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Non-sequential and non-stimulated bilateral adrenal vein sampling utility in primary aldosteronism: Case inform

José Juan Ceballos-Macías[a,*], Jorge Alberto Flores-Real[b], Joel Vargas-Sánchez[b], Guillermo Ortega-Gutiérrez[c], Ramon Madriz-Prado[d], Salvador Amézquita-Pérez[e], Gildardo Garrido-Sanchez[f], Anna Carolina Meneses-Pérez[b], Alfredo Hernández-Moreno[a], Alfredo Reza-Albarrán[g]

[a] Servicio de Endocrinología y de la Clínica de Enfermedades Crónicas de la Unidad de Especialidades Médicas, C.P. 53960, Edo Mex, Mexico
[b] Servicio Endocrinología del Hospital Central Militar, C.P. 11200, CDMX, Mexico
[c] Adscrito del Servicio Endocrinología del Hospital Central Militar, C.P. 11200, CDMX, Mexico
[d] Servicio de Endocrinología Pediátrica de la Unidad de Especialidades Médicas, C.P. 53960, Edo MX, Mexico
[e] Servicio Radiología del Hospital Central Militar, C.P. 11200, CDMX, Mexico
[f] jefe del Servicio Patología del Hospital Central Militar, C.P. 11200, CDMX, Mexico
[g] jefe del servicio de metabolismo mineral del Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, C.P.14000, CDMX, Mexico

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ABSTRACT

Purpose: To present a case of a 20-year-old Mexican woman with resistant high blood pressure and the procedures the medical staff underwent to identify the etiology of her illness, as well as the choice of treatment.
Material and methods: We present a case of a 20-year-old Mexican woman, who showed up to the emergency department at the Military Central Hospital of SEDENA, with decreased visual acuity, persistent headache, and high blood pressure. Her vital signs were a blood pressure of 220/120 mmHg, heart rate of 73 beats per minute, and a respiratory rate of 16 breaths per minute. An electrocardiogram was made and showed hypertrophy of the left cavities. The medical staff sent complementary studies that consisted of a renal ultrasound that showed a right and left kidney with regular dimensions and no signs of stenosis in both renal arteries. The hormonal reports of plasma renin activity were 1.06 ng/ml/h and plasma aldosterone concentration of 30 ng/dL. Plasma aldosterone/renin ratio (ARR) of 28.3 suggested a case of primary aldosteronism (PA).
Results: A simple and contrasted computed tomography of the adrenal glands was performed, which reported normal adrenal glands, without identifying focal lesions. Therefore, it was indicated an adrenal catheterization procedure using a non-sequential and non-stimulating technique to expose unilateral primary aldosteronism.
Conclusions: Unilateral adrenalectomy is the cure or means of improvement of the clinical signs and symptoms of patients with unilateral primary aldosteronism, we suggest every PA should undergo an adrenal vein sampling seeking lateralization even thought a CT scan shows no evidence of lesions in the adrenal glands. Further investigation of the effects of medical or surgical treatment on the quality of life of Mexican patients with PA is needed.

1. Introduction

In Mexico, the total population estimate for 2015 by the Consejo Nacional de Población (CONAPO) is 121 million inhabitants, of which 31% have a diagnostic of hypertension [1]. Due to many factors such as the socio-economic and cultural characteristics of the Mexican population, many of these patients do not adequately take their antihypertensive treatment [16]. Which makes the task of identifying patients with resistant hypertension a challenge.

Resistant hypertension defined as blood pressure that remains above goal despite the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic, and all agents should be at optimal dose amounts [2]. Diagnosis of resistant hypertension requires detailed information about the patient's history, including lifestyle characteristics, alcohol, and dietary sodium intake, interfering drugs or substances, and sleep history. A physical examination, with a focus on determining the presence of secondary hypertension. Laboratory tests to detect electrolyte abnormalities

* Corresponding author. Av. Industria Militar S/N, Col. Lomas de San Isidro, Naucalpan, Edo Mex, C.P. 53960, Mexico.
E-mail address: drjjceballos@hotmail.com (J.J. Ceballos-Macías).

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(hypokalemia), associated risk factors (diabetes), organ damage (advanced renal dysfunction). Moreover, confirmation of previous therapeutic adherence [3].

