Case Report

A Case of Cushing's Disease Successfully Treated with Bromocriptine

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A case of Cushing's disease is reported. The administration of bromocriptine was extremely effective in reducing excessive adrenocorticotrophic hormone (ACTH) and cortisol in the blood, which were previously not suppressed by 8 mg dexamethasone and persisted even after removal of the ACTH-producing adenoma in the hypophysis.

Key words: ACTH, Pituitary adenoma, Dexamethasone-suppression

Cushing's disease is a disease which was reported for the first time by Cushing (1) in 1932. It presents as systemic hypercortisolism due to increased secretion of adrenocorticotrophic hormone (ACTH) from the hypophysis. It can be endocrinologically diagnosed by virtue of the fact that the disease is not suppressed by 2 mg of dexamethasone but can be suppressed by an 8mg dose (2). The first step in treatment is excision of the hypophyseal adenoma. If clinical symptoms of hypercortisolism do not improve with surgery, adrenalectomy or pharmacotherapy with an inhibitor of cortisol synthesis is initiated (3). In this article, we report a case of Cushing's disease with excessive ACTH and cortisol in the blood which was not suppressed by 8 mg of dexamethasone and which persisted even after excision of the hypophyseal adenoma. Marked improvement was attained only with sustained administration of a dopamine agent, bromocriptine.

CASE

A 31-year-old housewife was admitted to our hospital because of hypertension and weight gain. She had been healthy previously, except for cessation of menstruation 2 years earlier following delivery of her first child. She consulted a doctor about her amenorrhea and was treated with induc-

tion therapy but menstruation did not resume. Her family noticed in March 1986 her face had become full and moon-like in shape. She had also gained about 10kg during the previous two years. She consulted an internist in March 1987 and Cushing's syndrome was suspected due to the hypertension and full moon-like facial shape. On April 21, 1987, she was transferred to Tokai University Hospital for the purpose of precise diagnosis and treatment. Her pregnancy had been complicated by manifestations of toxemia, including proteinuria, but these disappeared after delivery. There was nothing significant in her family history.

Her height was 158 cm, weight 58.5 kg, and blood pressure 150/106 mmHg. A full moon-like facial shape, pigmentation of both sides of the anterior neck and also a buffalo hump at the lower part of her posterior neck, were observed. No physical abnormalities of the heart or lungs were noted. Purple striae were observed on the abdominal skin. Hepatosplenomegaly was not palpable. The limbs were relatively thin compared with the trunk and were also hairy. Neurologically, there was bilateral muscle weakness in the lower limbs and bilateral hyperesthesia in the feet but deep sensibility and tendon reflexes were normal. Her laboratory examinations revealed no abnormalities in blood

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Table 1. Results of examinations at the time of hospitalization.

1) Blood picture			3) Blood chemistry		
RBC	$4.53 \times 10^6 / \mu\text{l}$		Albumin	4.6	g/dl
Hb	14.9	g/dl	GOT	14	u/l
Ht	44.3	%	GPT	36	u/l
MCV	98.0	μ^3	LDH	358	u/l
MCH	32.4	$\mu^2\text{g}$	ALP	58	u/l
MCHC	33.6	%	T-Bilirubin	0.5	mg/dl
WBC	$8.2 \times 10^3 / \mu\text{l}$		Cholesterol	254	mg/dl
seg	72	%	Triglyceride	91	mg/dl
stab	0	%	r-GTP	12	u/l
lymp	25	%	Glucose	139	mg/dl
mono	3	%	BUN	13	mg/dl
Plate	$21.3 \times 10^4 / \mu\text{l}$		Creatinine	0.7	mg/dl
2) ESR			Na	148	mEq/l
	4/h		K	3.5	mEq/l
	11/2h		Cl	107	mEq/l
			Ca	4.9	mEq/l
4) Urinalysis					
Protein	(-)				
Sugar	(-)				
Sediments: no abnormal finding					
5) 75g oral glucose tolerance test					
Time (min)	0		30	60	120
Glucose (mg/dl)	89		144	192	224
					180
					137

