Normokalemic Hyperaldosteronism in Patients with Resistant Hypertension

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Abstract

Background: Primary aldosteronism is a common cause of non-renal secondary hypertension. A correct diagnosis results in curing the hypertension or targeting appropriate pharmacotherapy. In patients with low renin resistant hypertension (after treatment with three or more different anti-hypertensive drugs the blood pressure remains above 140/90 mmHg), screening for aldosteronism is mandatory.

Objectives: To demonstrate that normal blood levels of potassium in resistant hypertensive patients do not exclude the possible presence of hyperaldosteronism, and to suggest the use of the plasma aldosterone concentration (ng/dl)/plasma renin activity (ng/ml/hour) ratio in screening for hyperaldosteronism.

Methods: Blood tests, suppression and stimulation tests (2 L normal saline IV/4 hours and 20 mg furosemide IV for 60 minutes in a standing position) were systematically performed in 20 low renin normokalemic resistant hypertensive patients. None had renal disorders, known endocrine abnormalities or heart failure. They did not receive anti-hypertensive drugs affecting PAC or PRA. Basal PRA and PAC were measured twice: PAC after saline infusion and PAC/PRA after stimulation.

Results:. PAC/PRA above 50 was used to denote hyperaldosteronism. Serum K was 4 $\pm$ 0.07 mM/L, PAC 22.8 $\pm$ 1.8 ng/dl, PRA 0.13 $\pm$ 0.02 ng/ml/hour, PAC/PRA 190 $\pm$ 22 (above 100 in 17). After suppression PAC decreased from 25 $\pm$ 1.8 to 11 $\pm$ 1 ng/dl (normal < 5 ng/dl). Stimulation did not affect PRA and PAC/PRA. Abdominal computed tomography scan revealed normal adrenal glands in 15 patients. Spironolactone (116 $\pm$ 60 mg/day) normalized blood pressure in all patients; it was used as a single therapy in 8, and in association with only one anti-hypertensive drug in the remaining 12 patients. In one patient the treatment was discontinued due to the presence of hyperkalemia.

Conclusions: Low renin resistant hypertension associated with normokalemia may be due to hyperaldosteronism. Normal aldosterone levels in the basal condition do not exclude the possibility of hyperaldosteronism. Using a PAC/PRA ratio above 50 as a screening test can aid the physician in deciding when to perform dynamic tests, thus increasing the sensitivity of the diagnosis of hyperaldosteronism. CT scan is frequently normal. Targeted pharmacotherapy leads to a normalization of blood values.

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Approximately 15–25% of the adult population in western industrialized countries suffers from hypertension. The most common cause is "essential or primary hypertension," which means the absence of any underlying disease that may increase blood pressure. The prevalence of primary aldosteronism in unselected patients with hypertension appears to be low (0.5–2%) [1]. Primary mineralocorticoid-induced hypertension in adults encompasses disorders due to overproduction of aldosterone or other MC precursors such as deoxycorticosterone [2].

The classical clinical presentation of this disorder is high blood pressure associated with hypokalemia (potassium < 3.5 mmol/L). However, recent reports claim that physicians should be aware of the possibility of MC-induced hypertension without hypokalemia. The present report investigates this specific population that was diagnosed and treated in our outpatient clinic.

Patients and Methods

Patients

We reviewed the clinical records of normokalemic patients with resistant hypertension in whom plasma aldosterone concentration and plasma renin activity were determined over an 18 month period. Exclusion criteria were: hypokalemia (serum K < 3.5 mmol/L), renal failure (serum creatinine > 1.4 mg/dl), heart failure, and a known diagnosis of primary hyperaldosteronism or other mineralocorticoid excess disease. The diagnosis of hyperaldosteronism was suggested by a repeated seated basal PAC/PRA ratio > 50 (see below).