The most common causes of secondary hypertension are primary aldosteronism, renal artery stenosis, chronic kidney disease, and obstructive sleep apnea. Less common causes include pheochromocytoma, Cushing's syndrome, and aortic coarctation [2]. Primary aldosteronism (PA) is the most frequent endocrinological cause of secondary hypertension. PA is a group of disorders in which aldosterone production is inappropriately high for sodium status, relatively autonomous of the significant secretion regulators (angiotensin II, plasma potassium concentration), and non-suppressible by sodium loading. Such inappropriate production of aldosterone causes hypertension, cardiovascular damage, sodium retention, suppression of plasma renin, and increased potassium excretion that (if prolonged and severe) may lead to hypokalemia [4]. PA has a significant variation of its prevalence, ranging from < 1% to 30% [5–8]. This indicates the necessity to report cases of primary aldosteronism in Mexico, with the purpose of detection, diagnosis, and treatment of these patients.

2. Material and methods

We present a case of a 20-year-old woman, who showed up to the emergency department at the Military Hospital of Mexico City, with decreased visual acuity, persistent headache, and high blood pressure. On examination, the medical staff found mean arterial pressure (MAP) > 160 mmHg. Upon questioning, the patient reported previous use of antihypertensive drugs prescribed by a private physician such as metoprolol 100 mg every 24 h, prazosin 2 mg every 6 hours, nifedipine 30 mg every 12 hours and hydrochlorothiazide 12.5 mg every 24 hours, without presenting a decrease in MAP or improvement of her symptoms.

Regarding her medical history, she mentioned a facial hemangioma in the lower right quadrant and surgery to correct strabismus during childhood. In the clinical examination performed by Internal Medicine, the patient had a blood pressure of 220/120 mmHg, a heart rate of 73 beats per minute, a respiratory rate of 16 breaths per minute, an electrocardiogram with sinus rhythm, a frequency of 73 beats per minute, electric axis to the left, a PR segment of 0.12, with data suggesting hypertrophy of the left cavities. Chest x-ray with cardiomegaly grade I data. There was a particular emphasis in the electrolyte measures; the patient never had potassium (K) below normal levels (at first contact with the patient the levels of K were of 4.2 mg/dL).

She was referred to numerous departments, specifically Nephrology and Cardiology. Complementary studies were sent with a report of the renal ultrasound showing a right and left kidney presenting dimensions of 9.7 × 4.2 × 5.9 cm and 10.3 × 5.1 × 5.1 cm respectively. There were no signs of stenosis in both renal arteries. An echocardiogram highlighted mobility with segmental and global thickening of the left ventricle at rest; without maneuvers indicative of ischemia. Ophthalmology evaluated her, reporting Grade 1 Retinopathy.

Finally, the patient went to the department of Endocrinology with the next hormonal reports: plasma renin activity (PRA) and plasma aldosterone concentration (PAC), results: PAC: 30 ng/dL, PRA: 1.06 ng/ml/h, plasma aldosterone/renin ratio (ARR) 28.3. Serum cortisol: 10 µcg/dL. Due to the above, we presumed primary aldosteronism. Spironolactone was added at a rate of 100 mg orally every 24 hours; the medical staff sent a CT scan in order to determine the presence of adrenal adenoma versus adrenal hyperplasia.

3. Theory

The two major PA subgroups are the single forms, mainly aldosterone-producing adenoma (APA), and bilateral forms, mostly adrenal zona glomerulosa hyperplasia (BAH), which require surgical or medical treatment, respectively. APA is a diagnostic certainty when 1) there is evidence of PA at the screening tests, with an inappropriately high aldosterone-to-renin ratio. 2) An adrenal vein sampling shows lateralization of the aldosterone secretion, 3) Pathology studies detect an adenoma, and, crucially important, 4) PA is corrected by adrenalectomy [15].

The initial evaluation of PA should consist in documenting a suppressed plasma renin activity (PRA), or plasma renin concentration (PRC) and that plasma aldosterone concentration (PAC) is inappropriately high for PRA (typically > 15 ng/dL [416 pmol/L]) [4]; the net effect is plasma aldosterone/renin ratio (ARR) greater than 20 (depending on the reference values of the laboratory). A high ARR and an increased PAC are prerequisites to make a diagnosis of PA. In most patients, a high proportion of ARR by itself does not establish the diagnosis of PA, which must be confirmed by the demonstration of inappropriate aldosterone secretion. The exception to the requirement for confirmatory tests is the patient with spontaneous hypokalemia, undetectable PRA or PRC, and ARR > 20 ng/dL. In this clinical context, there is no other diagnosis except primary aldosteronism to explain these findings. However, an aldosterone suppression test is generally required and can be performed with orally administered sodium chloride and the measurement of aldosterone excretion in the urine or with a load of saline solution at 0.9% waiting in response to an adequate suppression of PAC [4].

