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Primary hyperaldosteronism, associated metabolic comorbidities and cardiovascular risk

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ABSTRACT

Background: Primary aldosteronism is the most common cause of secondary hypertension. There is little information about this disease in the Mexican population. The objective of this study is to evaluate patients with primary aldosteronism at a reference center and to describe its association with metabolic comorbidities and cardiovascular risk. **Methods:** Retrospective study of patients with primary aldosteronism treated from January 1987 to May 2014. **Results:** Thirty-seven patients with primary aldosteronism were included. The most common presentation was hypertension with hypokalemia (29.7%). The most frequent etiology was an adenoma (54%). Seventy-six percent underwent a unilateral adrenalectomy. Hypertension was cured in 48% of cases and in 40% there was an improvement. The use of antihypertensive medications after surgery decreased significantly (p = 0.009). 27% had metabolic syndrome. The

RESUMEN

Objetivo: El aldosteronismo primario (AP) es la causa más común de hipertensión. Hay muy poca información sobre esta enfermedad en la población mexicana. El objetivo de este estudio es evaluar a pacientes con AP en un centro de referencia y describir su asociación con las comorbilidades metabólicas y el riesgo cardiovascular. **Métodos:** Estudio retrospectivo de pacientes con AP tratados desde enero de 1987 hasta mayo de 2014. **Resultados:** Se incluyeron 37 pacientes con AP. El cuadro más común fue de hipertensión con hipocalemia (29.7%). La etiología más frecuente fue un adenoma (54%). El 66% fue sometido a adrenalectomía unilateral. La hipertensión fue curada en el 48% de los casos y en el 40% se observó una mejoría. El uso de tratamiento antihipertensivo tras la cirugía descendió significativamente (p = 0.009). El 27% tuvo síndrome metabólico (SM). La mediana estimada de riesgo cardiovascular a 10 años

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median estimated 10-year cardiovascular risk was 5.2%. **Conclusions:** In our series the most frequent cause of primary aldosteronism was adenomas. Twenty-seven percent of the population had metabolic syndrome. (REV MEX ENDOCRINOL METAB NUTR. 2016;3:116-23)

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fue del 5.2%. **Conclusiones:** En nuestra serie, la causa más frecuente de AP fueron los adenomas. El 37% de los pacientes sufrió SM.

Palabras clave: Aldosteronismo primario. Hipertensión secundaria. Síndrome metabólico. Riesgo cardiovascular.

INTRODUCTION

Primary aldosteronism (PA) is considered the most common cause of endocrine hypertension. It has an estimated prevalence of 9.1% in patients with hypertension[1]. In Mexico, there is scarce information regarding the epidemiology of PA. One article reported a prevalence of PA of 7.5%[2]. There is no information about the Mexican population regarding the clinical, biochemical, and radiographic features of PA and its association with metabolic risk factors.

Once the diagnosis of PA is confirmed, it is necessary to determine the etiology in order to provide the appropriate treatment. The causes of PA include bilateral adrenal hyperplasia (BAH) in approximately 60% of cases, an aldosterone producing adenoma (APA) in 35%, and adrenal unilateral hyperplasia in 2%[3]. While an APA usually requires unilateral adrenalectomy, BAH is treated with medications[4].

Elevated aldosterone levels are associated with heart damage and increased cardiovascular morbidity and mortality[5,6]. In addition, increased aldosterone is associated with the presence of cardiovascular risk factors. In fact, a higher incidence of metabolic syndrome (MS) in patients with PA has been documented[7,8]. Therefore, it is relevant to detect and treat PA promptly in order not only to decrease the potential organ dysfunction associated to hypertension, but also to decrease the associated cardiovascular risk.

The aim of this study is to evaluate the clinical, biochemical, and radiological features of patients with PA at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, and to describe the prevalence of MS and the associated metabolic comorbidities and cardiovascular risk in this population.

