Primary hyperaldosteronism sensitive to glucocorticoid treatment

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Abstract

The authors describe the clinical case of a female patient with arterial hypertension, secondary to primary aldosteronism which proved to respond to treatment with glucocorticoid steroids. Emphasis is placed on the sequence of complementary tests leading to the final diagnosis, as well the contribution that ambulatory blood pressure monitoring had, in the process of diagnostic evaluation and efficient therapeutic control.

Key words: arterial hypertension, hyperaldosteronism, glucocorticoids, ambulatory blood pressure monitoring.

Introduction

The relationship between arterial hypertension (AHT), the incidence of cerebrovascular disease (CVD) and coronary artery disease (CAD) has been investigated in various studies. One particularly convincing demonstration of this association was provided by McMahon and collaborators who showed that the higher the blood pressure (BP) the greater the risk of CVD, CAD and premature death.[1] The risk associated with AHT is not immutable and can be reduced with antihypertensive therapy.[2] As a result, there has been growing and widespread interest in improving its detection, diagnosis, treatment and control.

Hypertension, hypokalaemia, suppressed plasma renin activity and increased aldosterone excretion are characteristics of primary hyperaldosteronism syndrome, which was first described in 1955. Subsequent experience has identified various subtypes of this entity: unilateral aldosterone-producing adenoma (APA), idiopathic adrenal hyperplasia (IAH), glucocorticoid-remediable hyperaldosteronism, angiotensin-sensitive aldosterone-producing adenoma, primary adrenal hyperplasia, and aldosterone-producing adrenocortical carcinoma.[3]

Glucocorticoid-remediable hyperaldosteronism is a rare form of adrenal hyperplasia in which the hypersecretion of aldosterone can be reversed by glucocorticoid therapy.[4,5] Normal individuals synthesize aldosterone in the glomerular zone, but not in the ACTH-sensitive fasciculata zone. One the other hand, in patients with glucocorticoid-remediable hyperaldosteronism, aldosterone production occurs in the ACTH-sensitive fasciculata zone. The primary defect in the majority of families with this disease is a hybrid gene in chromosome 8, in the region that regulates 11b-hydroxylase (the enzyme that promotes the conversion of deoxycortisol to cortisol), the coding sequences of the aldosterone synthase gene.[6-10]

Case report

On the 28th November 1995, a female patient, 33 years of age, married, employed as a cook and living in Cantanhede, a district of Coimbra, went, on her own initiative, to the Emergency Services at the Coimbra Hospital Center (CHC) with paroxystic appearance of palpitations, sweating, headache, dizziness and precordial chest discomfort. Physical examination detected high blood pressure (190/100 mmHg) and a degree II/VI diastolic heart murmur. Complementary diagnostic exams showed hypokalaemia (3.0 mmol/L).

A previous history of arterial hypertension was diagnosed in 1992 when she went to the Emergency Service of her local Central Hospital presenting the same

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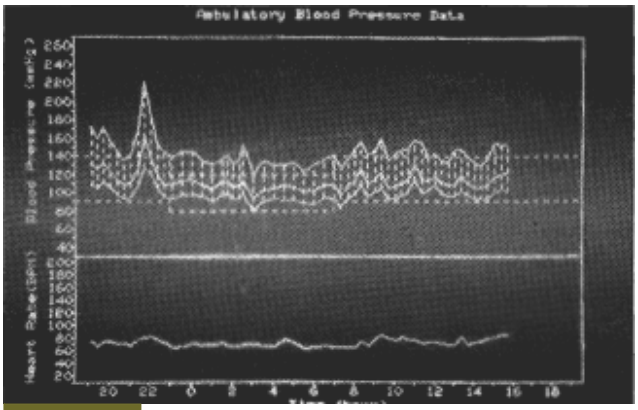
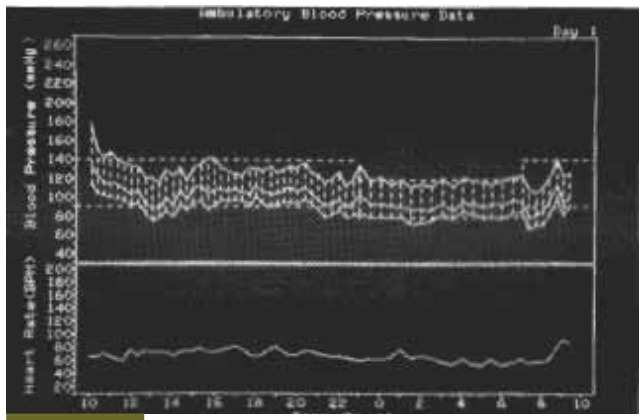
Received for publication on the 2nd Sept 1996



ABPM. 1



ABPM. 2

symptoms. After observation, she was discharged, medicated with an angiotensin-converting enzyme inhibitor (ACEI), lisinopril 5 mg/day, associated with an anxiolytic. Two years later, on the advice of the attending physician, treatment was discontinued. She remained asymptomatic and with blood pressure well under control until a week before she came to our hospital when a new symptomatic episode led her to seek emergency treatment at the city hospital. After observation, she was discharged, medicated with an ACEI – lisinopril 20 mg/day. There was no additional personal history.