The Endocrine Society Clinical Practice Guideline in the management of primary aldosteronism recommends that all patients undergo adrenal CT scan as the subsequent study to exclude large masses that may indicate adrenocortical carcinoma [4]. Also, it could be used to assist the interventional radiologist and surgeon when appropriate timing for intervention is considered [9].

Adrenal CT has several limitations, aldosterone-producing adenomas may appear as small hypodense nodules (usually < 2 cm in diameter) [9]. The adrenal glands in adrenal hyperplasia may appear to be healthy on CT or show nodular changes. Radiologists may incorrectly interpret the small aldosterone-producing adenoma as “idiopathic adrenal hyperplasia” based on the findings of typical bilateral or single adrenal nodules that appear on CT. Therefore, adrenal vein catheterization (AVC) is essential to direct appropriate therapy in patients with PA who seek a possible surgical correction [4,9].

Both the sensitivity and the specificity of adrenal catheterization (95 and 100%, respectively) to detect unilateral aldosterone excess are superior to those of adrenal CT (78 and 75%, respectively) [10,11]. CT has the potential of being frankly misleading when demonstrating unilateral adrenal nodules in patients with bilateral disease and therefore, leading to inappropriate surgery [11].

The adrenal vein sampling (AVS) is the standard Gold test to distinguish unilateral disease from bilateral disease in patients with PA [10]. Non the less, AVS can be a complicated procedure, especially in terms of successful cannulation of the right adrenal vein; and the success rate is proportional to the radiologist's experience.

There are three protocols for AVS: a) non-sequential or simultaneous non-stimulated bilateral AVS, b) sequential or simultaneous non-stimulated AVS followed by a sequential or simultaneous stimulated cosyntropin bolus bilateral AVS, and c) continuous infusion of cosyntropin with bilateral sequential AVS [9]. Because the normal adrenal gland produces cortisol in response to ACTH, venous cortisol levels are used as a positive control to determine whether the sample obtained from the adrenal veins is adequate. The level of cortisol in the adrenal vein (C_{av}) in each AVS are compared with peripheral samples taken from the inferior vena cava (IVC) or right common femoral vein, to generate a relationship (C_{av}: C IVC), since cortisol C_{av} must be several times greater than the peripheral levels.

Endocrinologists use a wide range of peripheral C_{av} index limits, in most centers, a cut-off value of 3 was used for AVS with stimulation with cosyntropin and 2 for AVS without stimulation [12]. This index shows that both adrenal veins samples are adequate. The next step is to determine if overproduction of aldosterone is only in one gland or both.

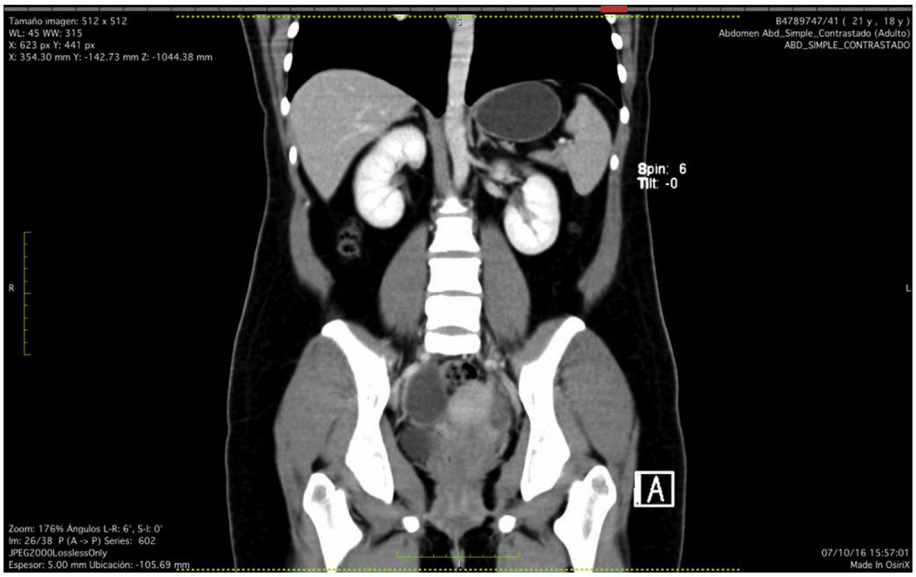

Fig. 1. CT scan in a coronal view. The image was taken to asses the anatomic state of both adrenal glands.