cells, urinalysis or blood chemistry (Table 1). Serum potassium was 3.5 mEq/l (normal range: 3.4–4.8 mEq/l). In an oral load test of 75g glucose, the patient was considered to have impaired glucose tolerance according to criteria established by the Japan Diabetic Society (Table 1). For the endocrinological evaluation, plasma ACTH, plasma and liquor CRF (corticotropin releasing factor) and urine cortisol were measured by radioimmunoassay in addition to the standard hormonal analysis. The levels of plasma ACTH and cortisol were high, 68 pg/ml (normal < 50 pg/ml) and 31.5 $\mu\text{g/dl}$ (normal range 5.6–21.3 $\mu\text{g/dl}$), respectively. The circadian rhythm of cortisol had disappeared (Table 2) (4). However CFR in plasma and cerebrospinal fluid had decreased to 0.7 pg/ml and 10.5 pg/ml, respectively (normal range 4–10 pg/ml for plasma and 20–30 pg/ml in liquor) (5). Cushing's disease was suspected on the basis of the increased ACTH and cortisol in the blood and a dexamethasone suppression test was conducted. The results did not show any suppression of plasma cortisol and ACTH at the loads of

0.5, 2.0 and 8.0 mg (Table 2). Simple Turkish saddle photography, Turkish saddle tomography, hypophyseal CT (computed tomography) scan and CT scan after intramedullary injection of metrizamide, revealed no abnormalities. Bilateral adrenal hyperplasia was observed on abdominal CT scan. For the purpose of confirming the diagnosis of Cushing's disease, ACTH was determined in venous blood collected bilaterally from the cervical veins and median cubital vein. The results were 63 pg/ml in the right cervical vein, 124 pg/ml in the left cervical vein and 53 pg/ml in the median cubital vein. In stimulation testing of the anterior lobe of the hypophysis with a tripartite load of insulin, TRH (thyrotrophin-releasing hormone) and LHRH (luteinizing hormone-releasing hormone) (Actrapid insulin 6 U + TRH 500 μg + LHRH 100 μg in 10 ml of physiological saline), secretion of LH (luteinizing hormone), FSH (follicle-stimulating hormone) and PRL (prolactin) were normal but secretion of GH (growth hormone) and TSH (thyroid stimulating hormone) were decreased (Table

Table 2.

1) Results of endocrinological examinations.

Items examined				Normal levels	
Hypothalamus	Plasma CRF	0.7	(pg/ml)	4-10	(pg/ml) ⁵⁾
	Liquor CRF	10.5	(pg/ml)	20-30	(pg/ml)
Hypophysis	ACTH	68	(pg/ml)	< 50	(pg/ml)
Adrenal system	Cortisol morning	31.5	(μ g/dl)	5.6-21.3	(μ g/dl)
	evening	24.6	(μ g/dl)		
Adrenal gland	Urine 17-OHCS	24.4	(mg/day)	2.5-10	(mg/day)
	17-KS	15.6	(mg/day)	6.0-15	(mg/day)
	Free cortisol	1243	(μ g/day)	50-175	(μ g/day)
Thyroid gland	TSH	0.26	(μ IU/ml)	< 5	(μ IU/ml)
	Free T ₃	2.40	(pg/ml)	3.0-5.5	(pg/ml)
	Free T ₄	1.29	(pg/ml)	0.7-2.2	(pg/ml)

17-OHCS: 17-hydroxycorticoids, 17-KS: 17-ketosteroids

2) Results of the Dexamethasone suppression test.

Dexamethasone		First Day	Second Day	First day	Second day
loading amount (mg)	0.5	2.0	2.0	8.0	8.0
Cortisol (μ g/dl)	20.2	22.4	25.5	16.8	18.5
ACTH (pg/ml)	58.0	43.0	42.0	31.0	44.0

3) Stimulation tests of the anterior lobe of the hypophysis by TRH, Insulin, and LHRH.

