Cushing's Syndrome Due to Huge Nodular Adrenocortical Hyperplasia with Fluctuation of Urinary 17-OHCS Excretion

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Abstract

A 51-yr-old male patient with Cushing's syndrome due to huge nodular adrenocortical hyperplasia is described. Urinary 17-OHCS was not suppressed by a high dose of (8 mg) dexamethasone and showed rather a tendency to paradoxical response. There was no response to metyrapone. Plasma cortisol showed a hyperresponse to insulin-induced hypoglycemia and a rapid response to corticotropin releasing hormone-lysine vasopressin (CRH-LVP) administration without an obvious ACTH response. Plasma cortisol responded to synthetic ACTH. Urinary 17-OHCS did not show parallel changes with plasma cortisol. These results and computerized tomography data suggested huge multiple nodular adrenocortical hyperplasia, which was confirmed later by surgery. The left and right adrenal glands weighed 105 and 45 g, respectively. Hyper-reaction of the adrenal gland to a small change in plasma ACTH or "unknown factors" may cause not only the discrepancy between cortisol and ACTH response but also the development of autonomous nodules in the adrenal gland.

We previously reported a case of Cushing's syndrome due to huge nodular adrenocortical hyperplasia (Hashimoto *et al.*, 1986). In that case, plasma cortisol responded to insulin-induced hypoglycemia without an obvious ACTH response. In view of the *in vitro* experiment results, we suggested that plasma cortisol responded

to a slight change in plasma ACTH which was not detected by ACTH radioimmunoassay, or to unknown factors other than ACTH which might be increased in plasma by hypoglycemia. In this paper, we report another case of huge nodular adrenocortical hyperplasia with a similar discrepancy between cortisol and ACTH response to insulin-induced hypoglycemia. A fluctuation in urinary 17-OHCS was observed in this patient, and we also found a tendency to paradoxical response of urinary 17-OHCS to dexamethasone.

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Case Reports

A 51-yr-old male was admitted to our hospital with hypertension and edema in September, 1987. Hypertension was pointed out at 48 yrs of age. Edema in lower extremities appeared at 49 yrs of age and increased three months before admission. His medical history revealed lung tuberculosis at 15 yrs of age. The patient's father had hypertension and his mother died of gastric cancer.

Physical examination revealed that the patient had a moon face, buffalo hump, hirsutism, gynecomastia, telangiectasia in the face, purpura in the truncus and extremities, and pretibial edema. There was no striae cutis distensae. His body height was 168 cm and body weight 56 kg. Blood pressure was 180/114 mmHg.

Laboratory findings revealed a red blood cell count of $422 \times 10^4 / \text{mm}^3$; hemoglobin, 13.4 g/dl; and hematocrit, 40.6%. The white blood cell count was $12300 / \text{mm}^3$ with 95% neutrophils and platelet count $22.3 \times 10^4 / \text{mm}^3$. Serum electrolytes were: Na 143 mEq/l; K 3.1 mEq/l; Cl 104 mEq/l, and Ca 8.3 mg/dl. Serum BUN was 21.9 mg/dl; creatinine, 1.01 mg/dl; and uric acid, 5.6 mg/dl. Total serum protein was 6.16 g/dl with 58.6% albumin; GOT, 30 IU/l; GPT, 33 IU/l; LDH, 808 IU/l; γ -GTP, 80 IU/l; and total cholesterol, 246 mg/dl. 75 g GTT: blood glucose concentrations were 135, 212, 256, 258 and 280 mg/dl at 0, 30, 60, 90 and 120 min, respectively. Urinalysis showed proteinuria (+).