The aldosterone/cortisol (A/C) ratios from the left AV (LAV) and right AV (RAV) are compared to determine whether aldosterone production is unilateral (making surgery a possibility) or bilateral (limiting treatment to mineralocorticoid receptor antagonists) [13]. This ratio-of-ratios (the more significant, 'dominant' A/C ratio divided by the smaller, 'non-dominant' A/C ratio) is called the lateralization index (LI) and values greater than 3–5 have been used to define lateralized aldosterone production [13].

The diagnosis of APA includes a demonstration of an adenoma. Classically depicted as a single and round macronodule in the adrenal gland, consisting of morphologically Zona Glomerulosa or zona fasciculata-like cells, or a combination of both [16]. The use of stains (Hematoxylin and eosin) to reveal the APA and discriminate between ZG- and ZF-like cells cannot provide any information on the function and steroidogenic potential of these cells [15].

4. Results and discussion

A simple and contrasted computed tomography (Fig. 1), of the adrenal glands, was performed, which reported normal adrenal glands, without identifying focal lesions. Therefore, to determine the etiology (adrenal adenoma versus adrenal hyperplasia), an adrenal catheterization procedure using a non-sequential and non-stimulating technique was performed (Fig. 2). The medical staff withheld spironolactone four weeks before the AVC procedure. The AVC showed the following results: peripheral serum cortisol took from the inferior vena cava (IVC) 10 µcg/dL, peripheral aldosterone (IVC) 7ng/dL.

Right adrenal vein (RAV): aldosterone 1 ng/dL (RAV), cortisol 171 µcg/dL, Left adrenal vein (LAV): aldosterone 85 ng/dL (LAV), cortisol 143 µcg/dL.

$C_{AVR}/C_{peripheral} = 17$

$C_{AVL}/C_{peripheral} = 14$

$A_{LAV}/C_{LAV} = 0.59$

$A_{RAV}/C_{RAV} = 0.006$

Lateralization Index (LI): 98

It comes to our attention that this patient had a plasma aldosterone/renin ratio (ARR) above the standard threshold, and there was no necessity of an AVS with cosyntropin to pinpoint the cause of secondary hypertension. So, the necessity of further invasive methods was reluctant.

With the results of the AVS, we made a final diagnostic of an aldosterone-producing adenoma, and surgery was indicated, which was

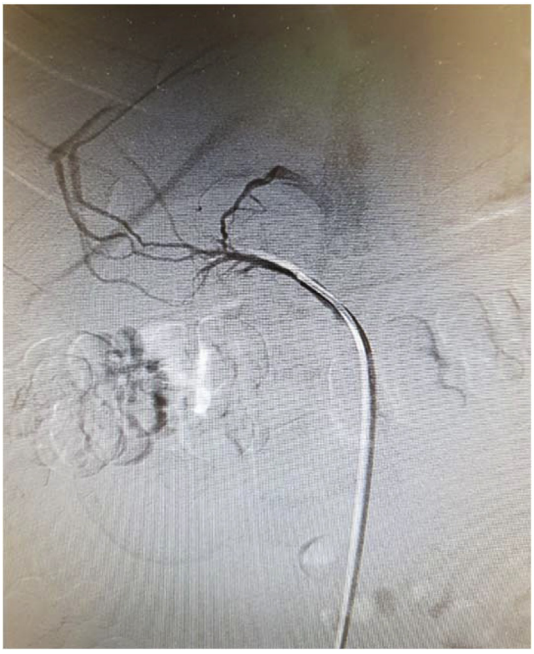

Fig. 2. Adrenal vein catheterization (Right). This image was taken to assess the position of the catheter.

programmed by the surgical Oncology department. They performed left laparoscopic adrenalectomy, with no incidents. With a sample from the adrenalectomy procedure, (Fig. 3, Fig. 4), the pathology department found a nodule containing large foamy lipid-rich cells.

In the postoperative period, the evolution was adequate, with systolic tensions between 140 and 150 mmHg and diastolic of 80–90 mmHg. The hospital discharged the patient with three antihypertensives: prazosin 1 mg orally every 8 hours, nifedipine 30 mg orally every 12 hours, metoprolol 100 mg at night. The use of spironolactone was not necessary at this point.

