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Case Reports

Küpers clinical prediction score in a case series of primary aldosteronism

Küpers score in a case series of primary aldosteronism

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ABSTRACT

Background: : Primary aldosteronism is a disorder due to excessive aldosterone production in the presence of low renin levels. It is an underdiagnosed pathology despite its simple screening. Establishing the unilateral or bilateral location represents the greatest diagnostic challenge and is crucial to define the therapeutic approach. Adrenal venous catheterization (AVC) is the best test to establish the location, but it is invasive and expensive. New predictive markers of laterality are being developed. **Case series presentation**: We present a case series of 8 patients diagnosed with primary aldosteronism due to arterial hypertension with hypokalaemia, elevated aldosterone-renin ratio and compatible computed tomography. 4 patients underwent adrenal venous catheterization. **Conclusion:** In patients who underwent catheterization as well as in those who did not, the Küpers score adequately predicted lateralization in 75% of cases and it could be a useful tool to discriminate unilateral from bilateral aldosteronism.

Keywords: Primary aldosteronism; hypertension; hypokalemia (Source: DeCS-BIREME).

RESUMEN

Introducción: El hiperaldosteronismo primario es un desorden debido a una producción excesiva de aldosterona en presencia de niveles bajos de renina. Es una patología infradiagnosticada a pesar de su simple tamizaje. Definir la localización unilateral o bilateral representa el más importante desafío diagnóstico y es crucial para el abordaje terapéutico. El cateterismo venoso adrenal (CVA) es la mejor prueba para establecer la localización, pero es invasivo y costoso. Nuevos marcadores predictivos de unilateralidad se encuentran en desarrollo. **Presentación de serie de casos:** Presentamos una serie de casos de 8 pacientes diagnosticados con hiperaldosteronismo primario debido a hipertensión arterial con hipocalemia, radio aldosterona-renina elevado y tomografía compatible. 4 pacientes fueron sometidos a cateterismo venoso adrenal. **Conclusión:** Tanto en los pacientes que fueron sometidos a cateterismo venoso adrenal como en los que no, el score de Küpers predijo adecuadamente la lateralidad en 75% de los casos y puede ser una herramienta útil para diferenciar el hiperaldosteronismo unilateral del bilateral.

Palabras Clave: Hiperaldosteronismo primario; hipertensión; hipokalemia (Fuente: DeCS-BIREME).

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BACKGROUND

Primary aldosteronism (PA) consists of an excessive production of aldosterone together with low levels of renin. Among its main causes are aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia of the glomerular zone (BAH). Both produce excessive aldosterone that subsequently increases the potassium excretion as well as sodium and water reabsorption, increasing the blood pressure (BP)[1]. However, the classic presentation of high blood pressure (HBP) with hypokalemia, only occurs in around 35 % of the cases[2]. Its diagnosis is based on the finding of an inappropriately high production of aldosterone in the context of a low plasma renin concentration[3,4]. PA is the main cause of secondary hypertension. The estimated prevalence is a 5% under patients with hypertension, 10% in patients with severe hypertension and up to 20% in resistant hypertension[5]. However, its current published prevalence remains low at around 1-3% due to the low search for cases; only a small proportion is diagnosed and treated[6].

The differentiation between unilateral and bilateral presentation is crucial, as the therapeutic approach depends on it, being the indication of surgical excision for APA and medical treatment for BAH. It is considered that the most accurate test to distinguish these presentations is adrenal venous catheterization (AVC)[7]. However, this procedure is invasive, expensive and only available in 2 tertiary hospitals in Peru[8,9].

Küpers published a clinical score that allows predicting laterality in AVC by using clinical, biological, and radiological characteristics. The score has a maximum score of 7, making up 3 points for the presence of a typical adrenal adenoma, 2 points for serum K+ less than 3.5 mmol/l and according to the glomerular filtration rate (GFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation, it adds between 0 and 2 points to the total score. Using this score, performing AVC could be avoided in 30% of the cases and proceed directly with surgical treatment[10]. In this study, we present a series of 8 PA cases from a tertiary hospital in Peru, in which the Küpers score was used to assess the laterality of the PA.