PAC = plasma aldosterone concentration
PRA = plasma renin activity

MC = mineralocorticoid

The study group comprised 20 patients with normokalemic hyperaldosteronism who referred to the outpatient hypertension clinic due to uncontrolled resistant hypertension. There were 14 males and 6 females with a mean age of 56 ± 2 years (range 39–73). The duration of hypertension was 12 ± 2 years (range 1–20 years). All patients were treated with at least three anti-hypertensive drugs (mean 3.6, range 3–5) at admission. Concomitant diseases were diabetes mellitus type 2, treated hypothyroidism, and Rendu-Weber-Osler syndrome (in one patient each), and ischemic heart disease and stroke (in two patients each). Doppler echocardiography was performed in 14 patients. Left ventricular hypertrophy was found in nine patients (64%).

Diagnostic evaluation

Seated basal PAC and PRA were assessed twice at an interval of 2–4 weeks. For this purpose all anti-hypertensive treatments were stopped for 2 weeks and the patients continued a normal diet without salt restriction. If blood pressure values increased more than 170/100 mmHg the patients were temporarily treated with a dihydropiridine calcium channel blocker and/or an alpha-blocker (doxazocine). The PAC/PRA ratio (ng/dl:ng/ml/hour) was calculated. The normal range of PAC was aldosterone 1–16 ng/dl and of PRA 0.2–2.8 ng/ml/hour. For calculation purposes, patients with undetectable levels of PRA (< 0.1 ng/ml/hour) were considered to have a PRA level of 0.1 ng/ml/hour. In patients with a reproducible PAC/PRA ratio above 50 diagnostic tests were proposed.

Suppression tests were performed according to the literature [3]. At 8.00 a.m., patients rested in the supine position for 1 hour, and at 9.00 a.m. basal PAC and PRA were measured. After an IV infusion of 2 L of a physiological solution (0.9% Na Cl) during 4 hours, PAC and PRA values were measured again. A normal response implied a decrease of PAC to values < 5 ng/dl.

PRA stimulation tests were performed on another day. Basal PAC and PRA levels were measured after 30 minutes of resting in a seated position. Then, 20 mg furosemide was administered IV and the patients were asked to stand for a further 60 minutes. At the end of this period PAC and PRA were measured again. Adrenal CT scan with fine 3 mm cut slices evaluated the presence of gland enlargement (uni or bilateral). A standard radioimmunoassay determined PAC and PRA values. Serum natrium, potassium and creatinine were assessed by standard laboratory methods.

Results were given as mean ± SEM. Differences between groups were assessed by analysis of variance. Non-parametric tests and Student's *t*-test for paired groups were used when appropriate. *P* values of 0.05 or less were considered as statistically significant.

Results

Laboratory data

- Basal data: The serum potassium levels ranged between 3.7 and 4.7 mmol/L (mean 4 ± 0.07 mmol/L). Serum creatinine levels were normal, from 0.8 to 1.4 mg/dl in all patients (mean 1.03 ± 0.03 mg/dl). The mean PAC and PRA values were 22.8 ± 1.8 ng/dl and 0.13 ± 0.02 ng/ml/hour respectively. The PAC/PRA ratio was 190 ± 22, being above 100 in 17 patients and 67, 75 and 75 in the other three.
- Diagnostic tests [Table 1]: After administration of 2,000 ml saline during 4 hours, PAC levels decreased in all patients from 25 ± 1.8 ng/dl (range 18–41) to 11 ± 1 ng/dl (range 5–18) (P <0.01). The response to the PRA stimulation test was negative in all patients, 0.14 ± 0.02 ng/ml/hour before and 0.13 ± 0.01 ng/ml/hour after stimulation. PAC levels were 16.9 ± 1.4 ng/dl before and 20.4 ± 1.2 ng/dl after stimulation (P= 0.08).

Adrenal computerized tomography was normal in 15 patients. One patient had bilateral enlarged glands and in four patients only one side was enlarged.