MATERIAL AND METHODS

We conducted a descriptive and observational study including cases of PA treated at the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran in Mexico City in the period from January 1987 to May 2014. The search of the cases was conducted using the following CIE-10 codes: E26.9 (aldosteronism), C74.9 (malignant adrenal tumor), C74.0 (malignant adrenal cortex tumor), D35 (benign adrenal tumor), I15.9 (secondary hypertension not otherwise classified), I15.2 (endocrine hypertension), and E876 (hypokalemia).

Before 2008, aldosterone concentration (PAC) was quantified using a radioimmunoassay. The reported coefficient variation (CV) for low values with this assay was 25% and for high values was 6%. After 2008, aldosterone was measured using tandem liquid chromatography mass spectrometry (Quest Diagnostics®). The CV for this assay is less than 10%. Plasmatic renin activity (PRA) was measured with a high-sensitivity radioimmunoassay (Quest Diagnostics®) with a CV of less than 10%. Primary aldosteronism was considered when the plasma PAC was

>15 ng/dl and the PAC to PRA measured in ng/ml/h ratio (ARR) was > 30[9]. Cases that did not meet the diagnostic criteria for PA and those with incomplete data were excluded.

In selected cases, a saline infusion confirmatory test was performed, infusing two liters of 0.9% saline over four hours. Aldosterone levels ≥ 10 ng/dl after the infusion confirmed PA.

The etiology of PA was determined using imaging techniques, such as adrenal computed tomography (CT) or magnetic resonance imaging (MRI). In cases with an undefined etiology, adrenal venous sampling was performed. The criteria published by Rossi, et al. were applied to indicate successful catheterization of the adrenal veins. Selective catheterization was defined by an adrenal vein/inferior vena cava cortisol ratio > 1. After successful catheterization, the PAC/cortisol ratio was obtained in both adrenal veins and lateralization was considered when the ratio between sides was > 2:1 without adrenocorticotropic hormone stimulation[10].

The following clinical variables were analyzed: gender, age at diagnosis, time since diagnosis of hypertension, and clinical presentation. Anthropometric data included height, weight, and body mass index (BMI), calculated by dividing the weight in kilograms by the square of height in meters. Biochemical variables including potassium, glucose, total cholesterol, triglycerides, and high-density lipoprotein (HDL)-cholesterol were analyzed using automated enzymatic assays (Beckman Synchron CX, Brea, CA). The low-density lipoprotein (LDL)-cholesterol (LDL-c) was calculated by the Friedewald formula. Blood pressure levels were registered at the first visit and after treatment. Left ventricular hypertrophy (LVH) was considered when the Sokolow index was ≥3.5 mV in an electrocardiogram[11] or by echocardiography. The Sokolow index has relatively low sensitivity (0.25-0.61), and high specificity (0.75-0.95) for the diagnosis LVH[12].

Hypertension outcome was classified as follows: (i) cured, when the blood pressure was < 140/90 mmHg without requiring medications after one year of follow-up, (ii) improvement, with a blood pressure < 140/90 mmHg taking antihypertensive medication, and (iii) no improvement, with a blood pressure > 140/90 mmHg in spite of medical treatment[9,13].

To define MS, the criteria of the 2009 consensus published by the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity was applied[14], with BMI as a surrogate of waist circumference[15]. Considering that all patients had one MS criteria because of the existence of hypertension, MS was defined by the presence of two of the following additional criteria: hypertriglyceridemia ≥ 150 mg/dl or use of medications, HDL-cholesterol < 40 mg/dl in men or < 50 mg/dl in women, fasting glucose ≥ 100 mg/dl or drug treatment, or BMI ≥ 30 kg/m^2. Cardiovascular risk was estimated using the 2013 AACC/AHA risk calculator[16].

Statistical analysis

Data are expressed as means and standard deviations, or median and interquartile ranges, as appropriate. Comparisons were performed with independent or paired Student *t* tests. Odds ratios were calculated. A p value < 0.05 was considered statistically significant. Analyses were performed using the SPSS software v. 21.

RESULTS

Of the 545 records reviewed, 45 patients were identified with PA, and eight were not included due to incomplete data or because they did not meet the diagnostic criteria for PA (Fig. 1).

