CASE REPORT

Aldosterone-producing adenoma without hypertension: a report of two cases

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Abstract

Normotensive primary hyperaldosteronism is exceedingly rare. We report two new cases of this syndrome in two middle-aged women, one of Asian origin. The presenting signs were tetany in one case and an adrenal mass in the other. Neither patient had hypertension, despite repeated measurements with a manual armlet. A typical biological profile of primary hyperaldosteronism was demonstrated in both patients, including hypokalemia with inappropriate kaliuresis, elevated resting plasma aldosterone, and undetectable plasma renin activity. The circadian rhythm of blood pressure was studied by ambulatory monitoring pre- and post-operatively. It confirmed the lack of hypertension, but the circadian rhythm of blood pressure was lost before surgery in one patient. Surgical removal of the histologically typical aldosterone-producing adenomas normalized the kalemia. The main finding in these two patients was spontaneously low blood pressure in the post-operative period. This suggests that excess aldosterone induced relative hypertension in these patients whose blood pressure was spontaneously very low. Genetic screening for dexamethasone-sensitive hyperaldosteronism was negative in both patients.

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Introduction

Primary hyperaldosteronism is the most common endocrine form of hypertension. It is usually associated with hypokalemia, renal potassium leakage, and arterial hypertension due to excessive aldosterone secretion (1, 2). However, the clinical and biological spectrum of primary hyperaldosteronism varies. In particular, hypokalemia is lacking in 7 to 38% of cases (3, 4). In contrast, normotensive primary hyperaldosteronism is exceedingly rare: to the best of our knowledge, only ten cases have been documented (5–14). We report two new cases studied by means of ambulatory blood pressure monitoring (ABPM). As the pathophysiology of normotensive primary hyperaldosteronism is unknown and as recent data have shown wide phenotypic variability among carriers of the chimeric CYP 11-beta/aldosterone synthase gene, we carried out a genetic analysis of the two patients to rule out a peculiar clinical presentation of dexamethasone (DXM)-sensitive hyperaldosteronism (15).

Methods

Plasma renin activity (PRA) was assessed by radioimmunoassay (Sorin Biomedica, Antony, France), with

within-assay variability between 5.4 and 9.9% for values between 1.6 and 17.9 ng/ml/h and between-assay variability of 5.6 to 11.5% for values between 1.6 and 15.2 ng/ml/h.

Plasma aldosterone was measured by radioimmunoassay (Behring Diagnostics, Rueil-Malmaison, France or Immunotech, Marseille, France) with within-assay variability between 2.5 to 8.3% for values between 140 and 1120 pmol/l, and between-assay variability between 3.9 and 10.4% for values between 70 and 700 pmol/l.

Urine aldosterone was measured by radioimmunoassay (Sanofi Pasteur Diagnostics, Marne-La-Coquette, France) with within-assay variability between 3 and 6.8% and between-assay variability around 9%. Plasma atrial natriuretic hormone (ANH) was measured by radioimmunoassay (Sanofi Pasteur Diagnostics) with within-assay variability of 7% and between-assay variability of 12.5%. The urinary steroid profile was assessed by means of high-performance liquid chromatography and mass spectrometry, as previously reported (16).

Genetic diagnosis of DXM-sensitive hyperaldosteronism was based on Southern blotting after DNA digestion, as previously described (17).

Case report 1

A 40-year-old woman born in Vietnam had been treated with corticosteroids for five years for Behcet's disease. There was no family history of hypertension. Hypokalemia fluctuating between 1.4 and 2.4 mmol/l had been diagnosed three years previously. An episode of tetany despite moderate doses of glucocorticoids (prednisone 20 mg/day) and the persistence of hypokalemia with inappropriate kaliuresis despite oral potassium supplementation led to further investigations. They were performed despite the treatment with prednisone which could only be reduced to 10 mg/day. Diet inquiry demonstrated a moderately low salt intake which the patient had been advised to follow because of corticotherapy. Her natriuresis varied between 75 and 125 mmol/24 h. Physical examination was normal. The body mass index was 21 kg/m². Repeated blood pressure values measured with a manual armlet were always below 140/90 mmHg. As shown in Fig. 1, ABPM confirmed the absence of arterial hypertension,

