Preclinical Cushing's Syndrome Presenting with Isolated Adrenocorticotropin (ACTH) Deficiency-like Manifestations and Severe Hypoalbuminemia without Overt Adrenal Masses in a Patient with Chilaiiditi Syndrome and Mental Retardation

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Abstract

A 52-year-old man with Chilaiiditi syndrome and mental retardation was admitted to Kanagawa Rehabilitation Hospital for severe hypoglycemic coma with malnutrition. This patient was first diagnosed as partial isolated adrenocorticotropin deficiency according to his symptoms and clinical course, but he was finally diagnosed as preclinical Cushing's syndrome. Manifestations of this case seemed unusual in spite of autonomic cortisol secretion and the detailed mechanisms of symptoms were unclear. The present case indicates that preclinical Cushing's syndrome may present with various manifestations, and careful diagnosis is necessary. (Internal Medicine 42: 410–415, 2003)

Key words: dexamethasone suppression test, hypothalamic-pituitary-adrenal axis, circadian rhythm of cortisol secretion

Introduction

Preclinical Cushing's syndrome is characterized as autonomic cortisol secretion and it is usually caused by clinically silent adrenal adenomas (1–6). But, previously, a case of preclinical Cushing's syndrome presenting with weight loss was reported (4). On the contrary, isolated adrenocorticotropin (ACTH) deficiency is commonly manifested by weight loss, hypoglycemia, anemia, and hypotension and is

characterized as low plasma ACTH, low serum cortisol levels, and decreased urinary excretions of 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS) (7). But some reports have described that certain cases of isolated ACTH deficiency have low normal plasma cortisol and/or ACTH levels, of which clinical symptoms could be improved by glucocorticoid replacement (8–10). We encountered a case presenting with symptoms similar to those of isolated ACTH deficiency, such as severe hypoglycemia, hypotension, emaciation, muscle atrophy, and anemia (7–17), subsequent to hypoproteinemia and hypoalbuminemia. In this case the symptoms were improved by glucocorticoid replacement in spite of a final diagnosis of preclinical Cushing's syndrome without overt adrenal masses. Herein, we describe and discuss the clinical features of this case.

Case Report

A 52-year-old man with Chilaiiditi syndrome and severe mental retardation was admitted to Kanagawa Rehabilitation Hospital on emergency because of severe hypoglycemic coma (plasma glucose (PG); 19 mg/dl), which was promptly improved by intravenous glucose administration, on March 29, 2001. This was his second hospitalization.

He had been followed up in a home for mentally retarded persons because of severe mental retardation. Prior to the first hospitalization in our hospital, hypoalbuminemia had gradually developed since January 2001 (Fig. 1). Anasarca was noticed and the laboratory findings in the outpatient clinic of our hospital revealed hypoproteinemia (5.0 g/dl) and hypoalbuminemia (2.5 g/dl) on February 14, although he

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Received for publication January 7, 2002; Accepted for publication January 25, 2003

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Figure 1. Clinical course of the present case. *: Intravenous albumin infusion (12.5 g/day), #: Intravenous albumin infusion (25 g/day), \$: Intravenous albumin infusion (11 g/day), ▲: Blood transfusion (2 units/day), solid line; serum albumin, dotted line; serum total protein, &—&: intravenous infusion of glucose or intravenous hyperalimentation, Hb: hemoglobin concentration, TC: total cholesterol, BMI: body mass index.

had eaten a complete 1,600 kcal diet in his home every day. Intravenous administration of human serum albumin was required and subsequently, anasarca improved. Thereafter, he was admitted to our hospital for large purpura on his legs, probably caused by warfarinization against deep venous thrombosis, and severe anemia (hemoglobin 4.8 g/dl) on February 19 (the first hospitalization). Serum albumin level was decreased to 1.9 g/dl on February 23 and human serum albumin was administered again. The laboratory findings revealed that hypoalbuminemia was not caused by nephrotic syndrome, liver disease, or congestive heart failure. Computed tomography (CT) revealed bilateral pleural effusion, which was also improved after human albumin infusion. CT of the abdomen did not reveal any abnormal lesions except gallbladder stone. In addition, the laboratory findings also indicated that his hypoalbuminemia was accompanied by malnutrition. During the first hospitalization, hypoglycemia (fasting plasma glucose (FPG); 41 mg/dl) had been already

noticed without obvious symptoms because of his severe mental retardation. Immunoreactive insulin (IRI) secretion was physiologically suppressed by hypoglycemia. But his FPG levels had been sustained above 60 mg/dl until discharge and his activity of daily life was not disturbed. Then, he was discharged from our hospital on March 22.