General characteristics

We included 37 patients with PA; 64.9% were women. The mean age at diagnosis of PA and of hypertension was 41.3 ± 14.5 and 32.6 ± 12.4

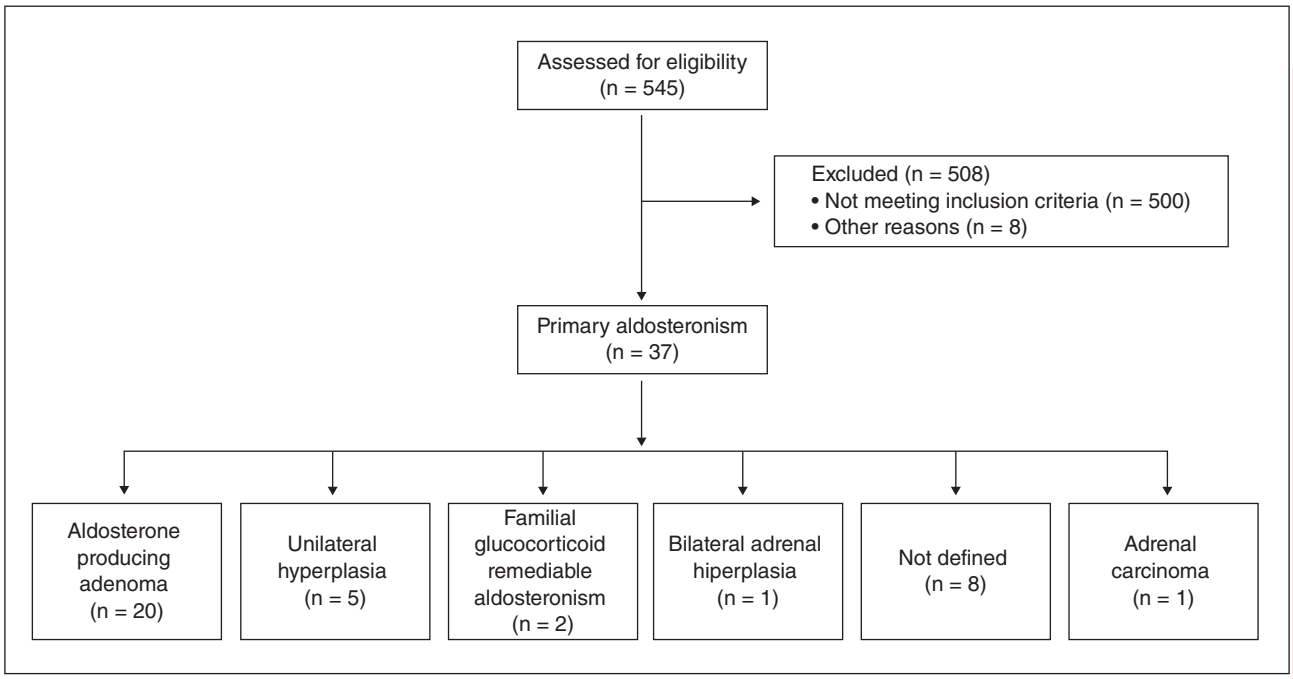

Figure 1. Diagram flow of included patients.

years, respectively. The median time elapsed between hypertension and PA diagnosis was 8 (interquartile range [IQR]: 3-12) years. The mean systolic (SBP) and diastolic (DBP) blood pressures at diagnosis were 148.2 ± 22.2 mmHg and 92 IQR: 90-100) mmHg, respectively, and potassium level was 3.3 ± 0.74 mEq/l IQR: 2-5). The median concentrations of PAC and PRA were 47 (IQR: 28-69) ng/dl and 0.24 (range, 0.1-0.46) ng/ml/h, respectively and the median estimated ARR was 253.7 (IQR: 67.5-550). In three cases, a saline infusion confirmatory test was performed. Table 1 describes the general characteristics of the studied population.