with a mean pressure of 134/94 mmHg; the sole abnormality was an abnormal circadian rhythm (mean diurnal pressure 132/91 mmHg; mean nocturnal pressure 138/95 mmHg). Renal function was normal. There was no proteinuria nor retinopathy. Plasma bicarbonates ranged between 27 and 31 mmol/l (normal range 23–33 mmol/l). As shown in Table 1, blood and urine aldosterone levels were increased and the PRA was very low. After four hours of ambulation, plasma aldosterone levels fell from 722 to 349 pg/ml. Blood ANH was normal. Computed tomography (CT; 5-mm slices) demonstrated a right hypodense adrenal mass of 15 mm with an apparently normal contralateral gland (Fig. 2, left). The patient then received 225 mg/day spironolactone for six months, which normalized the kalemia and dispensed with oral potassium supplementation. The adrenal gland was surgically removed, and the postoperative course was uneventful. The tumor had a diameter of 17 mm and was well delimited within a fibrous capsule. It mainly contained foamy clear cells with a

Figure 1 Patient 1: results of ambulatory blood pressure (BP) monitoring pre- and post-operatively. **Top panel, systolic profile:** before removal of the adrenal mass, mean systolic BP was normal at 134 mmHg and maximal systolic BP was 156 mmHg; the circadian rhythm was disrupted with a mean nocturnal systolic BP of 138 mmHg and a mean diurnal systolic BP of 132 mmHg. After removal, mean systolic BP was low at 82 mmHg and maximal systolic BP was 94 mmHg; mean nocturnal and diurnal systolic BP were respectively 82 and 94 mmHg; the circadian rhythm had reappeared. **Bottom panel, diastolic profile:** before removal of the adrenal mass, mean diastolic BP was 93 mmHg and maximal diastolic BP was 104 mmHg; the circadian rhythm was disrupted, with a mean nocturnal diastolic BP of 95 mmHg and a mean diurnal diastolic BP of 91 mmHg. After removal, the mean diastolic BP was low (63 mmHg), with a maximal diastolic BP of 77 mmHg; the circadian rhythm had reappeared.

Table 1 Patient 1: pre- and post-operative biological results. Normal range (N) in parentheses.

	Preoperative	Postoperative (2 months)	Postoperative (18 months)
Blood			
Potassium (N: 3.5–5 mmol/l)	1.4–3.2	3.7	3.6
PRA supine (N: 0.5–1.5 ng/ml/h)	<0.1	0.5	0.94
PRA orthostatism (N: 0.8–5 ng/ml/h)	–	–	2.06
Aldosterone supine (N: 83–277 pmol/l)	1553	80	108
Aldosterone orthostatism (N: 138–416 pmol/l)	968	–	–
ANH supine (N: 5–25 pmol/l)	24.5	24.2	–
Urine			
Potassium (N: 50–150 mmol/24 h)	76	–	–
Aldosterone (N: 5–40 nmol/24 h)	56	–	–

trabecular or cordonal distribution typical of an aldosterone-producing adenoma (APA). Mitoses were infrequent. Compact polyhedral cells with basophilic cytoplasm were observed, with rare reticular cells. Two months after surgery, without any treatment, ABPM showed lower blood pressure than before surgery, with 24-h mean values of 84/61 mmHg and recovery of a normal circadian rhythm (Fig. 1). As shown in Table 1, serum potassium and hormone values were normal 2 and 18 months after surgery despite the long-term treatment with prednisone because of Behcet's disease. Genetic tests on blood cells ruled out DXM-sensitive hyperaldosteronism.