Table 1. Laboratory results of baseline PRA, PAC, saline and fusid tests, K^+ and S creatinine before and after therapy

Laboratory data	MEAN + SEM
PRA (ng/ml/h)	0.13 ± 0.02
PAC (ng/dl)	22.8 ± 1.8
PAC/PRA	190 ± 22
Saline test	
PAC 0 min	25 ± 1.8
PAC 240 min	11 ± 1*
Fusid test	
PRA 0 min	0.14 ± 0.02
PRA 60 min	0.13 ± 0.01
K+ (mEq/L)	
Before	4 ± 0.07
After	4.8 ± 1.1*
Serum creatinine (mg/dl)	
Before	1.03 ± 0.03
After	1.1 ± 0.2

* $P < 0.01$.

Follow-up

All patients were treated with spironolactone at a mean dose of 116 ± 60 mg/day (range 50–300). Systolic blood pressure values decreased from 166 ± 3 to 130 ± 2 mmHg (P< 0.01) and diastolic BP values from 101 ± 2.6 to 80 ± 2 mmHg (P<0.01). The mean number of drugs required for control of BP decreased from 3.6 to 2 (P<0.05). In 35% of the patients BP was controlled with aldactone alone. In three patients the dose of this drug was reduced due to the appearance of gynecomastia. In one patient spironolactone was stopped due to hyperkalemia.

Discussion

Primary hyperaldosteronism is one of the few potentially curable forms of hypertension. The clinical features of this condition are not specific, but hypokalemia continues to be

BP = blood pressure

considered as a major criterion for the diagnosis of hyperaldosteronism. As mentioned in internal medicine textbooks, the standard clinical and laboratory manifestations of such a condition are hypertension, hypokalemia, hypernatremia and alkalosis.

However, hypokalemia ($K^+ < 3.5$ mmol/L) is far from being universal and normal blood levels of potassium are probably more frequent than previously expected. Bravo [4] reported normal levels of potassium in 27% of patients (22/80) with proven hyperaldosteronism. Other studies have reported a frequency of normokalemia ranging from 12 to 80%, the former basing the diagnosis of hyperaldosteronism on the PCA/PRA ratio. Recent reports consider that up to 40% of patients with surgically proven hyperaldosteronism are normokalemic [3]. Therefore, patients with resistant hypertension (high BP values despite treatment with three or more drugs, one of them a diuretic) should be screened even if hypokalemia is absent. The development of resistant hypertension in patients with low renin hypertension and high MC production is not only related to an increase in natrium and water retention. In fact, the activation of MC receptors potentiates the vasoconstrictive action of cathecholamines and angiotensin II and inhibits endothelial relaxation [5]. Bravo [4] demonstrated that plasma volume is expanded and total peripheral resistance elevated in most patients with hyperaldosteronism. Moreover, it was recently shown that mineralocorticoids may also affect blood pressure values through a central nervous system-dependent blood pressure control [6].

Taking into account that the standard parameters used to establish a firm diagnosis of aldosteronism are not always present, the elevated PAC/PRA ratio has been recognized as an acceptable and reliable diagnostic parameter [7]. In the presence of normal or low normal values of PAC levels this ratio may be elevated, suggesting that specific disorders in the steroid hormone production besides aldosterone may cause hypertension. The adrenal cortex has morphologically and functionally different zones. Aldosterone, the main mineralocorticoid, is produced in the zona glomerulosa and the glucocorticoids are secreted by the zona fasciculata, an inner region, under the control of adrenocorticotropic hormone [4]. The production of adrenal steroid hormones varies in magnitude between these two regions, the cortisol being released at a level of 10–20 mg/day and the aldosterone between 100 and 150 μg daily. Therefore, the cortisol circulates in 1,000-fold excess concentration compared to aldosterone [3].

