Hyperplasias should have indefinite medical treatment with spironolactone, which is not devoid of adverse events. We currently also have available eplerenone, an aldosterone receptor antagonist, which has better tolerability profile due to lower anti-androgenic and anti-progesterone activities, although there are still no studies on its efficacy in PHA patients.

In conclusion, hyperaldosteronism is a condition with an increasing prevalence. The important thing is establishing whether hormonal hypersecretion is uni- or bilateral, in order to define surgical or medical therapy. The surgical treatment does not imply a curative outcome, but clearly better hypertension management with less medication and a decrease in aldosterone levels with the subsequent decrease of cardiac and vascular toxicity from this drug.

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