Cortisol Responsiveness to Insulin-induced Hypoglycemia in Cushing's Syndrome with Huge Nodular Adrenocortical Hyperplasia

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Abstract

A 51-yr-old male patient with a 3 yr history of Cushing's syndrome is described. The baseline plasma cortisol level was elevated, while the plasma ACTH levels remained at an undetectable level. Dynamic testing of pituitary-adrenal function revealed no suppression after 8 mg of dexamethasone, and there was no response to metyrapone or CRF, while plasma cortisol showed a hyperresponse to synthetic ACTH. Plasma cortisol responded to insulin-induced hypoglycemia without an obvious ACTH response. These and the computerized tomography data suggested a "huge" bilateral nodular adrenocortical hyperplasia which was later confirmed by surgery. The left and right adrenal glands weighed 55 and 76 g, respectively. *In vitro* experiments, using the adrenal tissue, showed that there was an adrenal cortisol response to 1-39 ACTH but not to regular insulin, arginine vasopressin, angiotensin II, norepinephrine or epinephrine. These results indicate that plasma cortisol responded to a slight hypoglycemia-induced plasma ACTH change which was not detected in the ACTH radioimmunoassay or to factors other than ACTH which might be induced by hypoglycemia.

Bilateral adrenocortical hyperplasia is present in approximately 70-80% of Cushing's syndrome cases (Crapo, 1979; Neville and Mackay, 1976). Bilateral "adenomatous" or nodular hyperplasia accounts for 15-20% of all cases of adrenocortical hyperplasia (Neville and Symington, 1967). Diffuse bilateral hyperplasia and micronodular hyperplasia are ACTH dependent and known as

Cushing's disease. Macroscopic nodules are also the causes of Cushing's syndrome. The term macronodular adrenal hyperplasia is used to describe the presence of one or more macroscopically visible nodules up to 2.0-3.0 cm in diameter (Neville and Mackay, 1976). When these nodules are very large, the term huge nodular adrenal hyperplasia is used. Only several cases (Kirshner *et al.*, 1964; Hidai *et al.*, 1975; Ishihara *et al.*, 1977; Krivitzky *et al.*, 1980; Murayama *et*

al., 1983; Miura *et al.*, 1984) of huge bilateral nodular adrenocortical hyperplasia with an adrenal weight over 90 g have been reported. The pathogenesis of this nodular adrenocortical disorder is still unknown. Some authors (Cohen, 1966; Aron *et al.*, 1981) have proposed a primary pituitary origin and others (Meador *et al.*, 1967; Ruder *et al.*, 1974) a primary adrenal origin, and still others (Tucci *et al.*, 1965; Choi *et al.*, 1970; Smals *et al.*, 1984) dual control with predominance by the pituitary at one time and the adrenal at another.

This paper reports on a case of huge nodular adrenocortical hyperplasia with a plasma cortisol response to insulin-induced hypoglycemia without an obvious plasma ACTH response.

Case Report

A 51-yr-old male with a 3 yr history of truncal obesity, proximal muscle weakness and wasting, hypertension and decreased libido was admitted to our hospital in July, 1984. His medical history revealed a gastric ulcer at 31 yr of age and urinary stones

at 48 yr. The patient's mother died of cerebral apoplexy. The patient had a moon face, buffalo hump, gynecomastia, bruising, muscle atrophy, and pretibial edema. There was no obvious hirsutism, acne or striae cutis distensae. His body height was 164.5 cm and body weight 64 kg. Blood pressure was 190/110 mmHg.

Laboratory investigations revealed a red blood cell count of $430 \times 10^4/\text{mm}^3$, hemoglobin, 14.0 g/dl; hematocrit, 41.9%. The white blood cell count was $9300/\text{mm}^3$, and platelet count, $188000/\text{mm}^3$. ESR was 3 mm/hr. Serum electrolytes were: Na, 142 mEq/l; K, 2.8 mEq/l; Cl, 106 mEq/l; and Ca 8.4 mg/dl. Serum BUN was 14.9 mg/dl; creatinine, 0.64 mg/dl, uric acid, 11.0 mg/dl. Total serum protein was 6.03 g/dl; albumin 3.97 g/dl; globulin, 2.06 g/dl; GOT 9.0 IU; GPT, 12.0 IU; LDH, 476 IU; CPK, 18 IU; γ -GTP, 10 IU. 75 GTT: blood glucose levels were 142, 219, 206, 167 and 187 mg/dl at 0, 30, 60, 90 and 120 min, respectively.

Endocrinological investigations

The basal hormone levels are shown in Table 1 and Figures 1-3. ACTH levels

Table 1. Baseline endocrine data on the patient.

