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Reversible Panhypopituitarism due to Cushing's Syndrome

Kenji Watanabe, MD; Akira Adachi, MD; Ryuichi Nakamura, MD

• **A patient developed reversible panhypopituitarism due to an adrenal adenoma causing Cushing's syndrome. After removal of the adrenal adenoma, thyroid-stimulating hormone, corticotropin, growth hormone, follicle-stimulating hormone, luteinizing hormone, and prolactin responses to various stimuli recovered completely. The reversible panhypopituitarism of this patient may have occurred at the level of the pituitary gland as a result of hypercortisolemia.**

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The suppression of thyroid-stimulating hormone (TSH) with prolonged glucocorticoid therapy or Cushing's syndrome has been described by several investigators.[1-8] The condition is known as "corticogenic hypothyroidism" in the Japanese literature.[3-5] It is not clear whether secretion of other pituitary hormones is affected by glucocorticoids. The problem has not been extensively examined. In the case described herein, we examined the responses of anterior pituitary hormones before and after the removal of a cortisol-secreting adrenal adenoma and found that all suppressed levels of anterior pituitary hormones recovered. The suppressive effect may have occurred at the level of the pituitary gland.

REPORT OF A CASE

A 42-year-old woman was admitted to our hospital because of edema of the face and extremities. She was well until seven months before admission when she felt fatigue and developed facial edema. One month later, she noticed both edema of the extremities and alopecia. She was constipated and felt head heaviness. She had gained 6 kg in weight during the six months preceding admission. She was hypomenorrheic. Laboratory examination revealed that serum triiodothyronine (T_3) and thyroxine (T_4) levels were low. In August 1985, she was referred to our hospital for evaluation of hypothyroidism. Physical examination revealed a temperature of 36.3°C, a pulse rate of 80 beats per minute, and a blood pressure of 140/90 mm Hg. There were no skin striae.

There was no evidence of buffalo hump or central obesity. There was no evidence of hirsutism. The face and the extremities were edematous. The thyroid gland was not palpable. The neck, chest, and abdomen were normal on examination.

The white blood cell count was 13.2×10^9/L (13 200/mm^3), with 0.07 (7%) band forms, 0.64 (64%) segmented forms of neutrophils, 0 (0%) eosinophils, 0.01 (1%) basophils, 0.24 (24%) lymphocytes, and 0.04 (4%) monocytes. The fasting serum glucose level was 4.1 mmol/L (73 mg/dL), and the cholesterol level was 9.96 mmol/L (385 mg/dL). The serum values of sodium ion, potassium ion, and chloride were 142 mmol/L (142 mEq/L), 3.7 mmol/L (3.7 mEq/L), and 101 mmol/L (101 mEq/L), respectively. Tests for antithyroglobulin and antimicrosomal antibodies were negative.

A computed tomographic scan of the head showed no evidence of an abnormal mass in the pituitary fossa. Endocrine studies revealed that serum TSH, T_3, and T_4 levels were low (Table). The serum cortisol level was high, and its diurnal variation was lost. High-dose dexamethasone therapy did not suppress the serum cortisol levels.

An adrenal scintigram using iodine 131–adesterol (6β-iodomethyl-19-norcholest-5[10]-en-3β-ol-^{131}I), an abdominal computed tomographic scan (Fig 1), and an adrenal phlebogram revealed a left-sided adrenal tumor. In addition, the responses of the other anterior pituitary hormones to various stimuli were diminished (Figs 2 through 5).

We removed a 3.5 × 3.0-cm adenoma from the left adrenal gland. The surface of the tumor was yellow with red areas. The remnant of the adrenal cortex was slightly atrophic. Histologically, the adenoma was composed of clear cytoplasmic and compact cells. After removal of the adenoma, the serum T_3, T_4, and cortisol levels returned to normal, and the patient improved symptomatically. Ten months later, we stopped the administration of dexamethasone and reevaluated the responses of the anterior pituitary hormones (Figs 2 through 5). All of the hormone secretions had returned to normal.