CASE SERIES PRESENTATION

We present a cases series that include 8 patients with HBP diagnosed with PA and treated in a tertiary hospital in Peru between 2019 and 2021. The data was collected from the digital health management service system, as well as from the medical records of the patients. Data collection included: age, sex, comorbidities, time and treatment of hypertension, laboratory results (lowest potassium level, creatinine, glomerular filtration rate aldosterone, and plasma renin activity in a sitting position), computed tomography (CT) of the adrenal glands, adrenal vein catheterization results, adrenalectomy, pathology results and clinical outcome 1 year after adrenalectomy. PA was diagnosed following Endocrine Society guidelines, with no need for confirmatory testing if patient presents positive ARR, hypokalaemia, suppressed renin and PAC>20ng/dL[7]. Consequently, calculating the Küpers score, a cut-off points of 5 or more was taken as a predictor of lateralization[10]. The tabulation and descriptive analysis of the data was performed using Microsoft Excel. The confidentiality of the personal information of the patients was maintained at all times.

The present study included 8 adult patients, 4 men and 4 women, whose mean age was 43.1 ± 13.5 years (range 27 to 70 years). All patients had hypertension, 6 of them required 3 or more antihypertensive drugs. Hypokalaemia was defined as serum potassium levels below 3.5 mEq/L. All patients had potassium levels less than 3.0 mEq/L. Sex, age, antihypertensive medications, laboratory results, CT findings, characterization results, Küpers score, pathological anatomy results and clinical and biochemical outcome is summarized for patients studied with AVC (Cases 1-4 in Table 1) and patients that underwent surgery without AVC (Cases 5-8 in Table 1).

Investigation
To determine the Küpers score, all patients have GFR determined by the MDRD equation, serum potassium values and adrenal computed tomography.

Of the eight patients, seven had a Küpers score equal or greater than 5 points. Four patients underwent AVC, finding lateralization in all: three with lateralization to the left and one with lateralization to the right. Of the 4 patients who underwent AVC, 3 patients had a score equal or greater than 5 points, and 1 patient had a Küpers score of 3. This last patient did not present adrenal adenoma on CT but presented a slight enlargement in the left adrenal gland.

Of the four patients who did not undergo AVC, all patients had a Küpers score equal or greater than 5 points, and presented nodular image on CT.

Treatment
All patients included in the study underwent laparoscopic adrenalectomy. No postoperative complications were reported. Patients who underwent AVC presented pathology that revealed nodular adrenal hyperplasia in two cases and cortical adenoma with micronodular hyperplasia in the adrenal remnant in the other two cases.

Pathological study revealed 3 cases of cortical adenoma and 1 case of adrenal hyperplasia in patients who did not undergo AVC.

Outcome and follow-up
Clinical and biochemical outcomes were evaluated according with PASO consensus and classified in complete, partial or absent success. Clinical outcome was assessed by BP and need for antihypertensives. Patients had complete success in clinical outcome if they had normal BP without antihypertensives and partial success if they have controlled BP with less DDD of antihypertensives. Biochemical outcome was assessed by serum potassium and ARR. Patients had complete success in biochemical outcome if they had normokalaemia and normal ARR[11].

Adrenalectomy had a positive impact on BP control in the four patients who underwent AVC. Two patients had complete success in clinical outcome, and 2 patients had well