Family history: parents and a sister without any history of hypertension, two apparently healthy brothers, long-term emigrants in Switzerland who are difficult to contact. Three children, two female and one male, 15, 8 and 13 years old respectively.

On the day of admission, pressurometry was performed to obtain serial measurements (ABPM 1), recorded as follows: average systolic pressure of 146 mmHg, average diastolic pressure of 98 mmHg, maximum systolic pressure of 221 mmHg, maximum diastolic pressure of 128 mmHg and a blood pressure load of 96.5% for diastolic pressure and 80.7% for systolic pressure.

Additional tests were performed to confirm a suspicion of primary hyperaldosteronism (PHA), rule out other causes of secondary hypertension, evaluate impact to target organs, and rule out other risk factors associated with cardiovascular disease: serum ionogram with sodium level of 139 mmol/L and potassium level of 3.1 mmol/L; urine ionogram (24 hr. urine sample) with sodium level of 87.4 mmol/L and potassium level of 40.13 mmol/L; serum aldosterone 37.8 ng/dL (NV at lying down:1-16 ng/dL) and active renin 4.4 pg/mL (NV lying down: 3.0-28.2 pg/mL); arterial gasometry normal; serum creatinine 58 mmol/L (NV: 53-115); type-II urine normal; renal and adrenal ultrasounds normal; vanilmandelic acid with a value of 9.67 mg/24 hr. urine sample (NV< 10mg/24 hr.), fundoscopy normal; microalbuminuria 27.8 mcg/min (NV<15 mcg/min); ECG SR 70/m normal; echocardiogram: mild to moderate aortic regurgitation and good overall systolic function; glycaemia 81 mg/dL; total cholesterol 193 mg/dL; triglycerides 47.8 mg/dL; HDL cholesterol 72 mg/dL; LDL cholesterol 111 mg/dL; body mass index 24.4.

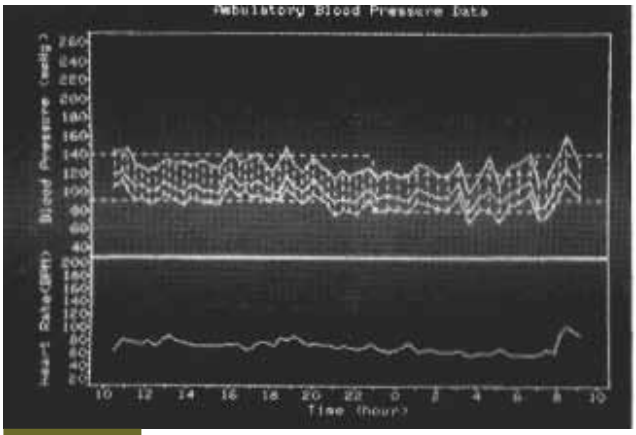
Additional tests were performed in a second phase to determine the primary hyperaldosteronism sub-type:

Postural test: measurements at rest (at 8 am) of serum aldosterone 26.6 ng/dL (NV 1-16 ng/dL), active renin 12.5 pg/mL (NV 3.0-28.2 pg/mL, and serum cortisol 13.7 mcg/dL (NV 5-25 mcg/dL), and after 4 hours in a standing position (at 12 pm), serum aldosterone 20.4 ng/dL and serum cortisol 7 mcg/dL. (*Graph 1*)

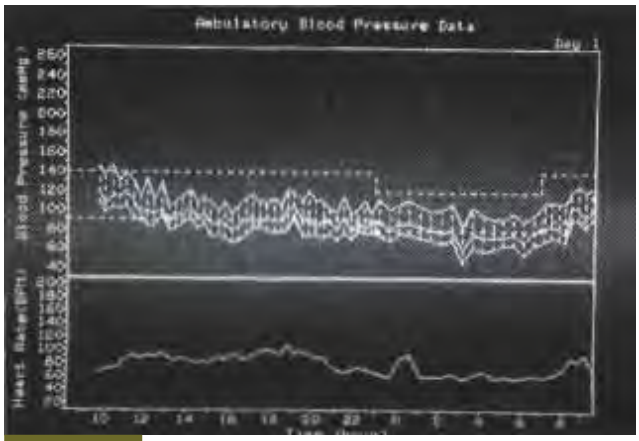
Axial computed tomography (CT) of the adrenal glands: "Slight enlargement of the proximal portion of the left adrenal gland, without the presence of any visible nodular lesion."