Nineteen patients (51.3%) had a potassium level < 3.5 mEq/l. In this group of patients with hypokalemia, the PRA was significantly lower (0.14 [IQR: 0.10-0.19] vs. 0.42 [IQR: 0.28-0.76] ng/ml/h; p = 0.001) and the ARR was higher (306.6 [IQR: 246.5-610.7] vs. 65.6 [IQR: 42.3-353.0]; p = 0.003). In addition, PAC showed a tendency to be higher in this group without reaching statistical significance (54 [interquartile range, 30.9-72.4] vs. 38.5 [IQR: 24-65] ng/dl; p = 0.258).

According to the Sokolow index, 62% of patients had LVH. In 16 patients (43.2%) an echocardiograph was done and 81.2% of them showed hypertensive heart disease.

In the majority of cases, the clinical presentation was hypertension and hypokalemia (18 cases, 48.6%). In this group, seven patients presented with a hypokalemic paralysis. Refractory hypertension was the second most common form of presentation (24.3%), followed by a hypertensive emergency (16.2%). The remaining clinical presentations included abdominal pain, an abdominal tumor, preeclampsia, and an adrenal incidentaloma (with one case each, 2.7%). Seventy-six percent of patients reported history of a hypertensive crisis before diagnosis.

Causes of primary aldosteronism

To identify the etiology of PA, an adrenal CT scan was performed in 34 cases and a MRI in the remaining three cases. The most frequent cause of PA was an APA (20 cases, 54%). Unilateral hyperplasia was diagnosed in five cases (13.5%), familial glucocorticoid

Table 1. General characteristics of the studied population (n = 37)

Characteristic	
Women, number (%)	24 (64.9)
Age at diagnosis of hypertension, years	32.6 ± 12.4
Age at diagnosis of PA, years	41.3 ± 14.5
Time between hypertension and PA diagnoses, years (range)	8 (3-12)
BMI, kg/m^2	25.6 ± 4.1
SBP before treatment, mmHg	148.2 ± 22.2
DBP before treatment, mmHg (range)	92 (90-100)
Potassium, mEq/l	3.3 ± 0.74
Glucose, mg/dl	97.9 ± 32.7
Total cholesterol, mg/dl	191.3 ± 30.7
LDL cholesterol, mg/dl	118.2 ± 25.3
HDL cholesterol, mg/dl	42.3 ± 12.0
Non-HDL cholesterol, mg/dl	148.7 ± 30.0
Triglycerides, mg/dl (range)	124 (91.0-211.5)
PAC, ng/dl (range)	47 (28-69)
PRA, ng/dl/h (range)	0.24 (0.1-0.46)
ARR (range)	253.7 (67.5-550)

Values are expressed as mean ± standard deviation or median and interquartile range.
ARR: plasma aldosterone concentration/plasma renin activity. BMI: body mass index. DBP: diastolic blood pressure. HDL: high-density lipoprotein. LDL: low-density lipoprotein. PA: primary aldosteronism. PAC: plasma aldosterone concentration. PRA: plasma renin activity. SBP: systolic blood pressure.

remediable aldosteronism in two (5.4%), and BAH in one case. In eight cases (21.6%) an etiology could not be defined. Finally, in one case an adrenal carcinoma associated with hyperaldosteronism was diagnosed (Table 2).

Adrenal venous sampling

In five patients, a successful catheterization of the adrenal veins was performed. In four cases, lateralization to the left adrenal gland was demonstrated, and in one case there was no lateralization. In two of the patients with lateralization, surgery was performed, and the histopathological diagnosis remained as left adrenal hyperplasia. In the case with no lateralization, the CT scan did not show any lesions and a diagnosis of bilateral adrenal hyperplasia was established.

Treatment

Twenty-eight (75.7%) patients underwent a unilateral adrenalectomy; in 26 a laparoscopic procedure was performed, and in the remaining two an open surgery was done. Nine patients received only medical treatment.