On the morning of March 29, he was transferred to our hospital on emergency in a comatose condition (Japanese coma scale 300). His plasma glucose level was very low (PG; 19 mg/dl), then, glucose was intravenously administered. He was admitted to our hospital for further evaluation and treatment for hypoglycemia.

He had a past history of total colectomy due to megacolon of Chilaiddi syndrome in 1980. His height was 142.5 cm and his body weight 29.4 kg on admission (body mass index (BMI); 14.5 kg/m²). His casual body weight before the first hospitalization ranged from 40 to 45 kg (BMI; 19.7 to 22.2 kg/m²). His body temperature was 33.3°C, heart rate 66/min,

Table 1. Laboratory Findings on Admission

WBC	7,200/ μ l	Sodium	137 mEq/l
Lymphocyte count	360/ μ l	Potassium	3.3 mEq/l
RBC	3,030,000/ μ l	Chloride	105 mEq/l
Hb	10 g/dl	Fe	55 μ g/dl
Ht	29%	UIBC	60 μ g/dl
MCV	95.7 fl	AST	50 IU
MCH	33 pg	ALT	44 IU
MCHC	34.5 g/dl	ChE	112 IU
PLT	97,000/ μ l	LAP	70 IU
Reti	10.3%	γ GT	78 IU
TP	5 g/dl	ALP	441 IU
Alb	2.5 g/dl	T. Bil	0.7 mg/dl
PG	51 mg/dl	AVP	0.7 pg/ml
IRI	not detected	Osmolality	277 osm
TC	89 mg/dl	PRA	2.2 ng/ml/h
TG	7 mg/dl	PAC	51 pg/ml
HDL-C	58 mg/dl	f-T3 (1.9–3.4)	1.1 pg/ml
DHEA-S	<50 μ g/dl	f-T4 (0.9–1.5)	1 pg/ml
		TSH (0.36–3.80)	1.61 μ U/ml

( ): normal range. WBC: white blood cell, RBC: red blood cell, MCV: mean corpuscular volume, MCH: mean corpuscular hematocrit, PLT: platelet count, Reti: reticulocyte, TP: total protein, Alb: albumin, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol, DHEA-S: dehydroepiandrosterone-sulfate, UIBC: unsaturated iron-binding capacity, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LAP: leucine aminopeptidase, γ GT: γ -glutamyl transpeptidase, ALP: alkaline phosphatase, T. Bil: total bilirubin, AVP: arginine vasopressin, PRA: plasma renin activity, PAC: plasma aldosterone concentration, f-T3: free triiodothyronine, f-T4: free thyroxine, TSH: thyroid stimulating hormone.

and blood pressure 94/46 mmHg. His emaciation was more conspicuous on the present hospitalization than before and muscles of upper and lower extremities were severely atrophic. His stature was passive supine position and he could not get up by himself. Other physical findings were nothing particular, including leg edema. Skull X-p revealed no abnormality in pituitary fossa. Magnetic resonance imaging (MRI) of brain revealed that the pituitary gland was slightly atrophic.

On the 2nd hospital day, laboratory findings, as shown in Table 1, revealed that he had normocytic and normochromic anemia and that his nutritional condition evaluated by prognostic nutritional index (PNI) (18) was 26.8. The laboratory findings revealed a low ACTH response to hypoglycemia in spite of the normal responses of other counter-regulatory hormones, such as growth hormone (GH, 8.45 ng/ml), noradrenaline (1,517 pg/ml), and glucagon (188 pg/ml) to hypoglycemia. Insulin response to hypoglycemia also seemed normal. CT of abdomen could not detect pancreatic and adrenal lesions. Plasma arginine vasopressin (AVP) level was 0.7 pg/ml and serum osmolality was 277 osm. Urinary cortisol and GH excretions were 47 μ g/day and 20.6 pg/mg Cr, respectively. Together with clinical symptoms, other laboratory findings and endocrinological examinations except for dexamethasone suppression tests (Tables 1–3), we first suspected hypofunction of hypothalamic-pituitary-adrenal axis (HPA-axis) although serum cortisol levels were

