Case Report

Conn's Adenoma. A Cause of Hypertension and Hypokalemia

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Secondary hypertension accounts for approximately 5 to 10% of the causes of arterial hypertension, among which primary hyperaldosteronism has an incidence ranging from 0.05 to 2% in hypertensive individuals with characteristic findings of hypokalemia, increased production of aldosterone, a reduction or suppression in renin, an increased aldosterone/renin ratio, and metabolic alkalosis. We report the case of a patient with controlled primary arterial hypertension, who evolved with adrenal adenoma and worsening of blood pressure levels.

The aldosterone-producing adenoma (aldosteronoma) is the most important cause of hyperaldosteronism and represents one of the few curable causes of secondary arterial hypertension. The patients may be asymptomatic or oligosymptomatic with symptoms resulting from hypertension itself or from the complications generated by hypokalemia (polyuria, nocturia, muscle cramps, excessive muscle weakness, paresthesias, tetany, and even muscle paralysis). The aldosterone-producing adenoma is characterized by arterial hypertension, hypokalemia, excessive urinary excretion of potassium, and metabolic alkalosis. We report the case of a patient with evolving primary hypertension for 31 years, who had satisfactory control over blood pressure and developed secondary hypertension with accentuated worsening of blood pressure levels.

Case report

The patient was a 52-year-old white female, married, housewife, born in the city of Potirendaba, in the State of São Paulo, and residing in the city of Nova Itapirema, in the State of São Paulo, who denied any health problems, except for palpitation crises for the preceding 31 years. She sought medical care, when arterial hypertension was diagnosed, and hydrochlorothiazide (50 mg/day) and methyldopa (1.5 g/day) were prescribed. Satisfactory blood pressure control was achieved, as indicated by ambulatory blood pressure monitoring (ABPM) performed in 1992 (fig. 1). The laboratory tests for assessing arterial hypertension were normal (potassium, creatinine, glycemia, total cholesterol, triglycerides, type I urine, and electrocardiography) at that time.

In 1999, the patient was using hydrochlorothiazide and methyldopa, but, as blood pressure control deteriorated, the prescription was changed to indapamide (2.5 mg/day), perindopril (4 mg/day), and nadolol (80 mg/day). However, no satisfactory blood pressure control was achieved, and the patient began to complain of intense weakness characterized by the incapacity to perform her normal activities, such as sweeping the floor, washing the clothes, and even answering the phone.

The patient reported the following personal antecedents: arterial hypertension for 31 years, gastritis for 8 years, and hypertriglyceridemia for 4 years. The patient denied having diabetes mellitus, Chagas' disease, stroke, acute myocardial infarction, or any other disease.

In regard to familial antecedents, the patient reported 4 hypertensive paternal uncles, 2 with deep venous thrombosis, 1 with myocardial infarction, and another with stroke. Her mother was hypertensive.

On physical examination, the patient was in regular general condition, eupneic, afebrile, acyanotic, hydrated, and with healthy coloring. Her pulse was 76 bpm; her BP in the sitting position (right upper limb) was 170/110 mmHg; her BP in the supine position (right upper limb) was 190/120 mmHg; her BP in the supine position (left upper limb) was 180/120 mmHg; and her BP in the standing position (right upper limb) was 170/110 mmHg.

On auscultation, her lungs were clear with no rales. Her heart auscultation showed regular cardiac rhythm with cardiac sounds of normal intensity and no murmurs. Her heart rate was 76 bpm. Her abdomen showed hydro-aerial noise, no visceromegaly, and no abdominal murmur. Her lower limbs showed symmetric palpable pulses and no edema.

Differently from the normal results of the various measurements of serum potassium in 1999, potassium levels were extremely altered (K^+= 1.5 mEq/L; normal = 3.5 – 5.3), and the patient was using indapamide, perindopril, and nadolol. All other routine laboratory tests were within the normal range (glycemia, creatinine, total cholesterol, and urinary sediment). Chest X-rays showed a normal cardiac area with no alterations in the pulmonary parenchyma. The electrocardiogram showed sinus rhythm and an alteration in ventricular repolarization of the anterolateral wall. The echocardiogram showed left ventricular hypertrophy (IVS = 13; LVPW = 13; LV mass = 292.8 g; LV mass index = 160.9 g/m^2).

