CASE REPORT

Cushing’s Disease: Evaluation of Mineralocorticoid-induced Hypertension

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A patient (32-year-old female) with Cushing’s syndrome due to pituitary adenoma and hypertension with hypokalemia is reviewed. Endocrinological studies demonstrated low plasma renin activity, low plasma aldosterone concentration and high plasma deoxycorticosterone concentration. Blood pressure response to exogenous angiotensin II was enhanced. After the withdrawal of cortisol replacement following surgery, her abnormal endocrinological findings, hypertension and serum potassium level returned to normal and her blood pressure response to exogenous angiotensin II was reduced. These results suggest that in this case deoxycorticosterone might have contributed to the development and maintenance of her hypertension accompanied with hypokalemia.

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Key words: renin-angiotensin-aldosterone system, glucocorticoid, deoxycorticosterone, corticosterone, hypokalemia

Introduction

It is widely recognized that hypertension is present in about 80% of cases of Cushing’s syndrome (1). There have been several hypotheses regarding high blood pressure, often accompanied by hypokalemia, observed in this syndrome. First, the overproduction of cortisol has been considered to induce these findings with its mineralocorticoid action (2), as well as its effect on hypertension by stimulating vascular sensitivity to catecholamines (3, 4). Second, deoxycorticosterone (DOC) and corticosterone in adrenal cancer and ectopic adrenocorticotropic hormone (ACTH) syndrome have been supposed to contribute to the electrolytes disturbance and hypertension (5). Third, other mineralocorticoids such as 17 alpha, 20 alpha-dihydroxyprogesterone, 17 alpha-hydroxyprogesterone (6) and 19-nordeoxycorticosterone (7) may cause the same symptoms. Last, enhanced production of plasma renin substrate by cortisol has been reported to elevate blood pressure through the renin-angiotensin-aldosterone system (8). Therefore, when discussing the genesis producing hypertension in Cushing’s syndrome it must be taken into account whether mineralocorticoid actions play an important role in the development and maintenance of hypertension.

The patient presented here has Cushing’s disease resulting from a pituitary adenoma, and has hypertension with low plasma renin activity (PRA), low plasma aldosterone concentration (PAC) and hypokalemia. We discuss the mechanism by which the hypertension was induced in this patient, compared with other forms of hypertension, including primary aldosteronism and Cushing’s syndrome due to adrenocortical adenoma and pituitary adenoma.

Case Report

A 32-year-old woman consulted our hospital for the evaluation of hypertension, truncal obesity and moon face. She had been aware of the obesity for about 10 years, when it had been pointed out by her parents. Several years after the first sign, she began to have intermittent headaches and palpitations. Acne on her face, petechiae on the extremities and then menopause occurred. Hypertension was first recognized when she consulted a nearby clinic complaining of a headache. She had never taken any kind of drugs. There were no other members of the family with known or suspected hypertension. She had no previous serious disease.

The physical examination on admission revealed that her weight was 53 kg and height 151 cm. Blood pressure was 170/110 mmHg with 72 bpm. Moon face, development of dorsal and supraclavicular fat pads and purpuric striae in lower extremities were also observed. The examination of her heart and chest...
Mean blood pressure was calculated using the formula:

diastolic blood pressure + 3 + diastolic blood pressure. All data obtained

Methods of analysis of the cause of hypertension in the present case

Protocol

1. Measurement of plasma renin activity, steroids, serum potassium level and blood pressure

The present patient was placed on a 114 mmol sodium diet. Each blood sampling and blood pressure measurement was performed in the supine position while fasting in the morning. Plasma cortisol, corticosterone, DOC and aldosterone concentration, and PRA were determined by radioimmunoassay (9, 10). Serum potassium levels were determined with an autoanalyzer. These results were compared with those obtained nine months after the termination of the six-month glucocorticoid replacement therapy following surgery. Further, these data were compared with the results obtained from seven hypertensive patients with Cushing's syndrome due to adenocortical adenoma, ranging from 26 to 53 years old, all female, whose accurate diagnosis was confirmed by the pathological findings of adrenal tumors taken surgically.

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from comparative groups were expressed as the mean±SEM.

2. Corticosterone and DOC responses to rapid ACTH infusion

Under the same conditions described in protocol 1, ACTH (Cortrosyn®, 0.25 mg, Daichi, Tokyo, Japan) was intravenously infused to stimulate corticosterone and DOC release from adrenal. Both steroids obtained in plasma at the time 0, 30, 60 and 120 minutes after the bolus infusion of ACTH were measured to compare with those in two hypertensive patients with Cushing's disease (pituitary Cushing's disease, female, ages 29 and 46), whose accurate diagnosis was confirmed by the pathological findings of pituitary adenoma taken surgically.