not consistently decreased. In addition, although imaging diagnostic procedures, such as gastrointestinal fibroscopy, scintigraphy using ^{67}Ga -citrate, and CT scanning of the chest and abdomen were examined repeatedly, no malignant lesions, which might cause emaciation, could be detected. Then, we once diagnosed as partial isolated ACTH deficiency and replacement with hydrocortisone (5 mg/day, p.o.) was initiated. Although serum albumin levels could not be maintained above 3.0 g/dl under taking 1,500 kcal-diet (approximately 34 kcal/kg ideal body weight, daily protein intake; 56 g/day) following intravenous hyperalimentation (1,320–1,760 kcal/day, glucose; 240–360 g/day, lipids; 20 g/day, amino acids; 41.4–62.2 g/day) (Fig. 1), after hydrocortisone replacement, serum albumin levels could be maintained at more than 3.0 g/dl. In addition, nutritional condition and anemia were gradually improved. Thereafter, hydrocortisone replacement had been up to 10 mg/day since July 17 (Fig. 1). The FPG levels had also been maintained at above 60 mg/dl. Maximum serum albumin level was 3.6 g/dl during hospitalization. Then, he was discharged on August 20, 2001. His serum albumin levels had been maintained above 3.0 g/dl since discharge (maximum serum albumin concentration was 3.7 g/dl during follow-up period, Fig. 1) and PNI was improved (PNI was 41.4 at 9 months after hydrocortisone replacement). Additional examinations were performed after cessation of hydrocortisone replacement because preclinical Cushing's syndrome should be differentially

Table 2. The Endocrinological Examinations

1. CRH, GRH, TRH, and LHRH Stimulation Tests						
Time (min)	0	15	30	60	90	120
ACTH (pg/ml)	<3	7	5	7	4	7
Cortisol (μg/dl)	16.9	22.8	24.7	23.1	19.8	18.4
GH (ng/ml)	6.12	15.1	24.2	25.2	14.6	11.1
TSH (μIU/ml)	0.58	4.74	6.04	5.44	4.8	4.41
f-T3 (pg/ml)	1.3					1.9
f-T4 (pg/ml)	0.8					0.9
LH (mIU/ml)	12.3	26.1	35.5	38.5	34.3	35.9
FSH (mIU/ml)	51.6	59.7	66.7	71.8	73.8	74
Prolactin (ng/ml)	5.9	67.8	70.8	58.2	43.1	32
2. CRH Stimulation Test after 5-day Consecutive Injection of CRH.						
Time (min)	0	15	30	60	90	120
ACTH (pg/ml)	<3	10	13	11	8	10
Cortisol (μg/dl)	12.7	13.9	13.6	17.4	17.8	11.8
3. Rapid ACTH Stimulation Test (tetracosactide acetate 0.25 mg).						
Time (min)	0	30	60			
Cortisol (μg/dl)	13	16.5	18.7			
4. Diurnal Rhythms of Plasma ACTH and Cortisol Levels.						
Hour	0800	1600	2400			
ACTH (pg/ml)	10	22	4			
Cortisol (μg/dl)	11	15.9	12.9			
5. Single-Dose Metyrapone Test.						
	Pre	Post				
ACTH (pg/ml)	28	103				
Cortisol (μg/dl)	14.2	4.9				
11-Deoxycortisol (μg/dl)	1.76	10.4				
6. 75g Oral Glucose Tolerance Test.						
Time (min)	0	30	60	90	120	180
PG (mg/dl)	79	118	138	122	114	76
IRI (μU/ml)	1.6	25.8	48.2	45.5	28.8	33.2
7. Dexamethasone Suppression Tests.						
	1 mg		2 mg		8 mg	
	Pre	Post	Pre	Post	Pre	Post
ACTH (pg/ml)	19	10	12	3	6	11
Cortisol (μg/dl)	9.4	3.3	16.1	2.7	36.4	2.3

CRH: corticotropin-releasing hormone, ACTH: adrenocorticotropin, GRH: growth hormone-releasing hormone, LHRH: leuteinizing hormone-releasing hormone, LH: leuteinizing hormone, FSH: follicle stimulating hormone, PG: plasma glucose, IRI: immunoreactive insulin.

Table 3. Urinary Excretions of Cortisol, 17-OHCS, and 17-KS (3-day consecutive intramuscular injections of tetracosactide acetate zinc (ACTH-Z) 1.0 mg/day)

Day	-3	-2	-1	1	2	3	4
Cortisol (μg/day)	47	163	94	6,010	21,100	13,800	17,800
17-OHCS (mg/day)	1.2	3.8	4.1	22.3	82.9	73.5	105
17-KS (mg/day)	1.9	1.7	1.6	4	9	10	14.6

diagnosed. The result of adrenal scintigraphy using ¹³¹I-adosterol was obscure because of abnormal accumulation due to the gallbladder stone. In addition, abdominal MRI and CT scan did not reveal any abnormal findings except for gallbladder stone. But single-dose dexamethasone suppression tests (19) using 1 mg, 2 mg, and 8 mg dexamethasone failed to suppress serum cortisol levels (Table 2). Thus, a

diagnosis of preclinical Cushing's syndrome was also considered. Although blood sampling from the adrenal vein, performed under sedation, suggested the existence of left adrenal adenoma (Table 4), we were forced to follow-up in our outpatient clinic without adrenalectomy because of the absence of overt adrenal masses and his severe mental retardation.