Endocrinological examinations

The baseline hormone levels are shown in Table 1. Plasma ACTH was always at

Table 1. Baseline endocrine data and provocative tests of pituitary hormones

Examination	Patients' value				Normal value
Urinary 17-OHCS (mg/day)	3.01-28.86				3-9
Urinary 17-KS (mg/day)	5.14- 9.53				3-9
Plasma cortisol diurnal rhythm ($\mu\text{g/dl}$)					
9 : 00	22.4				5.4-22.6
16 : 00	25.6				
23 : 00	20.0				
Plasma ACTH (pg/ml)	n.d.				10-75
Plasma renin activity (ng/ml/hr)	2.33				0.4-2.4
Plasma aldosterone (pg/ml)	79.0				15-125
Plasma DOC (ng/ml)	0.657				0.08-0.278
Plasma DHEA (ng/ml)	0.253				1.2-7.5
Plasma DHEA-sulfate (ng/ml)	87.3				400-1500
Plasma norepinephrine (ng/ml)	0.11				0.05-0.40
Plasma epinephrine (ng/ml)	0.14				<0.10
Serum T3 (ng/dl)	108.1				80-200
Serum T4 ($\mu\text{g/dl}$)	7.5				4.5-11.5
TRH+LHRH test					
	0	15	30	60	90 (min)
PRL (ng/ml)	15.4	24.9	24.8	18.8	18.3
TSH ($\mu\text{U/ml}$)	1.35	3.70	5.13	4.91	4.40
LH (mIU/ml)	10.1	34.8	50.4	51.8	40.9
FSH (mIU/ml)	5.5	9.0	11.1	12.2	12.1
Insulin test					
GH (ng/ml)	0.1		0.2	0.2	0.2

an undetectable level. Plasma cortisol and urinary 17-OHCS were normal or increased, while urinary 17-KS was within the normal range. Urinary catecholamines, plasma renin activity and the plasma aldosterone concentration were normal. Plasma deoxycorticosterone was increased, while plasma DHEA and DHEA-sulfate were low. Serum T_3 and T_4 were also within the normal range. Plasma cortisol did not show a

diurnal rhythm.

High doses of dexamethasone (8 mg: 2 mg every 6 hr) were administered in October 7–8 and November 21–22, when baseline urinary 17-OHCS was normalized spontaneously and then elevated again (Fig. 1). Dexamethasone failed to suppress urinary 17-OHCS and 17-KS and, paradoxically, rather tended to increase urinary 17-OHCS. Metirapone (500 mg every 4 hr

Fig. 1. Urinary 17-OHCS response to high doses (8 mg) of dexamethasone (Dexa, 2 mg given orally every 6 hr for 2 days) and metirapone (Met, 0.5 g given orally every 4 hr for 6 times: total 3 g).

Fig. 2. Provocative tests of pituitary-adrenal function in the patient. Regular insulin (0.1 U/kg), ovine CRF (1 μ g/kg)+LVP (5 mU/kg) or 1-24 ACTH (0.25 mg) was given iv.

for 24 hr, total 3 g) had no effect on urinary 17-OHCS (Fig. 1). In the insulin tolerance test (regular insulin 0.1 U/kg, iv) the blood glucose concentration decreased from 104 mg/dl to 42 mg/dl at 30 min. Plasma ACTH stayed at an undetectable level, while plasma cortisol showed a hyper-response (Fig. 2). Plasma cortisol showed a rapid response to an iv administration of ovine CRH (100 μ g) and LVP (5 mU/kg), whereas plasma ACTH stayed at an undetectable level. Plasma cortisol responded normally to an iv administration of 0.25 mg 1-24 ACTH (Cortrosyn) (Fig. 2).

The basal concentrations of serum GH, LH, FSH, PRL, TSH were within the normal range (Table 1). Serum GH showed no response to insulin-induced hypoglycemia. In the LH-RH (0.1 mg, iv) and TRH (0.5 mg, iv) test, serum LH and FSH responded normally, whereas PRL and TSH showed low responses. All hormones were measured with commercially available radioimmunoassay kits (ACTH: C.I.S. Gif-sur-Yvette, France; cortisol, LH, FSH: Daiichi Radio-

isotope Laboratories, Tokyo, Japan; GH, PRL, TSH: Dainabot Co. Tokyo, Japan).

An adrenocortical scintigram with 131 I-adosterol revealed a large bilateral uptake of the tracer with a higher concentration on the left side (Fig. 3). Computerized tomography showed an enlarged multinodular mass in both adrenal glands (Fig. 4). Skull X-ray and cranial CT revealed no abnormal findings.

Fluctuation of urinary 17-OHCS

These findings led us to suspect a huge bilateral nodular adrenocortical hyperplasia with hypersecretion of cortisol. Moreover,

Fig. 3. Adrenocortical scintigram using 131 I-adosterol without dexamethasone suppression.