The affinity of MC receptors is equal for cortisol and aldosterone [8,9]. Consequently, the mineralocorticoid effect of aldosterone on target cells depends on the adequate activity of the 11-beta-hydroxysteroid dehydrogenase type 2, which inactivates cortisol by transforming it to cortisone [10]. Therefore, a partial or complete inactivation of this enzyme activity will induce an increment in the cortisol MC effects, as seen in the AME syndrome (apparent mineralocorticoid excess syndrome) where the enzyme activity is non-existent [11]. This autosomal recessive inherited disorder is characterized by hypokalemia and low renin hypertension. Other acquired causes of decreased 11β-HSD2 activity are furosemide, carbenoxolone, liquorices or flavinoids (in citrus fruit or grapefruit juice) [12–15]. It is tempting to propose that the cause of high blood pressure in an unknown percentage of patients with low renin hypertension may be related to a lower 11β-HSD2 activity [16], without decrease in blood levels of potassium. An impaired activity of 11β-HSD2 has recently been shown in patients with "essential hypertension" [17]. It may explain the prolonged life of cortisol [18] and the increased susceptibility of blood pressure to salt load found in these populations [19].

Thus, it remains mandatory, in practice, to perform stimulating and suppressing tests to accurately diagnose low renin hypertension due to hyperaldosteronism. The adrenal response to stimulation or inhibition must be evaluated in all suspected patients. We used a saline suppression test and measured plasma aldosterone concentration and the PAC/PRA ratio before and after administration of 2 L of physiologic solution (0.9% Na Cl) during 4 hours. A baseline PCA/PRA ratio above 50 (measured twice) and aldosterone levels above 5 ng/ml after 2 L saline were considered diagnostic of primary hyperaldosteronism. In our series the PCA/PRA ratio was abnormal in all patients. The mean aldosterone value after saline was 11 ng/ml, confirming the diagnosis of hyperaldosteronism. The second test we used was a stimulation test (IV furosemide 20 mg and standing for 60 minutes). In such a situation an increase of PRA level is expected. The lack of increase in PRA found in our patients confirmed the suppressed PRA activity due to intravascular volume expansion.

Adrenal imaging is performed if the biochemical data support the diagnosis of hyperaldosteronism. The presence of adrenal enlargement was assessed by CT. In two-thirds of the patients the CT scan was interpreted as normal and in 33% it suggested bilateral hyperplasia or adenoma. However, the reliability of adrenal CT scan is controversial. Small adenomas or hyperplasia (less than 1 cm) are the most frequent and may be missed by CT scan [20]. Moreover, the presence of non-secreting adrenal tumors detected at CT scan is not rare. In unselected patients 30–40% of such adrenal enlargements were not secreting tumors [21]. Interestingly, it was suggested that adrenal vein sampling may indicate an aldosterone source in a normal gland when the contralateral non-secreting gland is found to be enlarged at CT examination [22]. Recent studies suggest that magnetic resonance imaging has a high specificity in the detection of adenomas [23]. Meanwhile, the gold standard procedure to differentiate between adenoma and hyperplasia is catheterization of the adrenal veins with measurement of the aldosterone/cortisol ratio [1,3]. As bilateral hyperplasia may be asymmetric and confounds with adenoma, this last procedure is recommended before any surgical procedure is undertaken.

In our patients, blood pressure values were elevated despite treatment with four different anti-hypertensive drugs. All the

11β-HSD2 = 11-beta-hydroxysteroid dehydrogenase type 2

patients were later treated with spironolactone. Blood pressure was effectively controlled with spironolactone alone in 8 patients, and with the addition of a second drug in the other 12 patients. Four patients suffered from adverse effects and spironolactone was discontinued in one. The use of spironolactone is associated with a relatively high percentage of adverse effects, mainly when the doses are above 100 mg/day. Since the use of this drug has increased considerably in recent years due to its beneficial effects in patients with heart failure, new anti-aldosterone drugs with fewer side effects are being developed. One of them, eplerenone, still an investigational drug, seems to be as effective as spironolactone and has fewer complications [24]. Surgery, when recommended, has become easier with the routine use of laparoscopic adrenalectomy [25].

In conclusion, normokalemia does not exclude the diagnosis of hyperaldosteronism. Patients with resistant hypertension should be systematically evaluated for this condition, using the PAC/PRA ratio and the suppression-stimulation tests.

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Doctor: A teacher, instructor; one who inculcates learning, opinions or principles.

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