Table 1. Clinical characteristics, Küpers score and outcome of patients with primary aldosteronism.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Sex	Male	Female	Male	Female	Female	Female	Female	Male
Age	50	70	49	27	40	30	39	40
Potassium (mEq/l)	1.8	2.6	1.5	1.7	2.9	2	2.9	2.6
Age HBP diagnosis	30	30	30	26	27	23	34	21
Antihypertensive medication	Irbesartan 2DDD, nifedipine 2DDD, hydrochlorothiazide 1DDD	Irbesartan 2DDD, nifedipine 2DDD, bisoprolol 0.5DDD, methyldopa 0.75DDD, spironolactone 0.33DDD	3Irbesartan 2DDD, nifedipine 2DDD, hydrochlorothiazide 0.5DDD	Diltiazem 0.5DDD	Irbesartan 2DDD, verapamil 0.33DDD, terazosin 1DDD, spironolactone 1.33DDD	Enalapril 4DDD, nifedipine 2DDD, carvedilol 0.66DDD, hydrochlorotiazide 1DDD	Methyldopa 1.5DDD	Irbesartan 2DDD, carvedilol 1.33DDD, amlodipine 2DDD hydrochlorothiazide 1DDD
GFR - MDRD (mL/min/1,73 m^2)	92	71	85	110	145.5	83.4	112	120
Aldosterone Referential value in supine (1-16 ng/dl)	79.1	45.4	106.3	40.7	12.6	34	29.9	34.8
PRA: Suppressed <1 ng/mL/h	0.2	0.4	0.3	<0.2	0.75	0.6	0.2	0.4
ARR	395.5	113.5	354.3	>203.5	16.8*	56.7	149.5	87
Tomography findings	Slight enlargement in the left adrenal gland	Left Adenoma	Nodule of 15x8mm in left adrenal gland (<10UH)	Nodule in right adrenal gland of 23x15mm (- 3 a +10 UH)	Right heterogenic adrenal nodule 11x12 mm (- 10 a +16 UH)	Right hypodense adrenal nodule of 15 mm (<10UH)	Right adrenal nodule of 20x12mm (<10UH)	Left adrenal nodule of 18x21mm (-2 UH)
Küpers score	3	5	6	7	5	5	7	7
AVC	Lateralize to the left	Lateralize to the left	Lateralize to the left	Lateralize to the right	Not performed	Not performed	Not performed	Not performed
Surgery	Left adrenalectomy	Left adrenalectomy	Left adrenalectomy	Right adrenalectomy	Right adrenalectomy	Right adrenalectomy	Right adrenalectomy	Left adrenalectomy
Anatomical pathology	Nodular hyperplasia	Multifocal adrenocortical nodular hyperplasia	Adrenocortical adenoma of 1.5x1.3cm. Adrenal areas of micronodular hyperplasia	Adrenocortical adenoma with atypia nuclear. Adrenal areas of micronodular hyperplasia.	Adrenocortical adenoma	adrenocortical adenoma	adrenocortical adenoma	Adrenal hyperplasia
Biochemical Outcome	Normokalaemia Normal ARR	Normokalaemia Normal ARR	Normokalaemia Normal ARR	Normokalaemia Normal ARR	Normokalaemia Normal ARR	Normokalaemia Normal ARR	Normokalaemia Normal ARR	Normokalaemia Normal ARR
Clinical Outcome	HBP controlled with Nifedipine 2 DDD	HBP controlled with Nifedipine 2DDD,	Normal BP without drugs	Normal BP without drugs	HPB: Irbesartan 2DDD verapamil 0.33DDD	Normal BP without drugs	Normal BP without drugs	HBP: Spironolactone 1.33DDD

PA: Primary aldosteronism, GFR: Glomerular filtration rate, SRA: Plasma renin activity, ARR: Aldosterone-renin ratio, HPB: High blood pressure, BP: blood pressure

**Patient submitted to a confirmative test, saline suppression test, with an initial result of serum aldosterone: 22 ng/dL without presenting suppression at the end of test.*

controlled hypertension with a reduction in antihypertensive medication.

Adrenalectomy had a positive impact too in the four patients who did not undergo AVC. Two patient had complete success in clinical outcome, and 2 patients had well-controlled HBP with reduction in antihypertensive medications.

Discussion

PA is an underdiagnosed pathology[2]. Its screening and diagnosis are relatively simple and should be considered in all patients with early HBP, resistant HBP or HBP associated with hypokalaemia[4]. However, a low index of suspicion among doctors and limited access to tests (serum aldosterone, plasma renin activity or concentration, and computed tomography) could make detection difficult[5].

The Endocrine Society guidelines suggest using the plasma aldosterone-renin ratio (ARR) for PA screening[7]. Patients with elevated RAR should undergo confirmatory tests[7].

