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Original article

Hypertension Caused by Primary Hyperaldosteronism: Increased Heart Damage and Cardiovascular Risk

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ABSTRACT

Introduction and objectives: Primary hyperaldosteronism is the most common cause of secondary hypertension. Elevated aldosterone levels cause heart damage and increase cardiovascular morbidity and mortality. Early diagnosis could change the course of this entity. The objective of this report was to study the clinical characteristics, cardiac damage and cardiovascular risk associated with primary hyperaldosteronism.

Methods: We studied 157 patients with this diagnosis. We analyzed the reason for etiological investigation, and the routinely performed tests, including echocardiography. We used a cohort of 720 essential hypertensive patients followed in our unit for comparison.

Results: Compared with essential hypertensive patients, those with hyperaldosteronism were younger (56.9 [11.7] years vs 60 [14.4] years; $P<.001$), had higher blood pressure prior to the etiological diagnosis (136 [20.6] mmHg vs 156 [23.2] mmHg), more frequently had a family history of early cardiovascular disease (25.5% vs 2.2%; $P<.001$), and had a higher prevalence of concentric left ventricular hypertrophy (69% vs 25.7%) and higher cardiovascular risk. Specific treatment resulted in optimal control of systolic and diastolic blood pressures (from 150.7 [23.0] mmHg and 86.15 [14.07] mmHg to 12.69 [15.3] mmHg and 76.34 [9.7] mmHg, respectively). We suspected the presence of hyperaldosteronism because of resistant hypertension (33.1%), hypokalemia (38.2%), and hypertensive crises (12.7%). Only 4.6% of these patients had been referred from primary care with a suspected diagnosis of hyperaldosteronism.

Conclusions: Hyperaldosteronism should be suspected in cases of resistant hypertension, hypokalemia and hypertensive crises. The diagnosis of hyperaldosteronism allows better blood pressure control. The most prevalent target organ damage is left ventricular hypertrophy.

Hipertensión por hiperaldosteronismo: más lesión cardiaca, mayor riesgo cardiovascular

Palabras clave:
Hiperaldosteronismo primario
Hipertensión arterial secundaria
Hipertrofia ventricular izquierda
Crisis hipertensivas

RESUMEN

Introducción y objetivos: El hiperaldosteronismo primario es la causa de hipertensión arterial secundaria más frecuente. Las concentraciones de aldosterona elevadas producen daño cardiaco y mayor morbimortalidad cardiovascular, por lo que un diagnóstico precoz modificará su evolución. El objetivo es estudiar las características clínicas, la repercusión cardiaca y el riesgo cardiovascular en el hiperaldosteronismo primario.

Métodos: Se estudió a 157 pacientes con este diagnóstico. Se revisó el motivo del estudio y las exploraciones complementarias, ecocardiograma incluido. Como comparador se utilizó una cohorte de 720 pacientes con hipertensión arterial esencial seguida en nuestra unidad.

Resultados: Los pacientes con hiperaldosteronismo eran más jóvenes que los hipertensos esenciales ($56{,}9 \pm 11{,}7$ frente a $60 \pm 14{,}4$ años; $p < 0{,}001$) y tenían presiones arteriales previas al diagnóstico etiológico mayores ($136 \pm 20{,}6$ frente a $156 \pm 23{,}2$ mmHg), más antecedentes de enfermedad cardiovascular precoz (el 25,5 frente al 2,2%; $p < 0{,}001$), mayor prevalencia de hipertrofia ventricular concéntrica (el 69 frente al 25,7%) y mayor riesgo cardiovascular. El tratamiento específico permitió el óptimo control de las presiones arteriales sistólica y diastólica (de $150{,}7 \pm 23{,}0$ y $86{,}15 \pm 14{,}07$ mmHg a $127{,}69 \pm 15{,}3$ y $76{,}34 \pm 9{,}7$ mmHg). Motivaron el estudio de hiperaldosteronismo: hipertensión resistente (33,1%), hipopotasemia (38,2%) y crisis hipertensivas (12,7%). Sólo el 4,6% de los pacientes llegaron remitidos desde atención primaria con diagnóstico de sospecha de hiperaldosteronismo.

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Conclusiones: Debe sospecharse hiperaldosteronismo en pacientes con hipertensión resistente, hipopotasemia o crisis hipertensivas. El diagnóstico de hiperaldosteronismo permite un mejor control de la presión arterial. La hipertrofia ventricular izquierda es la lesión de órgano diana más frecuente.