COMMENT

There are conflicting reports about the effect of glucocorticoids on each anterior pituitary hormone. Woolf et al[9] found that neither high nor small doses of glucocorticoids affected the TSH response to thyroid-releasing hormone (TRH). On the other hand, Wilber and Utiger[1] noted suppressive effects of glucocorticoids on TSH secretion, and they concluded from animal experiments in vivo and in vitro that this effect was due to TRH suppression. Otsuki et al[8] described a blunted TSH response to TRH in a normal man receiving glucocorticoids. They concluded that short-term (six months or less), low doses of glucocorticoids (≤60 mg of cortisol per day) suppressed the secretion of endogenous TRH, and that long-term (more than six months), high-dose administration of glucocorticoids (>60 mg of cortisol per day) inhibits TSH secretion not only at the suprahypophyseal level but also at the pituitary level. One study[10] showed laboratory evidence of hypothyroidism in 80% of patients with Cushing's syndrome. Other investigators[8] described three patients with Cushing's syndrome who had suboptimal TSH response to TRH and normal T_3 resin sponge uptake. More recently, subnormal TSH responses to TRH, normal total T_4 and free T_4, and

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From the Department of Internal Medicine, Ashikaga Red Cross Hospital, Tochigi, Japan. Dr Nakamura is now with the Department of Medicine, Ida Hospital, Kanagawa, Japan.

Reprint requests to Department of Medicine, Ida Hospital 1272, Nakahara, Kawasaki, Kanagawa, Japan (Dr Nakamura).

Endocrinologic Values Before and After Operation*		
	Before Operation	**After Operation**
TSH, mU/L (μU/mL)	<1.3	<1.3
T_3, nmol/L (ng/dL)	0.46 (30)	1.54 (100)
Free T_3, nmol/L (ng/dL)	0.001 (0.07)	0.004 (0.31)
rT_3, pg/mL	150	223
T_4, nmol/L (μg/dL)	57 (4.4)	95 (7.4)
Free T_4, pmol/L (ng/dL)	10 (0.81)	18 (1.4)
TBG, nmol/L (μg/dL)	180 (14)	240 (19)
Corticotropin, pmol/L (pg/mL)	<4 (<20)	<4 (<20)
Cortisol, nmol/L (μg/dL)	560 (20.2)	260 (9.3)
17-OHCS μmol/d (mg/24 h)	40 (14.5)	14 (5.0)
17-KS, μmol/d (mg/24 h)	20 (5.7)	8 (2.2)
Aldosterone, pmol/L (ng/dL)	128 (4.6)	290 (10.4)
PRL, μ/L (ng/mL)	13	20
LH, IU/L (mIU/mL)	5.6	19
FSH, IU/L (mIU/mL)	3.8	8.9
GH, μg/L (ng/mL)	0.9	0.9
ADH, pg/mL	2.4	2.8
^{131}I uptake, %/d	12.4	. . .
Diurnal Rhythm of Plasma Cortisol, nmol/L (μg/dL)		
8 AM	570 (20.8)	260 (9.3)
8 PM	620 (22.5)	60 (2.3)
Response to Dexamethasone Before Operation		
	Control	**2 mg/d**	**8 mg/d**
Cortisol, nmol/L (μg/dL)	730 (26.6)	500 (18.1)	550 (20.1)
Corticotropin, pmol/L (pg/mL)	<4 (<20)	<4 (<20)	<4 (<20)
17-KS, μmol/d (mg/24 h)	14 (3.9)	17 (5.0)	31 (8.8)
17-OHCS, μmol/d (mg/24 h)	39 (14.3)	39 (14.3)	58 (20.9)

*TSH indicates thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; 17-OHCS, 17-hydroxycorticosteroids; 17-KS, 17 ketosteroids; PRL, prolactin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; and ADH, antidiuretic hormone.

low total T_3 concentrations in the serum of 19 patients with adrenal adenoma and Cushing's syndrome were described.[3] Almost all of these patients had no clinical signs of hypothyroidism.

Hartog et al[11] described one patient with Cushing's syndrome due to adrenal carcinoma and seven patients receiving corticosteroid therapy who showed blunted growth hormone (GH) responses to insulin-induced hypoglycemia. Demura et al[12] described three patients with hypercortisolemia (two cases caused by adrenal adenomas and one case by adrenal carcinoma) who showed impaired GH secretion to various stimuli.

Stiel et al[13] postulated that the chronicity, constancy, and severity of glucocorticoid excess may be factors in the diminution of GH secretion.