3. Blood pressure response to exogenously infused angiotensin II

To evaluate the mineralocorticoid actions on the hypertensive in the present patient, blood pressure response to exogenous angiotensin II was examined in accordance to the modified method of Kaplan and Silah (11).

Five patients with primary aldosteronism, ranging from 35 to 48 years old, 2 males and 3 females, and eight normal subjects, ranging from 25 to 56 years old, 4 males and 4 females, served as comparative groups. Primary aldosteronism was diagnosed on the basis of hypertension, continuous hypokalemia, low PRA, which was sustained by standing for 2 to 4 hours, and high aldosterone levels in plasma and urine. They were all hospitalized and had a diet containing 114 mmol sodium a day, and all drugs were withdrawn at least two weeks before each examination. Every examination was performed more than 30 minutes after the stabilization of blood pressure in the supine position in the morning while fasting. While monitoring blood pressure, angiotensin II dissolved in saline was infused intravenously at a dose of 1.0 ng/kg/min with a motor-driven syringe (NS-1, Natsume Seisakusho, Tokyo, Japan) and the dose was increased step-wise by accelerating the infusion rate every three to five minute until obtaining 20 mmHg rise in diastolic blood pressure. Finally, the exact dose of angiotensin II to raise the diastolic blood pressure by 20 mmHg was calculated and defined as the required dose. Nine months after stopping the six-month glucocorticoid replacement therapy following surgery, this examination was repeated in the present patient.

Informed consent

Informed consent was obtained from all patients examined in this protocol.

Material

Angiotensin II was kindly provided by Ciba-Geigy (Basel, Switzerland).

Results

1. Measurement of plasma renin activity, steroids, serum potassium level and blood pressure

The present patient had a PRA of 0.11 ng/(L·s) and a PAC of 90 pmol/L. These values were lower than the mean PRA
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Fig. 1. Alterations in plasma renin activity, mean blood pressure, serum potassium level and steroids concentrations in plasma between pre- and post-operation, and the comparison of them with the results of seven patients with Cushing’s syndrome resulting from adrenocortical adenoma. PRA: plasma renin activity, PAC: plasma aldosterone concentration, DOC: deoxycorticosterone, MBP: mean blood pressure, PCC: plasma cortisol concentration. Stippled area shows the normal range.

(0.80±0.02) and PAC (260±60) in the seven patients with Cushing’s syndrome due to adrenocortical adenoma. The present patient’s surgery and the withdrawal of the six month postsurgery glucocorticoid replacement therapy normalized PRA and PAC to 0.52 ng/(L·s) and to 190 pmol/L, respectively (Fig. 1). Plasma DOC of 1,810 pmol/L in this patient, which was higher than the mean of 710±250 pmol/L (ranging from 390 to 1,190) in Cushing’s syndrome and the normal range (90–900) in our laboratory, decreased to 460 pmol/L at the termination of glucocorticoid replacement (Fig. 1, top left). Plasma cortisol level in this patient was as high as that in Cushing’s syndrome (730 vs 880±160 in nmol/L) and was lowered to 160 nmol/L by this therapy (Fig. 1, bottom left). The plasma corticosterone concentration in the present patient before and after treatment was 7,520 and 9,250 pmol/L, both of which were lower than the normal range in our laboratory (Fig. 1). The mean blood pressure and serum potassium level in this patient were also restored from 128.0 to 100.0 mmHg and from 2.7 to 4.7 mmol/L, respectively. On the other hand, those of the seven patients with Cushing’s syndrome demonstrated 117.9±3.8 mmHg and 4.0±0.2 mmol/L, respectively (Fig. 1, top and middle right).

2. Corticosterone and DOC responses to rapid ACTH infusion

The baseline DOC level in the present patient was higher than that in the other two patients with pituitary Cushing’s disease. Meanwhile, there was not much difference in the baseline corticosterone level among the three patients. After the bolus ACTH infusion, all three patients showed increased DOC and corticosterone concentrations in line with the time passed. However, DOC at each time in the present patient revealed a higher plasma concentration than that in the other two patients (Fig. 2).

3. Blood pressure response to exogenously infused angiotensin II

Figure 3 shows the required dose of angiotensin II to raise the diastolic blood pressure by 20 mmHg. The dose of angiotensin II in the present patient was 2.8 ng/kg/min, which was as low as the mean (2.6±1.0) obtained from the five patients with primary aldosteronism. On the other hand, exogenous angiotensin II was less potent in elevating the diastolic blood pressure in the eight normal subjects, with 8.2±1.2 ng/kg/min required to raise 20 mmHg. After the stabilization of all signs following surgery and the withdrawal of the six-month glucocorticoid replace-
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Fig. 2. Corticosterone and DOC responses to rapid ACTH infusion. Open circles with the solid line is the present patient with pituitary Cushing's disease. Closed circles with dotted lines are the two hypertensive patients with pituitary Cushing's disease as a comparison. Stippled area shows the normal range. DOC: deoxycorticosterone. See the text for detail.