Examination	Result	Normal range
Urinary 17-OHCS (mg/day)	20.7-23.6	3-9
Urinary 17-KS (mg/day)	2.4-3.2	3-9
Plasma cortisol ($\mu\text{g}/\text{dl}$)	19.5-26.9	5.4-22.6
Plasma aldosterone (pg/ml)	96.1	47-131
Plasma DOC (pg/ml)	280.0	20-200
Plasma corticosterone (ng/ml)	7.16	1-10
Plasma DHEA-S (ng/ml)	249.0	400-1500
Plasma testosterone (ng/ml)	1.5	4.0-14.5
Plasma ACTH (pg/ml)	10	10-80
Plasma renin activity (ng/ml/hr)	1.73	0.5-2.5
Plasma norepinephrine (pg/ml)	310.0	50-400
Plasma epinephrine (pg/ml)	10.0	10
Urinary norepinephrine ($\mu\text{g}/\text{day}$)	676.0	90
Urinary epinephrine ($\mu\text{g}/\text{day}$)	7.3	10
Urinary dopamine ($\mu\text{g}/\text{day}$)	6300.0	700
Urinary VMA (mg/day)	4.1	3-8

Fig. 1. Diurnal plasma cortisol rhythm and effect of iv administration of 1-24 ACTH (0.25 mg) on the cortisol level.

Fig. 2. Provocative tests of pituitary-adrenal function on the patient. Metyrapone (0.5 g) was given orally every 4 hr for 6 times (total 3 g). Ovine CRF (1 $\mu\text{g/kg}$) or regular insulin (0.1 U/kg) was given iv.

were always at undetectable levels. Plasma cortisol and urinary 17-OHCS were elevated, while urinary 17-KS levels were near the lower limits of the normal range. Urinary norepinephrine and dopamine were elevated. Plasma ACTH and cortisol levels did not show a diurnal rhythm. Plasma cortisol responded markedly to an iv administration of 0.25 mg 1-24 ACTH (Cortrosyn) (Fig. 1). Low and high dose dexamethasone tests (2 mg and 8 mg) failed to suppress the urinary 17-OHCS and 17-KS levels. Metyrapone (500 mg every 4 hr for 24 hr, total 3 g) pro-

duced a reduction in urinary 17-OHCS (Fig. 2). Plasma ACTH and cortisol did not show a response to an iv administration of ovine CRF (1 $\mu\text{g/kg}$). In the insulin tolerance test (regular insulin, 0.1 U/kg, iv) the blood glucose level dropped from 96 mg/dl to 33 mg/dl at 30 min. Plasma ACTH stayed at undetectable level, while plasma cortisol responded normally to insulin-induced hypoglycemia. The basal levels of serum GH, LH, FSH, PRL, TSH, T_4 , T_3 , T_3 -RSU were within the normal range. Serum GH showed no response to insulin-induced hypoglycemia.

Fig. 3. Effect of 1-39 ACTH, angiotensin II (A II), insulin, arginine vasopressin (AVP), norepinephrine (NE) and epinephrine (E) on cortisol release by nodular adrenocortical tissue. Sample tissue was obtained at surgical resection. Cortisol releasing activity is the ratio of cortisol released in the second incubation medium to that released in the first incubation medium expressed as a percentage.

In the LH-RH and TRH test, serum LH, FSH and prolactin showed normal responses, whereas serum TSH showed no response. Plasma ACTH and cortisol, and serum GH, LH, FSH, PRL and TRH were measured with commercially available radioimmunoassay kits.

Adrenocortical scintiscan using ^{131}I -adosterol revealed a large bilateral uptake of the tracer with a higher concentration in

the right side. Adrenomedullary scintiscan using ^{131}I -m-iodobenzylguanidine (MIBG) showed accumulations of the tracer on the right side. Computerized tomography showed an enlarged multinodular mass bilaterally in the adrenal glands. Selective venous sampling revealed cortisol elevations in both adrenal veins and a marked norepinephrine elevation in the right adrenal vein (Table 2).

Table 2. Plasma cortisol and norepinephrine levels in various sites of venous catheterization.

Vessel sampled	Cortisol ($\mu\text{g/dl}$)	Norepinephrine (pg/ml)
Inferior vena cava (below the renal vessels)	17.5	310
Right renal vein	18.7	260
Right adrenal vein	74.0	1300
Left renal vein	16.0	340
Left adrenal vein	56.0	460

Blood pressure did not show a positive response to glucagon, metoclopramide or phentolamine.

Surgical and morphological findings

These findings led us to suspect a huge bilateral nodular adrenocortical hyperplasia possibly with right adrenomedullary hyperplasia. Total bilateral adrenalectomy was performed in July 1984. Both halves of the adrenal glands showed huge multiple nodules ranging in size from 0.5 to 4.0 cm. The cut surface of the nodules was yellowish in color. The left and right adrenal glands weighed 76 and 54 g, respectively. Microscopic examination showed that the nodules were not encapsulated and were composed mainly of clear cells and partly of compact cells. The surrounding areas showed normal or compressed cortical cells. There was no evidence of malignancy. Pheochromocytoma was not found, and the existence of a right adrenomedullary hyperplasia was not confirmed because of a failure in staining.