However, in the clinical setting of spontaneous hypokalaemia, low plasma renin concentration or activity, and plasma aldosterone concentration (PAC) >20 ng/dL; or in patients without spontaneous hypokalaemia, but with low renin concentration and plasma aldosterone concentration >30 ng/dl, it excludes the need to develop confirmatory tests[12]. In our case series, of 7 out of 8 patients not only presented hypertension, spontaneous hypokalaemia, and low renin, but also a PAC > 20 ng/dl with low renin, so no confirmatory tests were used.

Computed tomography (CT) is the initial imaging study in patients with PA. It is a study with high sensitivity to detect adrenal tumours and allows to rule out adrenal carcinoma, but it has low specificity for functional nodules and those smaller than 1 cm due to the high prevalence of adrenal incidentalomas[13]. PET-CT with 11C-methomidate is a sensitive method and specific for the diagnosis of adrenocortical carcinoma, as well as a non-invasive alternative in the evaluation of PA[14,15]. Different predictive scores have been proposed to improve the diagnostic approach without resorting to confirmatory and/or invasive tests. Burello proposed the PA confirmatory test (PACT) score and found that male sex, antihypertensive medication, plasma renin level, aldosterone, potassium levels, and the presence of target organ damage, were associated with a confirmatory diagnosis of PA[16].

The identification of unilaterality or bilaterality is crucial for the therapeutic approach, which is why it is recommended to perform the AVC to determine the laterality of the aldosterone hypersecretion[17]. However, the prospective SPARTACUS study designed to compare the CT-based diagnostic approach versus the AVC, found no difference[19]. In addition, it is recognized that there are different protocols to perform the AVC depending on the experience as well as the availability of resources in each specialized centre or country. In our case series, 87.5% of adrenal lesions had typical characteristics of adenoma measuring at least 10mm on CT. Six of our patients were older than 35 years. In this age group, non-functioning unilateral adenomas are not uncommon, which can be indistinguishable from APA by CT, and AVC would be the study of choice to determine the lateralization of the PA[8]. AVC was performed in 4 patients, of which 3 had a Küpers score equal or greater than 5.

Previous studies found that, in patients younger than 40 years, typical adenomas of at least 10 mm on CT are associated with lateralization in the ACV[10]. In our study, of 4 patients who underwent AVC, 2 of them had BAH with adenomas larger than 10 mm on CT, a Küpers score > 5, and lateralization in the ACV. The other 2 patients presented discordant results. A 50-year-old male patient with mild left adrenal enlargement and a Küpers score <5, lateralized to the left in the AVC, with a nodular hyperplasia pathology and clinical improvement after left adrenalectomy; and in another 70-year-old female patient who presented a left adenoma smaller than 1 cm with a Küpers score > 5, lateralized to the left in the AVC, with a pathology of multifocal cortical nodular hyperplasia that responded to left adrenalectomy. Both were considered as unilateral adrenal hyperplasia. In the SPARTACUS study, BP control was considered the primary outcome, and clinical improvement is considered the gold standard for diagnostic and therapeutic procedures[19]. Clinicians also use the PASO score to predict clinical outcome and differentiate patients cured by surgery from those who need follow-up.

In our case series, the Küpers score predicted adequate lateralization in 3 out of 4 patients who underwent AVC, and the surgical decision was based on the laterality indicated by the AVC. The HBP remitted or improved with a reduction of pharmacological requirements and a remission of hypokalaemia after the adrenalectomy, indicated that the location of unilaterality was correct[20]. Two patients with Küpers score >5 presented pathology that revealed adrenocortical adenoma and remission of HBP, hypokalaemia and altered ARR. One patient with Küpers score <5 presented pathology that revealed nodular hyperplasia, and 1 patient with Küpers score of 5 presented nodular hyperplasia. In patients who did not undergo AVC, the Küpers score also predicted adequate lateralization in 3 out of 4 patients. These patients with Küpers score >5 presented pathology that revealed adrenocortical adenoma. Among the limitations of the study, we recognize: first, the number of patients included is low; second, it is a retrospective study, as we took data from medical records.

Conclusion

Küpers score could be a useful tool in the evaluation of patients with PA to discriminate unilateral from bilateral aldosteronism in patients with a typical Conn's adenoma.

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