One patient died before discharge, and two patients were lost to follow-up. Therefore, hypertension outcomes were assessed in 25 out of 28 cases that underwent surgery. The median follow-up was 26 (IQR: 7.6-74.5) months. In these cases, SBP declined from 148.4 ± 25.2 to 128 ± 23 mmHg ($p = 0.001$), and DBP from 93.7 ± 15.1 to 80.1 ± 13.6 mmHg ($p < 0.001$). Potassium concentrations increased after surgery from 3.23 ± 0.76 to 4.4 ± 0.60 mEq/l ($p < 0.001$). Hypertension was cured in 48% of these cases, in 40% there was an improvement, and in 12% no improvement was seen. The number of antihypertensive medications significantly decreased after surgery from 2 (IQR: 2-3) to 2 (IQR: 0-2) ($p = 0.009$). A higher preoperative SBP was significantly associated with hypertension persistence. A higher DBP and being older showed a tendency to be associated with hypertension persistence without achieving significance. Table 3 shows the variables associated with hypertension resolution.

Table 2. Contrast of imaging findings and etiology of primary aldosteronism

Image finding/ Etiology	Right APA	Left APA	Enlarged right adrenal	Enlarged left adrenal	Normal	Renal tumor	Abdominal tumor	Total
Right APA	9	1	1	0	0	0	0	11
Left APA	0	9	0	0	0	0	0	9
Undetermined	0	2	0	1	4	1	0	8
Unilateral hyperplasia	0	4	0	1	0	0	0	5
GRA	0	0	0	0	2	0	0	2
BAH	0	0	0	0	1	0	0	1
Adrenal carcinoma	0	0	0	0	0	0	1	1

APA: aldosterone producing adenoma. BAH: bilateral adrenal hyperplasia. GRA: glucocorticoid remediable aldosteronism.

Table 3. Variables associated with hypertension resolution in patients who underwent surgery (n = 25)

Variable	HTA cured (n = 13)	Persistent HTA (n = 12)	OR (range)	P
Age, years	33.8 ± 9.1	44 ± 12	1.09 (0.99-1.2)	0.058
Women, n (%)	9 (81.8)	10 (71.4)	1.8 (0.26-12.3)	0.549
Men, n (%)	2 (18.2)	4 (28.6)		
Body mass index, kg/m^2	24 ± 3.2	27.4 ± 4.7	1.3 (0.74-1.6)	0.074
Glucose, mg/dl	84.6 ± 16.4	95.3 ± 23.3	1.03 (0.98-1.1)	0.221
Triglycerides, mg/dl (range)	73 (63-115)	169.5 (124-220)	1 (0.99-1.0)	0.827
HDL-cholesterol, mg/dl	45.8 ± 16.8	42.2 ± 9.5	0.98 (0.91-1.0)	0.552
Preoperative SBP, mmHg	131.8 ± 17.7	157.0 ± 21.7	1.0 (1.01-1.1)	0.018
Preoperative DBP, mmHg	86 ± 8.8	98.0 ± 15.4	1.09 (0.99-1.2)	0.061
Hypertension evolution, years	6.2 ± 6.4	10.0 ± 6.0	1.11 (0.96-1.3)	0.134
≤ 2 antihypertensive drugs	7 (63.6)	5 (35.7)	2.04 (0.95-10.5)	0.394
Preoperative potassium level, mEq/l	1.3 ± 0.5	1.6 ± 0.5	0.98 (0.33-2.8)	0.972
Family history of EH (%)	9 (81.8)	11 (78.5)	1.22 (0.16-9)	0.840
Post-operative ARR	3.8 ± 2.3	7.7 ± 6.9	1.14 (0.82-1.6)	0.410

Values are expressed as mean ± standard deviation.
ARR: aldosterone to renin ratio. DBP: diastolic blood pressure. EH: essential hypertension. HTA: hypertension. OR: odds ratio (confidence interval). SBP: systolic blood pressure.

Metabolic comorbidities, metabolic syndrome, and cardiovascular risk

Of the studied population, 51.4% (n = 19) were classified as being overweight and 13.5% (n = 5) with obesity. Regarding dyslipidemias, 32.4% (n = 12) had triglyceride levels ≥ 150 mg/dl or were receiving treatment, 32.4% had cholesterol levels > 200 mg/dl, and 45.8% (n = 11) of women and 61.5% (n = 8) of men had low HDL-cholesterol levels. Finally, 24.3% (n= 9) had an abnormal fasting glucose (≥ 100 mg/dl) and 13.5% (n = 5) of them had diabetes. According to the 2009 consensus, 27% had MS. None of the MS criteria were associated with hypertension resolution after surgery (Table 3).