In vitro experiments

The plasma cortisol response to insulin-induced hypoglycemia without an obvious ACTH response led us to speculate that cortisol responded to insulin or an unknown substance elevated in blood by the insulin-induced hypoglycemia. To test this concept, *in vitro* experiments were conducted. The adrenal tissue obtained at surgery was cut into small fragments which were pre-incubated twice (each for 30 min) with Krebs Ringer bicarbonate buffer containing 0.25% bovine serum albumin and 0.2% glucose (KRBG). Then they were incubated with KRBG for 30 min (first incubation), followed by the second incubation for 30 min with regular insulin, 1–39 ACTH, angiotensin II (AII), arginine vasopressin (AVP), norepinephrine and epinephrine. The responses to these substances were expressed by the ratio of cortisol secretion in the second incubation medium to that in

the first incubation medium. Medium cortisol was measured with a commercially available cortisol radioimmunoassay kit (Daiichi Radioisotope Ltd.). Cortisol responded well to ACTH but not to other substances (Fig. 3).

Clinical course

After the operation the patient was treated with hydrocortisone. One year after surgery, when the signs and symptoms of Cushing's syndrome had regressed, the plasma ACTH level at 0900 hr was 123 pg/ml. Six months after surgery he suffered from subacute thyroiditis but recovered following prednisolone administration.

Discussion

We present a case of Cushing's syndrome in which the preoperative investigations suggested a non-ACTH dependent Cushing's syndrome, while computerized tomography and adrenocortical scintigram suggested a huge nodular adrenocortical hyperplasia. The latter was confirmed in surgery.

Adrenocortical nodules have been classified into micro-, macro- and huge nodules depending on their size or weight. Micro nodules are 0.1–0.5 cm in diameter, macro nodules are up to 2.0–3.0 cm and huge nodules are over 90 g or 100 g in weight (both adrenal glands). The pathogenesis of nodular adrenocortical diseases is not known. Some have suggested that it is fundamentally pituitary-dependent because of the non suppressed ACTH level (Choi *et al.*, 1970; May *et al.*, 1983), the high ACTH levels after adrenalectomy (Hidai *et al.*, 1975; Choi *et al.*, 1970), and coexistence of pituitary adenoma (Schteingart and Tsao, 1980; Furukawa *et al.*, 1981) in some patients. Smals *et al.* (1984) systemically compared the biochemical and pathological features of 13 patients with macronodular adrenocortical hyperplasia and 18 patients with

diffuse adrenocortical hyperplasia (which included 9 patients with micronodular adrenocortical hyperplasia), and they suggested that macronodular adrenocortical hyperplasia might be a result of long standing Cushing's disease with varying degrees of pituitary dependence and adrenocortical autonomy. Thus, it is possible that nodular adrenocortical hyperplasia results from an initial hypersecretion of ACTH that ultimately produces semi-autonomous or autonomous nodules (tertiary nodular hyperplasia). Others have suggested that it is primarily an adrenal disorder because the plasma ACTH level cannot be stimulated with metyrapone and lysine vasopressin before adrenalectomy, and in some cases of multiple adrenocortical micronodules, adjacent areas of the adrenal gland were atrophic with lymphocytic infiltrations (Meador *et al.*, 1967; Ruder *et*

al., 1974; Matsukura *et al.*, 1982; Takai *et al.*, 1983). Meador used the term "primary adrenocortical nodular dysplasia" to refer to these cases. Ruder *et al.* (1974) reported that low plasma ACTH levels (7/8), no suppression of dexamethasone (10/10) and no response to metyrapone (6/6) were common abnormalities in these cases and a response to ACTH was absent in 7/12 cases. Therefore, the pathogenesis of micronodular adrenocortical dysplasia may be different from micronodular adrenal hyperplasia (Nishisato *et al.*, 1979; May *et al.*, 1983; Smals *et al.*, 1984) which becomes macronodular adrenocortical hyperplasia after a long period.

Reported cases of macronodular adrenocortical hyperplasia whose pituitary adrenocortical functions were reported (27 cases) (Mellinger & Smith, 1956; Mosier *et al.*, 1960; Silverman *et al.*, 1963; Tucci *et al.*,

Table 3. Reported cases of huge nodular adrenocortical hyperplasia.