In the follow-up of the outpatient consultation six months later, she maintained adequate control of blood pressure, requiring the reduction of antihypertensive doses. Prazosin 1 mg orally every 12 hours, nifedipine 10 mg orally every 12 hours, metoprolol 50 mg every 24 hrs.

Her laboratory post surgery of plasma renin concentration (PRC)

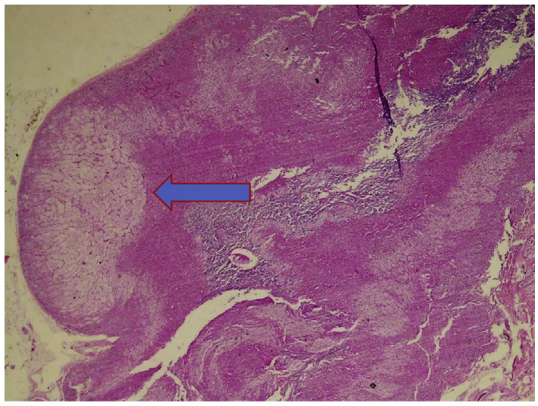

Fig. 3. Microphotograph ×2 of the adrenal gland. Sample obtained from adrenalectomy procedure, stained with hematoxylin and eosin. It shows a nodule containing large foamy lipid-rich cells. The arrow shows a clear cell nest in zona fasciculata.

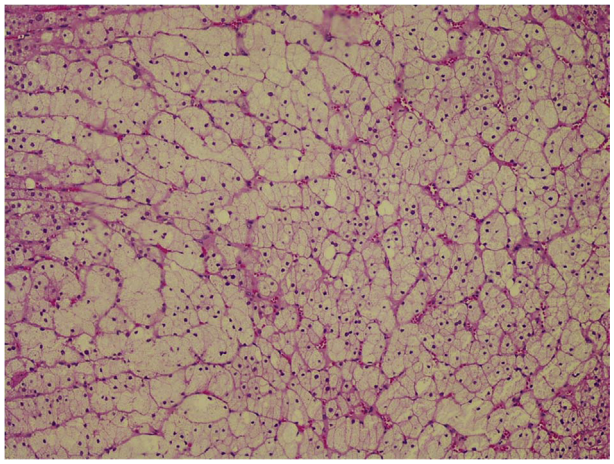

Fig. 4. Microphotograph 10× of the adrenal gland. Sample obtained from adrenalectomy procedure, stained with hematoxylin and eosin. It has a closer look at the cell type inside the nodule. We can observe clusters of cells with well-defined borders, with abundant foamy cytoplasm that resembles the zona fasciculata.

was 1.2 uU/mL, and plasma aldosterone concentration (PAC) was 6 ng/mL, which it turned in an ARR of 5.

Broadly 70% of patients with lateralized aldosterone secretion are cured by surgery, the MAP outcome of surgery is dependent not only on the severity of primary aldosteronism and its etiology but also on nonspecific features such as a family history of hypertension, known duration of hypertension and age at intervention. These nonspecific variables influence the MAP outcome in primary aldosteronism and all other forms of potentially correctable hypertension [14].

5. Conclusions

PA seems to be the most common form of treatable and potentially curable hypertension. The clinical and biochemical responses to specific treatment have been well described, with unilateral adrenalectomy resulting in the cure or improvement of hypertension and correction of hyperaldosteronism in patients with unilateral PA. We suggest every PA should undergo an adrenal vein sampling seeking lateralization without CT evidence of lesions in the adrenal glands. Unilateral adrenalectomy improves function, and it may cure the disease. A post hoc comparative effectiveness study within the Subtyping Primary Aldosteronism: A Randomized Trial Comparing Adrenal Vein Sampling and Computed Tomography Scan (SPARTACUS) trial have stated that treatment of PA results in substantial improvement of the quality of life of patients with PA. This improvement one year after adrenalectomy for APA not only exceeds that of the patients treated by mineralocorticoid receptor antagonists for BAH but also restores the quality of life to the level of the general population [17]. However, it does not address the Mexican population specifically. If we compare this study with our patient, her quality of life is exceedingly well. She can perform daily activities and exercise without any detriment. Further investigation of the effects of medical or surgical treatment on the quality of life of Mexican patients with PA is needed.

Declarations of interest

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jecr.2019.100049.

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