Demura et al[12] noted that the basal levels of luteinizing hormone (LH) and the responses of LH to insulin and vasopressin were slightly, but not significantly, suppressed by glucocorticoid therapy in a case of Cushing's syndrome. White et al[14] studied basal serum concentrations of LH and FSH and their responses to luteinizing hormone–releasing hormone (LH-RH) in a woman with Cushing's syndrome and they suggested that a sustained increase in the circulating level of cortisol by itself may have a direct inhibitory effect on the gonadotropin synthesis and/or release, but only when a critical level had been reached. Another

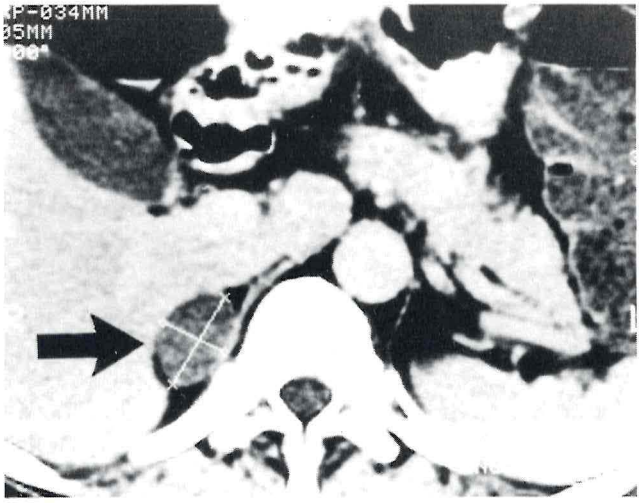

Fig 1.—Abdominal computed tomographic scan showing adrenal tumor.

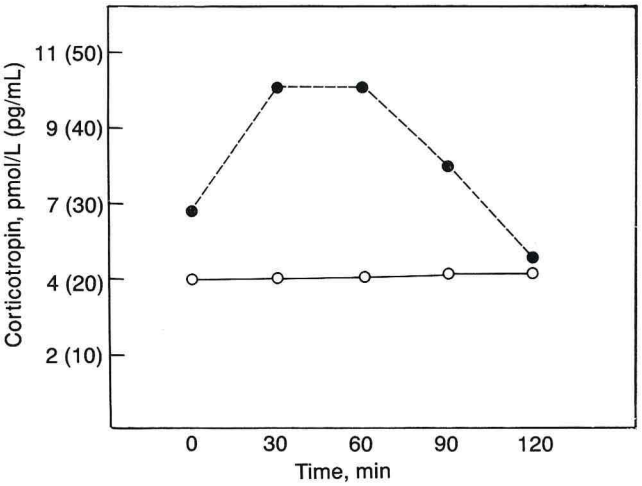

Fig 2.—Plasma corticotropin response to corticotropin-releasing factor (100 μg given intravenously) before (closed circles) and after (open circles) operation.

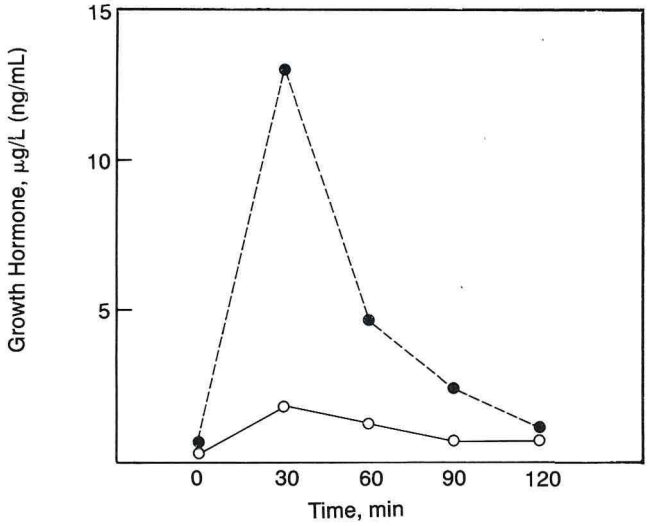

Fig 3.—Plasma growth hormone response to growth hormone–releasing factor (100 μg given intravenously) before (closed circles) and after (open circles) operation.