	Kirschner 1964	Hidai 1975	Ishihara 1977	Krivitzky 1980	Murayama 1983	Miura 1984	Our case
Sex	F	M	M	F	F	F	M
Age	40	47	51	39	49	62	51
Duration of disease (yrs)	9	2	4		9		3
Adrenal weight (g)							
left/right	44/50	105/56	141/85	30/80	86/64	73/35	55/76
total	95	161	226	110	150	108	131
Urinary 17-OHCS (mg/day)	11.9-20.4	16.9-25.7	17.5-18.5	14-21	18.7-20.1		20.7-23.6
Urinary 17-KS (mg/day)	23.6-37.4	7.7-13.0	5.2	13.0-14.5	8.0-11.5		2.4-3.2
Plasma cortisol (μ g/dl)	13-20	21-23	27.5-32	17-30	17.0-31.9	12-29	19.5-26.9
Plasma ACTH (pg/ml)							
before ADX		low	10-20	10	10	14-20	10
after ADX		850		19			
Dexamethasone (8 mg) suppression	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Metyrapone response		($\pm$)	(+)	(-)	(-)	(+)	(-)
ACTH response	(++)	(++)	(++)		(++)	(+)	(++)
Insulin response							
Plasma ACTH					(-)		(-)
Plasma cortisol					(+)		(+)

ADX, bilateral adrenalectomy.

(-), no response; ($\pm$), low response; (+), normal response; (++) , hyperresponse.

1965; Katz, 1966; Neville & Symington, 1967; Choi *et al.*, 1970; Hartemann *et al.*, 1971; Yamaoka, 1972; Burke & Beardwell, 1973; Huguenin *et al.*, 1973; Arce *et al.*, 1978; Josse *et al.*, 1980; Aron *et al.*, 1981; Furukawa *et al.*, 1981; Yamamoto *et al.*, 1981; Miura *et al.*, 1984) also indicated no suppression following the administration of 8 mg of dexamethasone (20/23). However, more than half of the cases (7/11) indicated responses to metyrapone, and most cases (17/22) showed a response to ACTH administration. Kirshner *et al.* (1964) first reported a patient with huge nodular adrenocortical hyperplasia whose adrenal glands weighed 94 g, and since then several cases of huge nodular adrenocortical hyperplasia with adrenal weight over 90 g have been reported (Table 3). Most cases including our case showed low plasma ACTH levels (5/5), no suppression to 8 mg dexamethasone (6/6) and a hyperresponse to ACTH (6/7). An impaired response to metyrapone was found in 4 of 6 cases. Therefore, huge nodular adrenocortical hyperplasia has more adrenal autonomy than macronodular hyperplasia, although it shows a hyperresponse to ACTH.

Lamberts *et al.* (1984) suggested from *in vitro* experiments that adenomatous or macronodular adrenocortical hyperplasia with a lower ACTH level may sustain a longer hypercortisol state than diffuse adrenal hyperplasia. This may occur more markedly in huge nodular hyperplasia. Two cases (2/2) with huge nodular hyperplasia including our case showed a cortisol response to insulin-induced hypoglycemia without an obvious plasma ACTH response. Our *in vitro* experiment showed that the nodular tissue had a cortisol response to ACTH but no response to other substances which might be elevated in peripheral blood by the insulin-induced hypoglycemia. There remains the possibility that cortisol might respond to other doses of these substances or to other agents which were not tested

and the *in vitro* studies should have been performed at various glucose concentrations in an attempt to reproduce the *in vivo* conditions, since the response to insulin induced hypoglycemia involved not only the insulin level but also the development of hypoglycemia. For example the epinephrine in the concentration used or in higher concentrations could have caused an increase in cortisol secretion at a different level of glucose than the one used in the present study. Although it is difficult to draw a definite conclusion concerning cortisol responsiveness to insulin-induced hypoglycemia, it is possible that adrenal cortisol responded to a slight change in plasma ACTH which was not detected in the ACTH radioimmunoassay, as plasma ACTH levels lower than 10 pg/ml could not be detected with the ACTH radioimmunoassay (Hashimoto *et al.*, 1985). ACTH receptors on hyperplastic adrenal cells might be up-regulated by low plasma ACTH levels.

The patient had high levels of urinary norepinephrine in conjunction with a positive MIBG uptake of the right adrenal medulla suggestive of right medullary hyperplasia, since a normal adrenal medulla does not image with MIBG. Unfortunately we did not confirm this histologically. After operation, urinary norepinephrine levels dropped to one third of the preoperative levels but were still a little high.

No conclusion can be drawn on the pathogenesis of huge nodular adrenocortical hyperplasia, although it appears likely that it may be a result of long standing macronodular adrenocortical hyperplasia. In summary, the results of this study of a huge nodular adrenocortical hyperplasia patient suggest that the characteristics of the disease are: low plasma ACTH level, no suppression with 8 mg dexamethasone, an impaired or no response to metyrapone, a cortisol hyperresponse to ACTH and a cortisol response to insulin-induced hypoglycemia.

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