The laboratory finding of important hypokalemia drew attention to the following 2 situations: hypokalemia secondary to the use of

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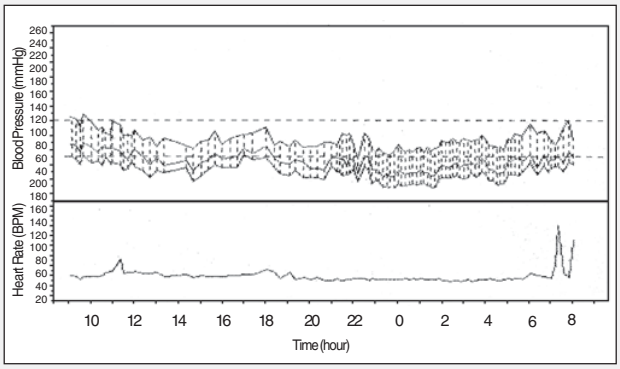

Fig. 1 - Ambulatory blood pressure monitoring performed in 1992 showing 24-hour blood pressure control with a mean blood pressure level of 113/67 mmHg, presence of nocturnal decrease, and 5% systolic and diastolic blood pressure load during wakefulness.

diuretic or hypokalemia due to primary hyperaldosteronism aggravated by the use of the diuretic. Based on this, a diagnostic investigation was carried out.

The measurements of sodium and potassium in the 24-hour urine were 192 mEq/L (normal = 50 to 250 mEq/L) and 59 mEq/L (normal = 25 to 125 mEq/L), respectively. With the suspension of indapamide, the clinical findings of the patient and her serum potassium levels significantly improved with no replacement (K^+= 3.2 mEq/L). The measurements of Na^+ and K^+ in the 24-hour urine after 10 days of no diuretic use were 135 mEq/L and 24 mEq/L, respectively. The plasma renin level was 0.6 ng/mL/h and aldosterone level was 56.2 ng/100 mL (normal = 1-16 ng/100 mL), the aldosterone/renin ratio being 93.6. Another ABPM was performed (fig. 2). The arterial blood gas analysis was as follows: pH = 7.50; pO_2 = 90; pCO_2 = 35; HCO_3 = 30 mEq/L; BE = + 6.0; O_2 Sat = 98%.

After using 100 mg/day of spironolactone + 5mg/day of amlodipine + 80 mg/day of nadolol, the BP normalized (BP = 130/90 mmHg), the asthenia and weakness significantly improved, and the serum levels of Na^+ and K^+ were 147 mEq/L and 4.8 mEq/L, respectively.

The patient underwent abdominal ultrasonography and tomography, which showed a nodular image in the right adrenal topography measuring approximately 1cm in diameter (fig. 3). The patient was referred to the endocrinology surgery service and underwent exeresis of the right adrenal gland and the gallbladder. The adrenal gland weighed 7.2 g and measured 4.7 x 4.5 x 1.5 cm. On sectioning, a single, well-delimitated, orangish nodule measuring 1.5 cm in diameter was revealed (fig. 4). Histologically, the adrenal gland showed an encapsulated epithelial neoplasia with cells of abundant clear cytoplasm and occasional bizarre nuclei; however, no mitoses were found (fig. 5). The anatomicopathological diagnosis was adenoma of the adrenal gland.

Approximately 3 years after surgery, the patient remains clinically stable using 1.5 mg/day of indapamide and nadolol and has adequate control over blood pressure levels observed on ABPM, with a mean blood pressure level of 138/71 mmHg during 24 hours (fig. 6).

Discussion

Our patient had a history of long-term arterial hypertension with satisfactory control over blood pressure levels during 24 hours