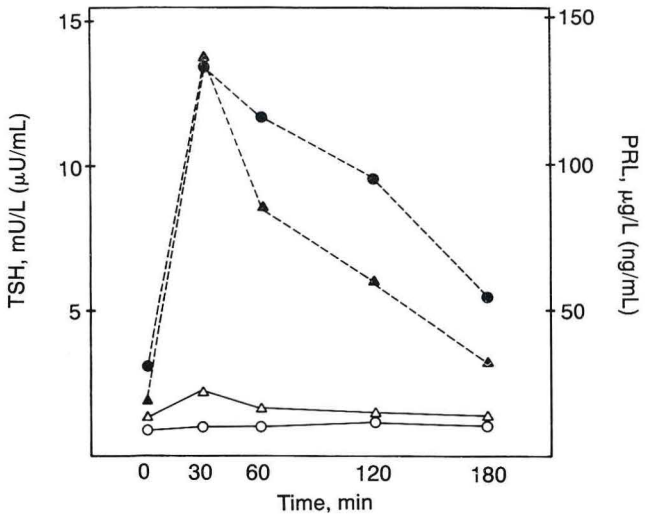

Fig 4.—Plasma thyroid-stimulating hormone (TSH) and prolactin (PRL) responses to thyrotropin-releasing hormone (100 μg given intravenously) before and after operation. Closed circles indicate TSH response before operation; open circles, TSH response after operation; closed triangles, PRL response before operation; and open triangles, PRL response after operation.

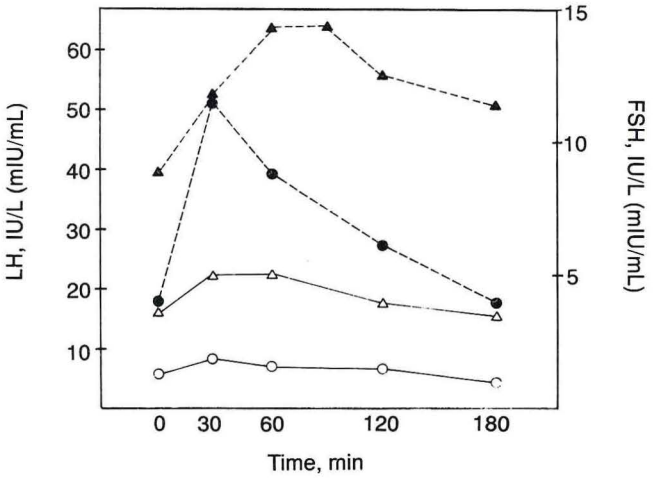

Fig 5.—Plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH) responses to luteinizing hormone–releasing factor (100 μg given intravenously) before and after operation. Closed circles indicate LH response before operation; open circles, LH response after operation; closed triangles, FSH response before operation; and open triangles, FSH response after operation.

investigator[15] noted that pituitary LH and FSH reserves were preserved in Cushing's syndrome due to adrenal adenoma. But in one case of adrenal carcinoma, LH and FSH responses to LH-RH were strongly suppressed. There might have been the possible inhibitory effect of adrenal androgen on the LH and FSH secretions, but all of these patients did not exhibit the hypogonadism.

Sowers et al[16] suggested that pharmacologic doses of glucocorticoid suppressed prolactin (PRL) secretion stimulated by metoclopramide. They postulated that the suppression was caused by a direct effect on the anterior pituitary gland.

Kasperlik-Zaluska and Jeske[17] demonstrated the slightly blunted response of PRL to metoclopramide in patients with Cushing's syndrome. Hashimoto[15] described normal PRL responses to TRH in three cases of Cushing's syndrome (two cases due to adrenal adenoma and one case due to adrenal carcinoma). Their basal PRL level and responses to TRH were normal. Similar findings were noted in another 25 patients with Cushing's syndrome (21 cases of adrenal adenomas and four cases of adrenal carcinomas).[18]

In a previous study[15] of patients with adrenal adenoma causing Cushing's syndrome, the TSH, corticotropin, and GH responses were suppressed, but the LH, FSH, and PRL responses were not appreciably suppressed. In the present case, the patient had Cushing's syndrome due to adrenal adenoma, and the responses of all anterior pituitary hormones were decreased. After removal of the adrenal adenoma, all reserves of anterior pituitary hormone secretions recovered. This result suggests that multiple secretions of the anterior pituitary gland may be inhibited by prolonged high serum levels of cortisol or another unknown steroid. In our case, the responses of all anterior pituitary hormones, including PRL, were suppressed. This finding suggests direct suppression at the level of the anterior pituitary gland.

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