Abbreviations

HT: hypertension
HTU: hypertension unit
LVH: left ventricular hypertrophy
PHA: primary hyperaldosteronism

INTRODUCTION

Aldosterone, the major and most powerful mineralocorticoid hormone in humans, is synthesized from cholesterol in the adrenal cortex[1] and governs the physiological control of renal electrolyte balance.[2] In healthy individuals, one of the effects of aldosterone is to maintain an optimal balance, which helps to preserve a healthy vascular system. However, when this balance is upset, the beneficial effects of aldosterone are lost and those that are detrimental to the vascular system predominate, leading to organ dysfunction[3] and hypertension (HT).

Currently, the prevalence of primary hyperaldosteronism (PHA) is much higher than the previously accepted rate, less than 1% of the hypertensive population, and in the specialist setting, may be over 10%.[4] The prevalence of PHA reported in Spain is between 5.1% and 6%[5,6] in internal medicine and cardiology units.

PHA is the most common endocrine cause of secondary HT.[7] This condition includes a variety of disorders characterized by an overproduction of aldosterone that is relatively independent of the renin-angiotensin-aldosterone system and is not suppressed with sodium overload.[8] This overproduction of aldosterone causes damage to the cardiovascular system, suppression of plasma renin, HT, sodium retention, and potassium excretion, which leads to hypokalemia. Prolonged exposure to high plasma aldosterone concentrations is associated with greater oxidative stress, cardiovascular remodeling, hypertrophy, and fibrosis.[9] This hormone is also involved in collagen synthesis and produces vascular remodeling and myocardial fibrosis in a process that is independent of its effect on arterial blood pressure (BP).[10,11]

All of the above translates into higher rates of cardiovascular morbidity and mortality in patients with PHA compared with essential hypertensive patients matched for age, sex, and BP.[12]

Moreover, aldosterone plays an important role in carbohydrate metabolism, with direct effects on pancreatic beta cells[13] and on insulin signaling,[14] and thus contributes, through its role in endothelial dysfunction, to the metabolic syndrome which, in turn, exerts its effect on the development of refractory HT and cardiovascular disease.[15] Indeed, a higher incidence of cases of metabolic syndrome has been documented in PHA.[16]

For all these reasons, some authors have postulated that screening should be performed in all hypertensive patients,[17] even in the context of mild HT, when there is no hypokalemia or family history, since the later the diagnosis, the longer the exposure to high aldosterone concentrations and the greater the likelihood of irreversible morphological changes.

PHA has classically been characterized as an uncommon disease with a benign course that is suspected only in the presence of hypokalemia. This profile has changed substantially due to findings published in recent years. The prevalence of PHA can be as high as 10% among hypertensive patients,[4] and some reports show that hyperkalemia is present in approximately half of cases of PHA and that the cardiovascular risk of these patients is higher.[10,11]

Objectives

Given the importance of this secondary cause of HT and the small number of published studies on the subject, we proposed to:

- Determine the characteristics of patients with PHA in terms of the reason for performing etiological study, as well as the clinical and biochemical picture, morphological pattern, and profile of the disease course in those individuals diagnosed with this disease in the Hypertension Unit (HTU) of *Hospital Clínico San Carlos* in Madrid, Spain.
- Assess the cardiac and renal damage and cardiovascular risk of patients with PHA.
- Compare the clinical profile of patients with PHA with that of a cohort with essential HT from our HTU.

METHODS

For this retrospective study, we selected 172 patients from the HTU who had been diagnosed with PHA between 1983 and March 2010. Of the 172 patients selected, we enrolled 157 who met the following inclusion criteria for the diagnosis of PHA: *a)* aldosterone concentration above the mean, with suppressed plasma renin activity and an aldosterone (ng/dL) to renin (pg/dL) ratio greater than 38, and evidence of abnormal adrenal anatomy (hyperplasia or adenoma) according to imaging techniques; *b)* demonstration, by means of scintigraphy with radiolabeled cholesterol, of functional activity, despite pharmacological suppression, and/or *c)* in those in whom the possibility of surgical treatment was evaluated, demonstration of the lateralization of aldosterone secretion in adrenal vein sampling, with determination of the aldosterone and cortisol concentrations, prior to the invasive procedure.

For comparison, we used a population of 720 patients with essential HT[18] in representation of the hypertensive population being followed in our HTU.

Patients with incomplete data on the results of circulating renin:aldosterone determination or missing results of imaging study were excluded (n=15).

Office BP was measured using validated devices and by personnel trained according to the guidelines proposed by the European Society of Hypertension.[19] BP was recorded both on arrival at the HTU and during the visit following diagnosis and the initiation of specific treatment. The personal data and anthropometric measurements, personal and family history of cardiovascular disease and risk factors, and time interval since the diagnosis of HT were collected from the medical records. In addition, we recorded the reason for investigating secondary HT that led to the