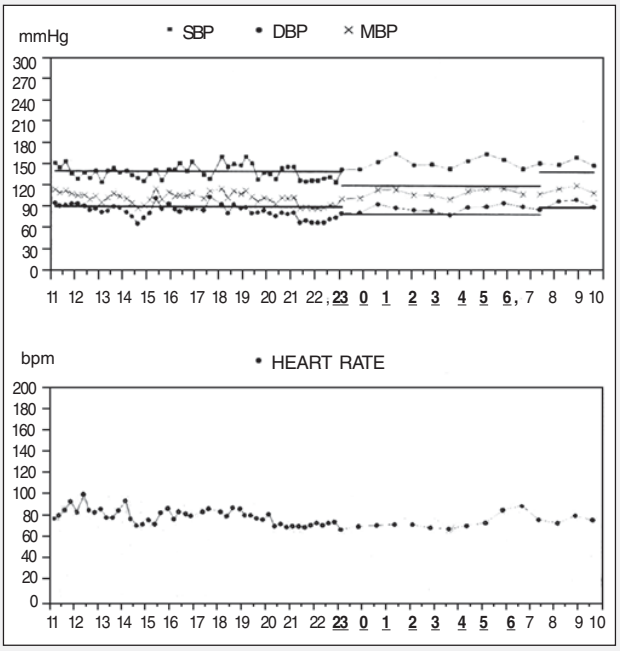

Fig. 2 - Ambulatory blood pressure monitoring showing blood pressure oscillation with levels above normality during wakefulness and sleep, a mean blood pressure level in 24 hours of 142/85 mmHg, no nocturnal decrease, 44% systolic blood pressure load during wakefulness, and systolic and diastolic blood pressure load during sleep of 100% and 91%, respectively.

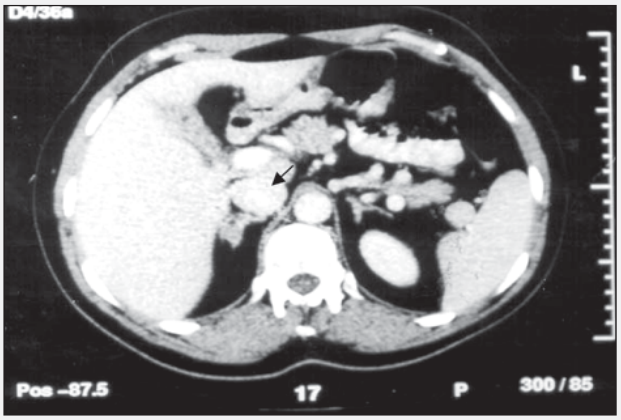

Fig. 3 - Tomographic section of the abdomen, showing a nodular image in the right adrenal topography, enlarging the adrenal gland (arrows).

as shown on the ABPM performed in 1992 (fig. 1), which favors the initial diagnosis of controlled primary hypertension, despite its beginning at an age suggesting secondary hypertension. That was not investigated, because the results of the basic laboratory tests (potassium, glycemia, total cholesterol, triglycerides, type I urine, and electrocardiography) were within the normal range. In addition, the patient had a favorable response to the treatment used, with normalization of blood pressure levels, and these criteria rendered the hypothesis of secondary hypertension very remote at that time. The lack of blood pressure control with elevated levels of arterial blood pressure detected in 1999 together with intense weakness, adynamia, and significant hypokalemia led us to consider a cause of hypertension secondary in origin superimposed on primary hypertension. It is worth noting that the patient did not have hypokalemia during the initial follow-up at our service, another fact contrary to the presence of hypertension due to primary or secondary hyperaldosteronism, on that occasion. On the other

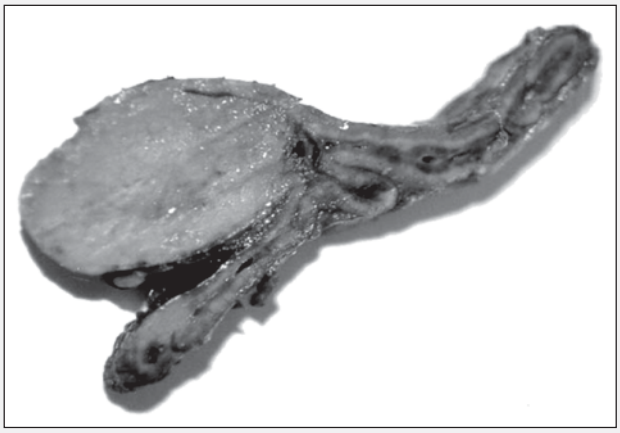

Fig. 4 - Gross appearance of the adrenal gland and gallbladder. Adrenal gland measuring 4.7 x 4.5 x 1.5 cm with a single nodule of 1.5 cm in diameter. The gallbladder showed no alterations.