Case report 2

A 43-year-old woman was referred to the Endocrinology Department to check an adrenal mass. Her father had polycystic kidney disease and her mother had type 2 diabetes. There was no known family history of arterial hypertension. Her personal history included stage IV endometriosis and small cysts in both kidneys. A few weeks before admission, a melanoma on the right thigh had been surgically removed. Abdominal CT prescribed to detect metastases showed a right hypodense adrenal mass of 15 mm and no significant abnormalities of the left gland (Fig. 2, right). Demonstration of this adrenal mass led to further investigations.

The patient only complained of nycturia. Diet inquiry demonstrated normal salt intake and her natriuresis varied between 100 and 150 mmol/day. Physical examination was normal with a body mass index of 20.2 kg/m². ABPM showed a mean blood

pressure of 123/79 mmHg (129/83 mmHg by day and 108/66 mmHg by night) (Fig. 3). Renal function was normal. There was no proteinuria nor retinopathy. Plasma bicarbonates ranged between 31 and 32 mmol/l (normal range 23–33 mmol/l). As shown in Table 2, laboratory tests revealed hypokalemia with inappropriate kaliuresis, a low PRA, and increased blood and urine aldosterone levels. The plasma ANH level was increased. The circadian rhythm of plasma aldosterone concentrations was normal (0800 h: 438; 1000 h: 274; 1200 h: 197; 1600 h: 211; 2000 h: 105; 2400 h: 86 pmol/l; normal range supine: 83–277 pmol/l). A salt loading test with two liters of isotonic saline lowered the blood aldosterone level from 330 to 191 pmol/l, while the blood pressure slightly varied from 126/67 to 128/72 mmHg. A suppression test with 4 mg/day DXM for 10 days reduced the aldosterone level to 38 pmol/l (normal range supine: 83–277 pmol/l). The circadian rhythm of plasma cortisol levels was normal as follows: 0800 h: 386; 1600 h: 207; 2400 h: 74 nmol/l. Normal values were obtained for other plasma hormones (adrenocorticotropin, 17-hydroxyprogesterone, S-dehydroepiandrosterone, and 11-deoxy-cortisol) and urinary steroids (free cortisol, tetrahydrocortisol, tetrahydrocortisone, tetrahydro-deoxycorticosterone, tetrahydrocorticosterone). ¹³¹I noriodocholesterol scintigraphy with DXM administration (4 mg daily) demonstrated unilateral right adrenal uptake. Genetic tests ruled out DXM-sensitive hyperaldosteronism. The right adrenal gland, bearing a yellowish tumor, was removed by celioscopy; the immediate postoperative outcome was uneventful. Histologically, the tumor was a typical well-delimited APA measuring 15 mm in diameter,

Figure 2 Adrenal computed tomography (5-mm slices) with injection of radioiodine contrast medium. Left panel, patient 1: right hypodense adrenal mass measuring 15 mm in diameter (arrowhead). Right panel, patient 2: right hypodense adrenal mass with a normal opposite adrenal gland.

consisting mainly of foamy clear cells. Mitoses were infrequent. Peritumoral adrenal tissue was normal.

Two months after surgery the patient felt tired and had symptomatic postural hypotension. She had had an episode of acrosyndrom one month after surgery. The nycturia had disappeared. ABPM showed lower blood pressure than before surgery, with a mean 24-h value of 100/67 mmHg (103/69 mmHg by day and 92/57 mmHg by night) (Fig. 3). The kalemia was normal but the patient had low levels of PRA and aldosterone that nevertheless increased with time (Table 2). The circadian rhythm of plasma cortisol levels was normal (0800 h: 303; 1600 h: 168; 2400 h: 27 nmol/l) as was free urinary cortisol (95 nmol/day; normal range 30–300 nmol/l).

Discussion

We describe two cases of normotensive primary hyperaldosteronism revealed by tetany in one case and an adrenal mass in the other. Despite the lack of arterial hypertension, hyperaldosteronism was confirmed by hypokalemia, low levels of PRA and increased urinary and plasma aldosterone levels. Both cases were secondary to APA, as shown by a fall in aldosterone levels on postural stimulation, the presence of an adrenal mass on CT with a morphologically normal contralateral gland, a histologically typical adenoma with clear cells, and normalization of kalemia after surgery.