Fig. 4. Computed tomography of adrenal gland.

in this case, urinary 17-OHCS showed a spontaneous normalization 3 days after admission (Fig. 5), whereas urinary 17-KS

stayed at the upper limit of the normal range. When we treated the patient with trilostane (240 mg/day) for 2 weeks, urinary

17-OHCS stayed near the lower limit of the normal range, whereas urinary 17-KS was increased. Urinary 17-OHCS was increased again after the patient stopped taking trilostane, and the high concentration continued until operation. During the period when urinary 17-OHCS was normalized, no parallel reduction in plasma cortisol was evident. Plasma cortisol in the morning sometimes tended to be reduced to the upper limits of the normal range during trilostane administration.

Fig. 5. Urinary 17-OHCS, 17-KS excretions and plasma cortisol levels before surgery. CRF-LVP: CRF-LVP test, Dexa: dexamethasone suppression test, Insulin: insulin test, Met: metyrapone test.

Fig. 6. Macroscopic findings for bilateral adrenal gland.

Surgical and morphological findings

Total bilateral adrenalectomy was performed on December 15, 1987. The bilateral adrenal glands were enlarged with huge multiple nodules. The cut surface of the nodules was yellowish in color. The left and right adrenals measured $10.0 \times 8.2 \times 2.0$ cm and $8.8 \times 6.4 \times 1.6$ cm and weighed 105 and 45 g, respectively (Fig. 6). Microscopic examination showed that the nodules were encapsulated and were composed mainly of clear cells. Brown granules were not abundant. The surrounding areas showed compressed and atrophic cortical cells. There was no evidence of malignancy (Fig. 7).

Clinical course

Since the operation the patient has been treated with hydrocortisone. Eight months after surgery, the plasma ACTH concentration at 0900 hr was 42.8 pg/ml,

and the signs and symptoms of Cushing's syndrome have gradually disappeared.

Discussion

We present a case of Cushing's syndrome due to huge nodular adrenocortical hyperplasia which was confirmed in surgery. Bilateral adrenocortical hyperplasia is present in approximately 70–80% of Cushing's syndrome cases. Bilateral nodular hyperplasia accounts for 15–20% of all cases of adrenocortical hyperplasia (Neville and Symington, 1967). Adrenocortical nodules have been classified into three groups depending on their size and weight, and huge nodules are defined as those 90–100 g in weight (Hashimoto *et al.*, 1986). Although the pathogenesis of adrenocortical nodular hyperplasia has not been clear, two main hypotheses have been postulated. First, it is pituitary dependent because of the high

Fig. 7. Histological findings.

ACTH concentration after adrenalectomy (Choi *et al.*, 1970; Hidai *et al.*, 1975), the coexistence of pituitary adenoma (Aron *et al.*, 1981) or the development of pituitary adenoma after adrenalectomy (Raux *et al.*, 1975), and so on. Second, it is primarily an adrenal disorder because of the lack of response of plasma ACTH to LVP and metyrapone, the paradoxical response of urinary 17-OHCS to dexamethasone, and the atrophic adjacent areas of the adrenal gland, and so on (Meador, 1967; Ruder *et al.*, 1974; Shenoy *et al.*, 1984). Several authors (Levin, 1966; Cohen, 1966; Choi *et al.*, 1970; Ishihara *et al.*, 1977; Smals *et al.*, 1983; Miura *et al.*, 1984) have suggested that initial hypersecretion of ACTH gradually leads to the development of adrenocortical hyperplasia, which finally produces semi-autonomous or autonomous nodules, and then the hypothalamo-pituitary system is suppressed due to a negative feedback mechanism. Therefore, each case shows varying degrees of pituitary dependence and adrenocortical autonomy. The suppression by high dose dexamethasone and the response to metyrapone is usually observed in the early stages but not in later stages of this disorder. In this case, the patient had low plasma ACTH, no suppression of urinary 17-OHCS by 8 mg dexamethasone and no response to metyrapone. Plasma ACTH has been normalized and is not elevated eight months after surgery. Furthermore, the microscopic findings revealed that the surrounding areas were atrophic. These data suggest that this case might have adrenocortical autonomy rather than pituitary dependence, although further follow up will be needed to confirm this.