Nuclear magnetic resonance (NMR) of the adrenal glands: "NMR study of the adrenal glands did not reveal any morphological changes or any change in signal intensity that could be attributed to anything of pathological significance, namely, images suggesting a lesion occupying space".

Dexamethasone suppression test: Dexamethasone



ABPM. 3



ABPM. 4

was administered at 12 pm (1 mg orally) and at 6 am (0.5 mg orally). Serum aldosterone collected at 8 am had a value of 2.8 ng/dL (aldosterone<5 ng/dL for diagnostic test).[11]

Results of the postural test indicated an ACTH-sensitive PHA. CT and NMR did not identify any adenoma. The dexamethasone suppression test was compatible with glucocorticoid-remediable hyperaldosteronism.

To confirm the diagnosis, trial treatment with dexamethasone (0.5 mg every 6 hours) for three weeks was prescribed. During this period, the patient remained under clinical and laboratory surveillance by means of serial serum ionograms, monitoring of blood pressure, and ABPM administered on the eighth and twenty-first days of treatment (*ABPM 2 and 3*). Normalization of serum potassium and a significant reduction in blood pressure were verified. On the 8th day of dexamethasone treatment, *ABPM 2* showed average systolic pressure of 126 mmHg (a reduction of 20 mmHg), average diastolic pressure of 87 mmHg (a reduction of 11 mmHg) and a significant decrease in blood pressure load (-62.2% in systolic and -47.3% in diastolic pressure). It should be noted that on day 8 of the tests, the dexamethasone-induced blockage of ACTH resulted in serum cortisol values<1.0 mcg/dL and serum aldosterone of 2.4 ng/mL. Active renin was 5.4 pg/mL. On the 21st day of testing, *ABPM 3* confirmed a reduction in blood pressure (average systolic pressure of 129 mmHg and diastolic pressure of 89 mmHg) and blood pressure load (-54% for systolic and -34.8% for diastolic).

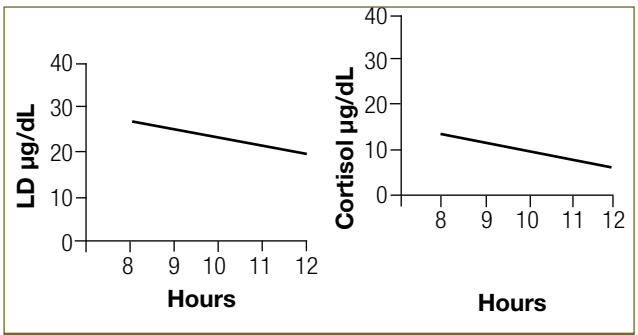
Graph 2 shows the evolution of systolic and diastolic blood pressure prior to, on the 8th and on the 21st days of dexamethasone treatment.

The patient is currently taking spironolactone, 100 mg/day. Serum potassium values are within the normal range (4.0 mmol/L at the last reading). To document perfect blood pressure control verified in routine exams, an ABPM was performed after one and a half months of diuretic therapy (*ABPM 4*). Average values of 112 mmHg for systolic pressure, 78 mmHg for diastolic pressure and a blood pressure load of less than 20% for both were documented.

Comments

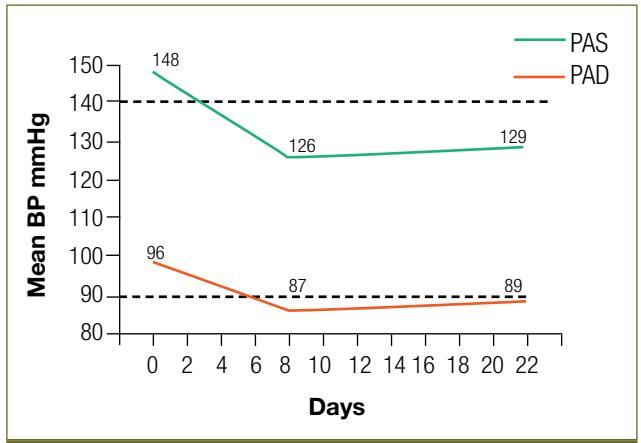
In the hypertensive population, the incidence of hypertension secondary to a PHA may be higher than the 0.05% to 2% originally estimated.[3] Recent studies in which non-selected hypertensive patients were screened based on aldosterone/renin ratios showed that 60% to 70% of patients with PHA are normokalaemic. Some centers suggest that 10% of non-selected patients with AHT may have a PHA.[10]

Since Conn's original description of a patient with hypertension, neuromuscular symptoms and hypokalaemia associated with an aldosterone-producing adrenal adenoma, it has been discovered that the same clinical and biochemical symptoms can also be produced by other situations, in which an excess of aldosterone is seen, without the existence of an adenoma.[10] This is the case with glucocorticoid-remediable hyperalderostonism, a condition characterized by hypertension, hypokalaemia, hyperaldosteronism, and suppressed plasma renin activity, and treatable with small doses of therapeutic glucocorticoid. The disorder is rare, with fewer than 100 cases reported in the literature that meet the criteria cited above.[11-13]



Postural Test.