Only 16 cases of normotensive primary hyperaldosteronism have been reported in the literature, with only 10 in the English literature (5–14). About 75% of cases were described in Eurasians (especially Japanese). The patients are middle-aged (23 to 56 years

old) and 60% are women. The diagnosis is usually raised by signs of hypokalemia (fatigue, paresthesia, tetany and paraplegia). Two-thirds of cases are secondary to APA. No familial cases have been described. The age, sex and ethnic origin (in the first case) of our patients, and the etiology of the primary hyperaldosteronism, are in keeping with the literature.

The blood pressure profile of our patients was studied by ambulatory monitoring. The first patient's mean blood pressure (134/93 mmHg) was lower than usual in primary hyperaldosteronism but the mean nocturnal diastolic pressure was higher than that of normotensive subjects of similar age (65 ± 8 mmHg) (18). The second patient's mean blood pressure was normal, and treatment of APA was poorly tolerated.

The normal blood pressure in these rare cases of primary hyperaldosteronism is not fully understood. Arterial hypertension could be related to the early diagnosis of hyperaldosteronism (5, 7, 8, 10, 11). However, the 3-year history of hypokalemia in the first patient, and the second patient's blood pressure stability for more than one year before surgery despite hypokalemia, argue against this hypothesis.

The arterial hypertension of primary hyperaldosteronism is usually explained by an increase in sodium resorption related to the effect of aldosterone on distal renal tubules. This transient hypervolemia, but also the direct effect of aldosterone, induce secretion of natriuretic factors such as ANH (19, 20). Blood pressure remains high because of several factors, including increased peripheral vascular resistance, a direct hypertensive effect of aldosterone on the central nervous system (CNS), and increased vascular sensitivity to pressor drugs such as angiotensin and adrenalin.

Figure 3 Patient 2: results of ambulatory blood pressure (BP) monitoring before and two months after surgery (with permission of SpaceLabs Medical, Inc.). Systolic BP ($\square$); diastolic BP (+); mean BP ($\times$); pulse (beats per min) ($\diamond$). Horizontal dashed lines, normal range for BP. **Top panel, preoperative profile.** Systolic BP: the mean BP was normal at 124 mmHg; the maximal BP was 163 mmHg; the circadian rhythm was not disrupted, with a mean nocturnal BP of 108 mmHg and a mean diurnal BP of 129 mmHg. Diastolic BP: the mean BP was 79 mmHg; the maximal BP was 103 mmHg; the circadian rhythm was not disrupted, with a mean nocturnal BP of 66 mmHg and a mean diurnal one of 83 mmHg. **Bottom panel, post-operative profile.** Systolic BP: the mean BP was low at 100 mmHg, with a maximal BP of 119 mmHg; the circadian rhythm remains normal with a mean BP of 103 mmHg during the day and 92 mmHg at night. Diastolic BP: mean BP was low (67 mmHg) and maximal BP was 81 mmHg; the circadian rhythm remains normal, with a nocturnal mean of 57 mmHg and a diurnal mean of 69 mmHg.

Table 2 Patient 2: pre- and post-operative biological results. Normal range (N) in parentheses.