![Graph showing corticosterone and DOC responses to rapid ACTH infusion](image)

Fig. 3. Alterations of the required dose of exogenously infused angiotensin II to raise diastolic blood pressure by 20 mmHg between pre- and post-operation, and the comparison of them with the result of each group of primary aldosteronism and normal subjects. ang. II: exogenously infused angiotensin II. Parentheses show the number.

![Graph showing alterations of required dose of angiotensin II](image)

Discussion

The origins of Cushing's syndrome are heterogeneous. In ectopic ACTH syndrome and adrenal cancer which induced Cushing's syndrome, Christy and Laragh (2) have reported that hypokalemic alkalosis is very closely correlated with plasma mineralocorticoids levels and is accompanied with hypertension due to the mineralocorticoid action of cortisol. Recently, Ulick and associates (12) also have reported that marked hypersecretion and incomplete peripheral metabolism of cortisol in ectopic ACTH syndrome are the predominant cause of mineralocorticoid-induced hypertension by cortisol itself. On the other hand, Schambelan and associates (5) have indicated that ectopic ACTH syndrome, as well as 17-hydroxylation deficiency syndrome, showed an increased production of DOC and corticosterone, potent mineralocorticoids. It has also been demonstrated that chronic ACTH stimulation in normal subjects increased production of DOC and corticosterone, additional to cortisol, but failed to stimulate aldosterone production (13). Thus, the possibility has been raised that DOC and corticosterone overproduced by excess amounts of ACTH induce electrolyte imbalance and body fluid accumulation, and consequently produce hypertension.

The present patient reported on here had Cushing's disease resulting from a pituitary adenoma; another type of Cushing's syndrome due to overproduced ACTH. Her plasma cortisol level as well as high blood pressure did not differ from that in the seven patients with adrenocortical adenoma, however, this level was not as high as that in ectopic ACTH syndrome as indicated by Ulick and associates (12), suggesting the lack of marked hypersecretion or incomplete peripheral metabolism of cortisol in pituitary Cushing's disease. Meanwhile, the serum potassium level in this patient had been lower than the mean of the other seven patients. Additionally, these seven patients demonstrated relatively high PRA, indicating the lack of mineralocorticoid action by cortisol at this level, which is as high as that in the present patient. Therefore, from these findings it seems unlikely that in the present patient the hypokalemia was caused by cortisol with its mineralocorticoid action.

On the other hand, the present patient showed a DOC
concentration of about twice as high as the upper normal range. By contrast, the mean DOC in the seven patients were within the normal range. Thus, it is likely that the high DOC concentration was produced by oversecreted ACTH from the pituitary adenoma. The fact that DOC concentration was normalized after surgical treatment, which was followed by reduced ACTH secretion from the pituitary, supports this notion. Under the pretreatment condition in this patient, overproduced DOC could reduce PRA and PAC by its mineralocorticoid action. The results obtained from the exogenous angiotensin II infusion test indicate that mineralocorticoid action promoted the pressor hypersensitivity to exogenous angiotensin II due to the suspected upregulation of angiotensin II receptors, as was seen in the patients with primary aldosteronism, one of the most typical forms of mineralocorticoid-induced hypertension. Taken together, it was suspected in the present patient that excessively produced DOC, caused by a large amount of ACTH from the pituitary adenoma, decreased PRA, PAC and serum potassium levels, and elevated blood pressure. However, 1,810 pmol/L of DOC is not very high to produce hypertension, compared to the value of 3,020 pmol/L, the standard concentration to elevate blood pressure, as indicated Biglieri (14). Recently, 19-nordeoxycorticosterone, a mineralocorticoid, has been reported to cause hypertension in Cushing’s syndrome (7). Hence, although we did not measure other mineralocorticoids such as 19 nor-deoxycorticosterone glucuronide in urine, the possibility can not entirely be precluded that other undetermined mineralocorticoids in the present patient might also have produced low PRA, low PAC, hypokalemia and hypertension.

It is unclear why the present patient revealed mineralocorticoid (mainly DOC)-induced hypertension. We have experienced two other hypertensive patients with pituitary Cushing’s disease. However, they did not show high plasma DOC concentration with an exaggerated response to ACTH, as was seen in the present patient, although corticosterone response to ACTH was the same among the three patients. A difference in activity of intermediate metabolic enzymes such as 11B-hydroxylase might have caused DOC-induced hypertension in this patient.

In pituitary Cushing’s disease, mineralocorticoid action, not by aldosterone or cortisol, but by other mineralocorticoids such as DOC have not been disclosed so far. To the best of our knowledge, this is the first patient with Cushing’s syndrome resulting from pituitary adenoma in which mineralocorticoid action by DOC might have played a partial role in contributing and maintaining hypertension with hypokalemia.

References