Spontaneous fluctuation of ACTH and/or cortisol secretion have been found in Cushing's syndrome due to pituitary adenoma (Brown *et al.*, 1973; Liberman *et al.*, 1976; Sakiyama *et al.*, 1984; Atkinson *et al.*, 1985), ectopic ACTH-producing tumor (Bailey, 1971; Chajek and Romanoff, 1976;

Estopinan *et al.*, 1987) and adrenal adenoma (Green *et al.*, 1975). The cycle periods ranged from 7 to 85 days. Plasma ACTH, cortisol and urinary 17-OHCS generally showed parallel changes. In this case, urinary 17-OHCS showed spontaneous normalization and was then increased again. As we followed this case up only three months before the operation, we may not diagnose this case as 'cyclic' Cushing's syndrome. Longer term follow up might have led us to diagnose cyclic hormonogenesis. However, in this case, urinary 17-OHCS changes did not parallel plasma cortisol changes. This might indicate that a disorder of cortisol metabolism is present in this case. But we could not find any disorder affecting corticosteroid metabolism; for example, hypothyroidism and severe liver damage. We could not find the cause of spontaneous normalization (Shimizu and Tanaka, 1984).

The paradoxical response to dexamethasone has been described in micronodular adrenocortical dysplasia (Ruder *et al.*, 1974), adrenal adenoma or carcinoma (Scott *et al.*, 1962) and, most frequently, pituitary adenoma (Linn *et al.*, 1967; French *et al.*, 1969) without cyclic hormonogenesis. French *et al.* (1969) suggested that this phenomenon might result from upsetting of a negative feedback effect of glucocorticoid or a paradoxical positive feedback stimulation of ACTH. However, Brown *et al.* (1973) suggested that the paradoxical response to dexamethasone might happen to coincide with the upward slope of the hormonal cycle in cyclic Cushing's syndrome, and that one should carefully examine periodicity if it is observed. In fact, other investigators (Liberman *et al.*, 1976; Estopinan *et al.*, 1987) have also reported that this phenomenon occurred coincidentally with high levels of cortisol secretion in cyclic Cushing's syndrome. On the other hand, in increasingly recognized cases of cyclic Cushing's syndrome, a paradoxical response to dexamethasone has been observed during pe-

riods with normal cortisol baseline levels (Atkinson *et al.*, 1985) and normal suppression by low dose dexamethasone in a hormonally normalized period (Sakiyama *et al.*, 1984). Thus, the mechanisms of paradoxical response has not been clarified, and it is necessary to recognize the variation in the dexamethasone suppressibility in cyclic Cushing's syndrome. In this case, urinary 17-OHCS tended to show a paradoxical response to dexamethasone, especially when the basal urinary 17-OHCS concentration was low.

We have already reported a very similar case with huge nodular adrenocortical hyperplasia (Hashimoto *et al.*, 1985). In that case, cortisol also responded to insulin-induced hypoglycemia without an obvious plasma ACTH response. The *In vitro* experiment revealed that the nodular tissue showed a cortisol response to ACTH but not to other substances which might be increased in peripheral blood by insulin-induced hypoglycemia. We speculated that cortisol might respond to other doses of such substances, to other different substances or to a slight change in plasma ACTH which was not detected by ACTH radioimmunoassay. In this case, the patient showed the same discrepancy between cortisol and ACTH response, not only to insulin-induced hypoglycemia but also to intravenous administration of CRH-LVP. In this patient, similar features are felt to be the cause of plasma cortisol response without obvious ACTH response. In this patient, plasma cortisol responded more strongly to insulin-induced hypoglycemia than exogenous 1-24 ACTH. This suggests that cortisol responded to some "unknown factors" which might be increased in plasma in insulin-induced hypoglycemia. We cannot conclude from the present results what the "unknown factors" are in this case. However, we emphasize again that the discrepancy between ACTH and cortisol response may be one of the char-

acteristics in huge nodular adrenocortical hyperplasia. "Unknown factors", which might induce this discrepancy, might also be responsible for the development of adrenal nodules.

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