	Preoperative	Postoperative (2 months)	Postoperative (6 months)
Blood			
Potassium (N: 3.5–5 mmol/l)	3.2–3.5	4.3–4.7	4
PRA supine (N: 0.5–1.5 ng/ml/h)	<0.1	<0.1	<0.1
PRA orthostatism (N: 0.8–5 ng/ml/h)	<0.1	<0.1	0.4
Aldosterone supine (N: 83–277 pmol/l)	480	28	86
Aldosterone orthostatism (N: 138–416 pmol/l)	571	64	272
ANH supine (N: 5–25 pmol/l)	108	19.1	–
Urine			
Potassium (N: 50–150 mmol/24 h)	47–74	46	47
Aldosterone (N: 5–40 nmol/24 h)	85	4	11

It has been suggested that the absence of volemic expansion (8, 10) or a low salt diet may account for the lack of arterial hypertension. However, hypervolemia is mainly responsible for the early increase in blood pressure and is then supplanted by other mechanisms. Plasma ANH levels were normal in our first patient, arguing against major hypervolemia. Neither patient had a very low salt intake. In literature, the pressure response to drugs has been studied in four cases of normotensive primary hyperaldosteronism (7, 8, 10, 13); the response to angiotensin II was unexpectedly normal in these four cases, and one patient was responsive to adrenalin (10). These results suggest that the variability of the pressure response to some agents cannot alone account for the normal blood pressure. Excessive production of vasodilators such as prostaglandin E and kallikrein is largely speculative (7, 11, 13).

The possible role of glucocorticoid therapy in the maintenance of normal blood pressure must be discussed, on the basis of the effect of glucocorticoids on the CNS, and the possibility of DXM-sensitive hyperaldosteronism. Glucocorticoids have the same affinity as mineralocorticoids for mineralocorticoid receptors (MR) (21). In epithelial cells MR are protected from glucocorticoids through inactivation of the latter by 11-beta-hydroxysteroid dehydrogenase. Moreover, glucocorticoids, which are agonists of MR in the kidney, have effects opposite to those of MR in the CNS and inhibit the central hypertensive effect of aldosterone. In patient #1 this central response to aldosterone could have been modified by long-term treatment with glucocorticoids, although prednisone, used in this patient, has a very low affinity for MR (22). Moreover,

excess glucocorticoids usually have a hypertensive action (23). DXM-sensitive hyperaldosteronism was also considered in both patients because recent data have shown that carriers of chimerism of the 11-beta-hydroxylase/aldosterone synthase gene have a broad range of phenotypes and do not necessarily have arterial hypertension. Moreover, our second patient had a clear fall in plasma aldosterone levels when she received DXM. Despite denial of a family history of arterial hypertension, both patients were tested for DXM-sensitive hyperaldosteronism and the results were negative. The tumor itself was not studied because of the negative findings in previous studies of glucocorticoid-responsive aldosteronism (24). Normotensive primary hyperaldosteronism is thus not explained by a peculiar phenotype of DXM-sensitive hyperaldosteronism. Nevertheless, chronic glucocorticoid therapy may have modified the circadian rhythm of blood pressure, which is usually maintained in APA (25). Indeed, exogenous administration of glucocorticoids can eliminate or reverse the circadian rhythm of blood pressure (26).

ABPM after removal of the adenoma threw light on the pathophysiology of this unusual form of APA. Indeed, both patients had a marked fall in blood pressure after surgery: the difference between mean systolic and diastolic blood pressure values before and after surgery was 49/33 mmHg in patient #1 and 23/12 mmHg in patient #2. Therefore, the normal blood pressure found in this form of APA could in fact correspond to relative hypertension in subjects with very low spontaneous blood pressure. This suggests that hyperaldosteronism induces relative hypertension and a qualitative alteration (diurnal rhythm) of blood

pressure, but that blood pressure never reaches pathological levels in our patients because of very low spontaneous baseline levels. Such phenotypic variations have also been observed in DXM-sensitive hyperaldosteronism among members of different families (15). The degree of arterial hypertension in a given individual may therefore result from an interaction between environmental hypertensive and hypotensive factors on the one hand and genetic factors on the other hand. Indeed, normotensive primary hyperaldosteronism has been described more frequently in Eurasians, pointing to a role of genetic factors in the response to excess aldosterone.

Whether or not this relative arterial hypertension is deleterious remains to be demonstrated, but our observations call for primary hyperaldosteronism assays in patients with hypokalemia and renal potassium leakage.

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