The estimated 10-year cardiovascular risk was 5.2% (IQR: 2.4-9.8) and the life-time cardiovascular risk was 39.1% (IQR: 38.8-50.2).

DISCUSSION

This study describes the characteristics of 37 cases with PA from a reference institution. The most common etiology of PA was an APA. In addition, the prevalence of MS in this group of patients was 27%, and the median estimated 10-year cardiovascular risk was 5.2%.

In Mexico there is only one published study regarding the prevalence of PA[2] and there is no data regarding the clinical, biochemical, and etiology of PA. Similarly, the association between PA and metabolic comorbidities, MS, and cardiovascular risk has not been described.

In this group of patients with PA, we found a higher proportion of affected women and an average age at diagnosis of 41 years. The main clinical presentation was hypertension in combination with hypokalemia, followed by refractory hypertension. Other authors have described refractory hypertension as the most frequent presentation[17].

In our study, the most frequent finding detected on radiological studies (CT and MRI) was a nodular image. This finding was correctly correlated to the histopathological diagnosis in 95% of cases. In the majority of cases, the definitive PA cause was an APA. However, in a high proportion of cases the etiology could not be established, which could have underestimated the cases with BAH.

In comparison to individuals with essential hypertension, patients with PA have a higher risk of target organ damage. In our study, LVH was documented in 62% of patients, even though the Sokolow index has a low sensitivity for establishing LVH, and an echocardiogram was performed in a subgroup of patients. Finally, 8% had a history of stroke.

Aldosterone excess may be associated with metabolic abnormalities[18]. In this series, we found that 65% of patients were classified as being overweight or with obesity, which is lower than the reported 71.3% prevalence in the Mexican adult population[19], 45.8% (n = 11) of women and 61.5% (n = 8) of men had hypoalphalipoproteinemia, 35.1% hypercholesterolemia, and 32.4% hypertriglyceridemia. Comparing these figures with data from the adult Mexican population, the Encuesta Nacional de Salud y Nutricion (ENSANUT) 2012 reported 60.5% (95% CI: 58.2-62.8) prevalence of hypoalphalipoproteinemia, 43.6% (95% CI: 41.4-46.0) of hypercholesterolemia, and 31.5% (95% CI: 29.3-33.9) of hypertriglyceridemia[20]. It was found that 24.3% of patients had impaired fasting glucose and 13.5% had diabetes. The frequency of diabetes in this group of individuals with PA is lower compared to the latest prevalence of 14.4% found in a National Survey[21]. Finally, 27% of these patients fulfilled the criteria for MS, using BMI as a surrogate for waist circumference[15]. This prevalence is similar to the described prevalence in general Mexican population[22]. Fallo, et al. reported a higher prevalence of hyperglycemia in Caucasian patients with PA compared to patients with essential hypertension (27.0 vs. 15.2%) and also a higher prevalence of MS (41.1 vs. 29.6%)[23].

Hypertension was resolved in 13 of the 25 patients that were followed-up after surgery. In a study performed at the Mayo Clinic including 97 patients, a younger age, absence of family history of hypertension, a shorter length of hypertension, and the use of two or less antihypertensive drugs were associated with a better postoperative hypertension outcome[13]. We found that only a lower preoperative SBP was associated with hypertension resolution.

The limitations of this series include its retrospective nature, the small number of identified patients with confirmed PA, and the absence of a reference group. However, this work represents a description of the main characteristics of a series of Mexican patients with PA. In addition, the association of PA with metabolic comorbidities, MS, and cardiovascular risk are described.

CONCLUSIONS

In summary, in our study the most common etiology of PA was an APA. Only SBP was associated with hypertension persistence. Metabolic syndrome was

present in 27% of this group of patients, which is not superior to the described prevalence in the Mexican population, and the 10-year estimated cardiovascular risk of 5.2%.

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