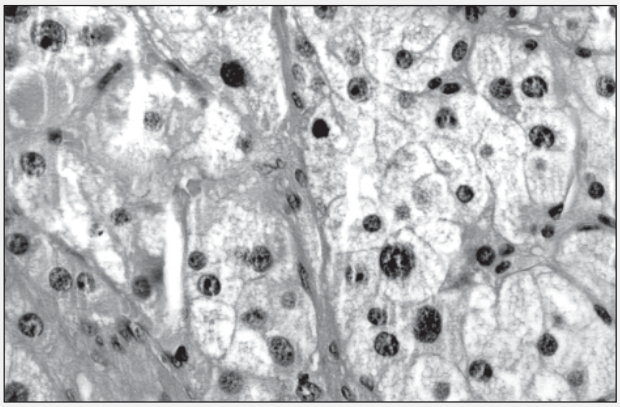

Fig. 5 - Microscopic appearance of the adrenal gland. Note the encapsulated epithelial neoplasia with cells of abundant clear cytoplasm and occasional bizarre nuclei. The anatomicopathological diagnosis was adenoma of the adrenal gland. HE, 400X.

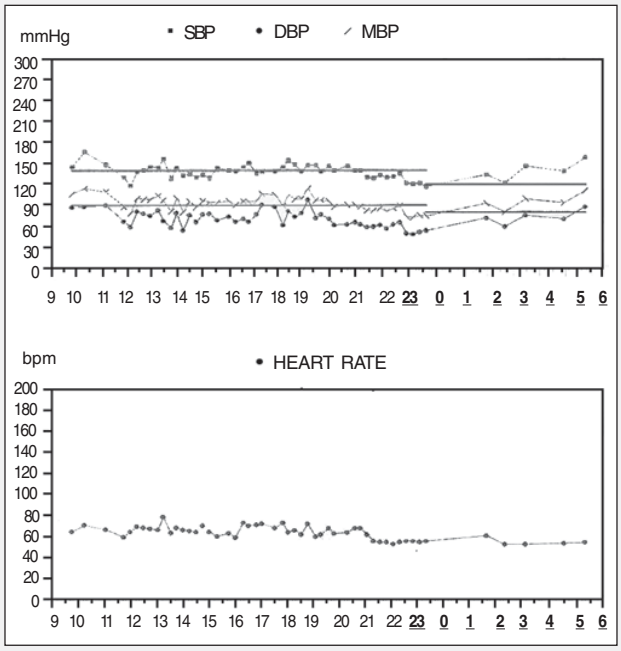

Fig. 6 - Ambulatory blood pressure monitoring performed after exeresis of the adrenal gland. Note the more satisfactory 24-hour control of blood pressure (mean = 138/71 mmHg), attenuation of the nocturnal decrease, and systolic blood pressure load during sleep (83%).

hand, the severe diuretic-induced hypokalemia, more discrete after suspension of the diuretic, was suggestive of hyperaldosteronism. The following factors pointed to the diagnosis of primary hyperaldosteronism, which was confirmed on abdominal tomography: use of spironolactone with good control of arterial blood pressure and normalization of potassium levels; urinary potassium level > 30 mEq/L/24 hours; metabolic alkalosis due to an increase in the serum level of bicarbonate resulting from the urinary loss of potassium and hydrogen ions; and elevated plasma aldosterone with hyporeninemia.

The aldosterone-producing adenoma (aldosteronoma), the most important cause of hyperaldosteronism (60% of the cases), was first reported by Conn in 1955 [1,2]. Currently, it is one of the few potentially curable causes of arterial hypertension. These tumors are usually small (less than 2cm in diameter) and benign, have a yellowish capsule, and different adrenal cell types visible on microscopy [3,4]. After Conn's report, several other causes of hyperaldosteronism were reported, such as idiopathic hyperaldosteronism, and bilateral (20 to 40% of the cases) [1,3,5] or unilateral (less frequently) adrenal hyperplasia [6,7]. The occurrence of adrenocortical carcinoma is rare, and only a few patients with ectopic aldosterone-producing tumors have been reported [8]. Genetic forms of hyperaldosteronism responsive to glycocorticoids occur as a dominant autosomal inheritance [3].

The incidence of primary aldosteronism ranges from 0.05 to 2% of the hypertensive population [4,9-16]. Some patients are completely asymptomatic or have minimum symptoms resulting from hypertension (ex: headache) and hypokalemia (polyuria, nocturia, muscle cramps). Occasionally, excessive muscle weakness, paresthesias, tetany, and even muscle paralysis may occur [1,3,4]. Usually, primary aldosteronism is characterized by hypertension, hypokalemia, excessive urinary excretion of potassium, hypernatremia, and metabolic alkalosis [4].