Time	Cortisol μ g/ml	ACTH pg/ml	GH ng/ml	TSH μ IU/ml	LH mIU/ml	FSH mIU/ml	PRL ng/ml
Basal level	28.1	69	0.5	0.36	5.5	10.3	10.3
30 min	26.9	48	2.3	2.05	92.6	46.3	85.3
60 min	23.2	39	0.6	2.02	62.1	42.5	34.6
120 min	33.1	109	0.5	1.38	43.4	43.3	17.3

2). Free T₄ (L-thyroxine) and Free T₃ (3,5,3'-triiodo-L-thyronine) were normal. On the basis of these findings, Cushing's disease was diagnosed and a microadenoma in the anterior lobe of the hypophysis was excised on June 11, 1987. A microadenoma of 5 × 4 mm was macroscopically observed. The adenoma was diagnosed as a basophilic adenoma by HE staining of the extracted sample. Enzyme antibody staining using ACTH antibody demonstrated that cell groups consisted of 15-30 ACTH-positive cells accompanied by

Crooke's hyaline changes (Fig. 1). This histological finding agrees with the diagnosis of Cushing's disease. One part of the adenoma specimen was immunostained employing monoclonal antibody against glial fibrillary acidic protein to determine whether or not the adenoma possessed neurofilament. No neurofilament was observed.

CLINICAL COURSE

The postoperative course was favorable with no development of diabetes insipidus and plasma

Fig. 1. Histopathological picture of the adenoma obtained from the hypophysis. Immunological staining using ACTH antibody ($\times 300$). Groups of approximately 15–30 ACTH-producing cells (surrounded by small arrows) are accompanied by Crook's hyaline changes (indicated by the large arrow).

cortisol and ACTH were normalized (Fig. 2). However, cortisol and ACTH began to increase again 7 days after surgery to $31.6 \mu\text{g/dl}$ and 70 pg/ml , respectively. This elevated level of cortisol in the blood was not suppressed either by 2.0 mg or 8.0 mg of dexamethasone. In contrast, when hydrocortisone sodium succinate was administered by intravenous instillation (Fig. 3), the ACTH level

in the blood began to decrease at 30 minutes after the start of instillation and had decreased by approximately 50%, 60 minutes later. Consequently, the excision of the adenoma secreting ACTH was considered to have been incomplete. The administra-

Fig. 2. Postoperative clinical course. The left vertical axis shows determined levels of ACTH and cortisol in the blood and the right vertical axis shows the levels of free cortisol in the urine.

Fig. 3. Changes in the levels of plasma ACTH and plasma cortisol at the time of intravenous instillation of hydrocortisone sodium succinate are shown. As a control, a 30-min instillation of 0.5% physiological saline solution (0.5 ml/min), and then, 2 hours later, the administration of hydrocortisone sodium succinate (50 mg/h.) were carried out. Levels of ACTH and cortisol in the blood were determined.

tion of 2.5 mg of bromocriptine was started 24 days after the operation and was increased to 5.0 mg, 41 days post-operatively. Menstruation resumed on the 20th day of administration and blood pressure had improved to 130/80 mmHg. The buffalo humps disappeared on the 97th day of administration. In parallel with the clinical course, levels of ACTH and cortisol in the blood were also normalized. At present (July, 1989), bromocriptine has been reduced to 2.5 mg per day, and levels of ACTH and cortisol have not yet increased.