Graph. 1



Dexamethasone 0.5 mg every 6 hours.

Graph. 2

In the case study presented here, a hypothesis of PHA was suggested by the hypokalaemia (3.0 mmol/L), within in the context of a hypertensive patient. The fact that ACEI treatment was being administered accentuated the strangeness of the findings. We prescribed a normal saline diet and discontinued the use of the ACEI, opting instead for a therapeutic anti-hypertensive with nifedipine just in case blood pressure values involving immediate risk of increased blood pressure. On the fifth day of the normal saline diet, we found persistent hypokalaemia (3.1 mmol/L) accompanied by abnormal kaliuresis (40.13 mmol/24hr).

The PHA diagnosis was confirmed by elevated plasmatic aldosterone levels (37.8 ng/dL) together with an active renin value close to the lower limit of the normal range (4.4 pg/mL). A few comments about the significance of these values follow. Classically, active renin is determined indirectly by its enzyme activity, i.e. the plasma renin activity (PRA) expressed in ng/ml/hr. This method is advantageous because it is the most widely used by, and most familiar to the majority of physicians, but it has the disadvantage of being influenced by various incubation conditions, and by the quantity of angiotensinogen present in the plasma. Some time ago, our hospital laboratory began to determine renin activity directly, by its concentration. An immunoradiometric assay of active renin concentration is not dependent on the amount of angiotensinogen present, is faster and more standardized, and should replace PRA for diagnostic purposes. The active renin value obtained is expressed in pg/ml and can be correlated with PRA by the following equation: active renin (pg/mL)=PRA (ng/mL/hr) 8.8+6.1.[14]

Using this method, the active renin value recorded is equivalent to a theoretic PRA value of 0.193 ng/mL/hr, which in practical terms, represents a marked suppression. Similarly, the active renin value of 12.5 pg/mL measured at rest in the postural test is equivalent to a PRA of 0.72 ng/mL/hr. Considering the aldosterone values measured (26.6 ng/mL), we calculate an aldosterone/PRA ratio>20, a value referred to in the literature as suggestive of PHA.[3]

APAS account for 64% of cases of PHA, while IAHs account for 32% of the remaining cases. This distinction is fundamental to the adoption of appropriate treatment.[3]

The postural test was conducted with this goal in mind: after a night of rest, at 8 am, we took blood samples to test aldosterone, active renin and cortisol levels. After 4 hours of walking, we took new blood samples to test aldosterone and cortisol levels. The reduction in serum cortisol (13.77 mcg/dl) after standing, validated the test.[3,10] The parallel decrease of serum aldosterone (26.6 20.4 ng/dL), in contrast to an increase, which is the physiological response and is also observed in patients with IAH, clearly points to an ACTH-sensitive PHA, probably an APA that was not confirmed by the imaging tests – CT an NMR.

These apparently contradictory data are, however, compatible with two rare forms of ACTH-sensitive PHA: glucocorticoid-remediable hyperaldosteronism and primary adrenal hyperplasia.[3,10]

The dexamethasone suppression test, which was the next step, revealed a serum aldosterone

level clearly below the cutoff point (<5ng/dL) which separates patients with glucocorticoid-remediable PHA from those with APA.[10] Finally, the therapeutic dexamethasone test normalized serum potassium and blood pressure readings and so confirmed the diagnosis.

The decision to use spironolactone therapy instead of corticotherapy for chronic treatment was made based on the fact that it has comparable efficiency, but with less risk of side-effects.

Ambulatory blood pressure was measured using SpaceLabs 90207 devices. We defined a daytime period from 7 am to 11 pm, with readings taken every 20 minutes, and a nighttime period from 11 pm to 7 am, with readings taken every 30 minutes. The blood pressure load was determined by the percentage of readings equal to or above 140/90 mmHg during the daytime period and 120/80 mmHg during the nighttime period. By quickly dispelling any doubts about the AHT diagnosis and by so clearly demonstrating the reduction in pressure readings under dexamethasone therapy, the ABPM proved to be a valuable technique for diagnosis. It also enabled us to determine that the dosage of spironolactone required to achieve normokalaemia was equally effective in controlling blood pressure. ■

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