The following are the 10 major situations in which primary hyperaldosteronism should be suspected [13,14]: 1) spontaneous hypokalemia (K< 3.5 mEq/L); 2) severe hypokalemia (K< 3.0 mEq/L) or diuretic-induced hypokalemia; 3) difficulty in maintaining normal potassium levels despite the concomitant use of supplements or potassium-sparing diuretics; 4) potassium levels that do not normalize 4 weeks after suspending the diuretic; 5) refractory hypertension; 6) satisfactory therapeutic response to spironolactone regarding blood pressure levels and serum and urinary potassium levels; 7) elevated plasma aldosterone levels (> 20 ng/mL); 8) inadequate kaliuresis (urinary potassium > 30 mEq/L); 9) renin < 1 ng/mL/h; and 10) presence of a tumor image in the adrenal gland on tomography.

Although the presence of spontaneous hypokalemia in a hypertensive patient is a strong indicator of aldosteronism, less than 20% of the patients with primary hyperaldosteronism have potassium levels below normal, while other hypertensive patients have hypokalemia without primary aldosteronism, a fact that may be explained by the use of diuretics or by the presence of secondary hyperaldosteronism [3].

The activity of plasma renin is suppressed in most patients with untreated primary hyperaldosteronism and in some patients with primary hypertension [15], while in secondary hyperaldosteronism, renin plasma levels are elevated. Currently, measurement of serum potassium and plasma renin is recommended as the most reliable method for the initial investigation of primary hyperaldosteronism [3,16].

The relation between plasma aldosterone and plasma renin activity in untreated hypertensive individuals remains the most accepted screening test for distinguishing patients with primary hypertension from those with primary aldosteronism; the cut off point remains around 30 or 50 in most cases with primary aldosteronism [11,12,16,17].

Recent reviews [3,13,16] recommend that all spontaneous or diuretic-induced hypokalemia should be investigated. Patients with difficult to control hypertension and low serum potassium levels (≤ 3.5 mEq/L) should be assessed, and a plasma aldosterone/plasma renin ratio greater than 30 indicates that a more detailed evaluation should be undertaken [3].

The definitive biochemical diagnosis of aldosteronism may also be established with both the inhibition and stimulation of the secretion of renin and aldosterone using physiological maneuvers of sodium overload and depletion, respectively. In hypertensive patients (with no treatment or 2 weeks after suspension of medications), a high aldosterone urinary excretion rate with a sodium-rich diet (2 to 3 g of salt in each meal for 2 or 3 days) or a high aldosterone level after intravenous infusion of saline solution, together with a low renin activity in conditions of low sodium consumption or use of a diuretic, are highly suggestive of primary hyperaldosteronism [3,5].

In conclusion, primary aldosteronism is the generic term for a series of disorders associated with a chronic excess of aldosterone. The most common cause is a solitary aldosterone-producing adenoma. Hypertensive patients complaining of weakness and malaise are not rarely labeled as having a somatoform disorder, being referred to mental health care professionals. Our patient had a history of 31 years of hypertension, which was adequately controlled until 1999. The diuretic-induced hypokalemia, which in our case was indapamide at the dosage of 2.5 mg/day (the only available dose on the market at the time), led us to consider the possibility of secondary hypertension (primary hyperaldosteronism) and to proceed with the investigation for its diagnosis. The therapeutic test with the use of spironolactone normalized blood pressure, which per se is an important presumptive fact of excessive aldosterone levels.

In the postoperative period, the patient evolved with adequate blood pressure control, according to ABPM (fig. 6), with low doses of 2 antihypertensive drugs. It is worth noting that secondary hypertension is not equivalent to curable hypertension in all cases. The use of antihypertensive drugs may be reduced or even eliminated in hypertensive individuals, when a curable cause is found. However, later, some patients with primary hypertension may have stenosis of the renal artery or associated aldosterone-producing adrenal adenoma, and, in these cases, despite the removal of the secondary cause, BP does not normalize. This is due to the existence of a component of subjacent "essential" (primary) hypertension, with a possible structural and functional alteration already in place, which justifies the later use of antihypertensive drugs for blood pressure control, as occurred in the present case. The characteristics that help in identifying individuals with a greater chance of remaining hypertensive after an intervention in cases of secondary arterial hypertension, include the more advanced age of the patient, known duration of hypertension longer than 5 years, and familial history of hypertension in first-degree relatives. These characteristics were found in the history of our patient with primary hyperaldosteronism.

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