DISCUSSION

Cushing's disease is hypercortisolism induced by an ACTH-producing adenoma in the anterior lobe of the hypophysis (1). Unlike prolactinomas and GH-producing tumors, ACTH-producing adenomas tend to be microadenomas rather than macroadenomas. Consequently, abnormalities are noticed in only about 10% of cases by simple photography of the Turkish saddle and in 30% by tomography of the Turkish saddle and by CT scan. For this reason, diagnosis is often difficult by imaging alone (6). Therefore, endocrinological examinations are required for making the correct diagnosis. In particular, the disease is characterized by the fact that the high level of cortisol in the blood is suppressed not by a load of 2.0 mg of dexamethasone but by an 8.0 mg dose (2). However, Cushing's disease which is not suppressed even by an 8.0 mg dexamethasone load is known to occur. The frequency is reported to be 16% in Japan (6) and 10–20% in the United States and Europe (7). The interesting question is how the 8 mg dexamethasone non-suppressible Cushing's disease differs from those cases which are suppressed by this dose. In general, particular differences are not noticed between hypophyseal ACTH-producing adenomas not suppressed by 8.0 mg dexamethasone and those which are suppressed by this dose, in terms of the degree of suppression of hormone secretion from the anterior lobe of the hypophysis, size of the tumor and clinical course after the extraction of the adenoma in the hypophysis (6). Carey (8) found that a two-hour intravenous instillation of hydrocortisone sodium succinate in a patient with 8 mg dexamethasone non-suppressible Cushing's disease decreased the level of blood ACTH to 25% of the original

level. Thus he concluded that the hypothalamus-ACTH-adrenal axis of the ACTH-producing adenoma in the hypophysis which is not suppressed by 8.0 mg dexamethasone, cannot specifically recognize dexamethasone as a suppressor. When hydrocortisone sodium succinate was administered to the patient in the present study by intravenous instillation, the high level of ACTH was suppressible. Consequently, it was proved that the ACTH-producing adenoma in the hypophysis of this patient could not recognize dexamethasone as a suppressor but could recognize hydrocortisone sodium succinate. Lamberts et al (9, 10) observed that Cushing's disease caused by excessive CRF in the blood was not suppressed by 8.0 mg dexamethasone and recognized the presence of multiple microadenomas as a histological characteristic in the anterior lobe of the hypophysis. They reported that bromocriptine is an effective treatment. Although excessive CRF in blood was not observed in our patient, bromocriptine was experimentally administered based on the postoperative finding that the persisting high level of ACTH in blood was not suppressed by 8.0 mg dexamethasone and because diffuse microadenomas were observed histologically. As a result, bromocriptine proved to reduce excessive ACTH and cortisol in the blood and to improve clinical symptoms. These facts suggest that bromocriptine was an effective treatment for the ACTH-producing adenoma in the hypophysis of our patient, even though the CRF level in the blood was low, unlike the cases of Cushing's disease accompanying excessive CRF in the blood, reported by Lamberts et al (9, 10). There is only one limited report on the efficacy of bromocriptine for Cushing's disease by Kapcala and Jackson (11). A patient with Cushing's disease whose high level of cortisol was not suppressed by 8.0 mg dexamethasone had the adenoma surgically excised. Since the hypercortisolism was not corrected by surgery, 2-week administration of 5.0–30 mg/day bromocriptine was tried but the results were unfavorable. Consequently, they were forced to conduct proton therapy and bilateral adrenalectomy. In contrast, our case shows that excessive ACTH and cortisol in the blood can be controlled for the relatively long period of 18 months by a small amount of bromocriptine, i.e. 2.0–5.0 mg/day.

Bromocriptine proved to be effective in some cases of Cushing's disease which could not be suppressed by 8.0 mg of dexamethasone, regardless of the presence/absence of complications of excessive CRF in the blood. To examine one of the possible mechanisms of action of bromocriptine, a specimen from the adenoma was immunostained employing monoclonal antibody against glial fibrillary acidic protein to determine whether or not the adenoma possessed neurofilament. No neurofilament was observed. Thus it could not be confirmed that the suppressive effect of bromocriptine on the pituitary-adrenal axis was mediated through dopaminergic stimulation.

Further study will be required to determine which patients with Cushing's disease would benefit from bromocriptine therapy.

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