Table 4. Adrenovenous Blood Sampling

	ACTH (pg/ml)	Cortisol (μg/dl)	DHEA-S (μg/dl)	PRA (ng/ml/h)	PAC (pg/ml)
Upper part of IVC	16	5.2	87	1.6	<10
Lower part of IVC	10	5.6	102	1.7	<10
Right adrenal vein	27	6.3	59	2.6	<10
Left adrenal vein	16	21.0	76	1.8	197
Right renal vein	14	4.6	92	2.4	<10
Left renal vein	20	6.3	99	2.2	16

IVC: inferior vena cava, ACTH: adrenocorticotropin, DHEA-S: dehydroepiandrosterone-sulfate, PRA: plasma renin activity, PAC: plasma aldosterone concentration.

Discussion

The clinical features of preclinical Cushing's syndrome are characterized by autonomic cortisol secretion and are often discovered as adrenal "incidentalomas". In addition, it was also reported that the majority of preclinical Cushing's syndrome patients lack the specific signs and symptoms of classical Cushing's syndrome (1–3, 5, 6). The laboratory findings and endocrinological examinations of the present case (Tables 1–3) showed data compatible with preclinical Cushing's syndrome, whereas the clinical manifestations resembled isolated ACTH deficiency. Iwami et al recently reported a patient of preclinical Cushing's syndrome with body weight loss (4) and they discussed that body weight loss in preclinical Cushing's syndrome might be caused by the difference of cortisol actions on steroid type I (so called mineral corticoid receptor, MR) and type II receptors (so called glucocorticoid receptor, GR) on nutrient intake (20). The present case manifested mal-nutritional conditions, such as severe hypoglycemia and hypoalbuminemia, in addition to weight loss. Chilaiiditi syndrome, which commonly occurs in mentally retarded adults, usually has an asymptomatic finding in adults of no clinical importance (21). In addition, his body weight had been maintained for 20 years since total colectomy. Because no malignant lesion could be detected, such conditions were unlikely to be causes of hypoglycemia and weight loss. The disappearance of circadian rhythm of plasma ACTH levels (Table 2) in the present case might be caused by autonomic secretion of cortisol. ACTH secretion had been suggested to be regulated or modulated by MR at the pituitary level independent of GR at the pituitary level, which was activated by the lower concentration of plasma glucocorticoids compared with GR in extra-pituitary brain regions (22–28). Consequently, such a condition might result in disruption of carbohydrate intake because GR in extra-pituitary brain regions, which was suggested to have a higher threshold than MR and GR in the pituitary gland, might be involved in the induction of carbohydrate intake (20, 23, 28, 29). In addition, the clinical course after hydrocortisone replacement in the present case seemed to imply that endogenous cortisol secretion was not enough to activate nutrient intake in spite of autonomic cortisol production. Namely,

one of the putative causes of severe hypoglycemia might be the disruption of glucose supply, but the precise mechanisms of manifesting hypoglycemia and malnutrition in the present case were unclear.

The second major problem of this case was the absence of overt adrenal mass. Patients with preclinical Cushing's syndrome usually have unilateral or bilateral adrenal mass(es) (1–6). Although blood sampling from the adrenal vein suggested that a cortisol-producing tumor could be existed in the left adrenal gland (Table 4), imaging procedures, such as abdominal CT, abdominal MRI, and adrenal scintigraphy using ¹³¹I-adosterol, could not detect any adrenal tumor. We had to follow-up this patient because of the risks in the perioperative period due to his severe mental retardation, in addition to the absence of overt adrenal mass. Further studies are necessary to determine the surgical approach in such cases.

In summary, although the present case was initially diagnosed as partial isolated ACTH deficiency because of his clinical symptoms and response to hydrocortisone replacement, this case was finally diagnosed as preclinical Cushing's syndrome. Manifestations in the present case seemed paradoxical in spite of autonomic cortisol secretion, the exact causes of hypoglycemia and emaciation, however, could not be identified in spite of endocrinological examinations and repeated imaging diagnostic procedures. The clinical course of the present case indicates that symptoms of preclinical Cushing's syndrome could present various manifestations, such as not only the manifestations of classical Cushing's syndrome but also manifestations like isolated ACTH deficiency. Thus, careful endocrinological evaluation is necessary in such cases.

Acknowledgements: Authors thank Dr. Tetsuo Nishikawa, Professor Kozo Hashimoto, and Professor Toshihiro Suda for their noteworthy discussion.

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