Improved Response of Growth Hormone to Growth Hormone-releasing Hormone and Reversible Chronic Thyroiditis after Hydrocortisone Replacement in Isolated Adrenocorticotropic Hormone Deficiency

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We report a 44-year-old Japanese man who showed a reversible blunted response of growth hormone (GH) to GH-releasing hormone (GRH) stimulation test and reversible chronic thyroiditis accompanied by isolated ACTH deficiency. He was admitted to our hospital because of severe general malaise, hypotension, and hypoglycemia. He showed repeated attacks of hypoglycemia, and his serum sodium level gradually decreased. Finally, he was referred to the endocrinology division, where his adrenocorticotropic hormone (ACTH) and cortisol values were found to be low, and his GH level was slightly elevated. An increased value of thyroid stimulating hormone (TSH) and decreased values of free triidothyronine and free thyroxine were observed along with anti-thyroglobulin antibody, suggesting chronic thyroiditis. Pituitary stimulation tests revealed a blunted response of ACTH and cortisol to corticotropin-releasing hormone, and a blunted response of GH to GRH. Hydrocortisone replacement was then started, and this improved the patient's general condition. His hypothyroid state gradually ameliorated and his titer of anti-thyroglobulin antibody decreased to the normal range. Pituitary function was re-evaluated with GRH stimulation test under a maintenance dose of 20 mg/day hydrocortisone and showed a normal response of GH to GRH. It is suggested that re-evaluation of pituitary and thyroid function is useful for diagnosing isolated ACTH deficiency after starting a maintenance dose of hydrocortisone in order to avoid unnecessary replacement of thyroid hormone.

Key words: Isolated ACTH deficiency, growth hormone, reversible chronic thyroiditis

INTRODUCTION

Isolated adrenocorticotropic hormone (ACTH) deficiency is a rare cause of secondary adrenal insufficiency. It is known that patients with isolated ACTH hormone deficiency sometimes show an abnormal response of anterior pituitary hormone to stimulation tests, and possess antibodies against endocrine glands [1]. Here we describe a case of isolated ACTH deficiency associated with an impaired response of growth hormone (GH) to GH-releasing hormone (GRH) stimulation test and hypothyroidism due to chronic thyroiditis. The impaired response of GH to GRH stimulation test was improved after hydrocortisone replacement. The hypothyroidism was also improved with a decreased titer of anti-thyroid antibody.

CASE REPORT

A 44-year-old Japanese man was admitted to our emergency room because of severe general malaise. He had begun to develop general malaise and anorexia approximately 5 years prior to admission. Subsequently, he had gradually lost 25 kg in weight and his mental activity had decreased. On admission, he was 173 cm in height and weighed 50 kg. His blood pressure was 80/40 mmHg, pulse rate, 89/min and regular, and body temperature 37.4 °C. Examination of the chest and abdomen revealed nothing abnormal. There was no abnormal skin pigmentation, axillary and pubic hair were preserved, and no edema was noted. Tendon reflexes showed slow relaxation. There were no pathological reflexes or sensory disturbance. He did not have any medical history and family history.

Hematological tests showed an elevated white blood cell count of 10400/μl. Blood chemistry examination showed some abnormal values as follows: plasma glucose 36 mg/dl, creatine kinase (CK) 188 U/l, lactate dehydrogenase (LDH) 660 U/l, aspartate aminotransferase (AST) 107 U/l, alanine aminotransferase (ALT) 47 U/l, and C-reactive protein (CRP) 4.49 mg/dl. Serum sodium, potassium, and chloride concentrations were 136 mEq/l, 4.0 mEq/l, and 97 mEq/l, respectively (Table 1). Chest X-ray, brain computed tomography (CT), and abdominal CT showed no abnormality. Spinal puncture yielded normal spinal fluid.

Isotonic fluid infusion with glucose, dopamine, and oxygen supplement was started. Meropenem, 1 gram/day, was given because of suspected sepsis. But, sputum, blood, spinal fluid, and urine cultures were negative. The patient suffered repeated attacks of hypoglycemia and developed hyponatremia (130 mEq/l)

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Table 1 Laboratory Findings on Admission

Complete blood cell counts	value	normal range
WBC (/μl)	10400	4000–8000
RBC ($\times 10^4$/μl)	441	380–480
Hemoglobin (g/dl)	12.9	11.5–15.5
Hematocrit (%)	36.7	34.0–42.0
MCV (fl)	83.2	84.0–99.0
MCH (pg)	29.3	27.0–32.0
MCHC (%)	35.2	32.0–36.0
Platelet ($\times 10^4$/μl)	14.2	14.0–40.0

Blood chemistry	value	normal range
Plasma glucose (mg/dl)	36	70–109
CK (U/l)	188	30–140
LDH (U/l)	660	110–219
AST (U/l)	107	<30
ALT (U/l)	47	<35
Total protein (g/dl)	7.2	6.5–8.0
Albumin (g/dl)	3.9	3.9–4.8
Total cholesterol (mg/dl)	128	140–220
Triglyceride (mg/dl)	154	50–150
Urea nitrogen (mg/dl)	16	8–20
Creatinine (mg/dl)	1.0	0.5–0.8
Sodium (mEq/l)	136	136–145
Potassium (mEq/l)	4.0	3.5–4.8
Chloride (mEq/l)	97	98–108
CRP (mg/dl)	4.49	<0.3

WBC, white blood cell; RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; CK, creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

regardless of glucose and sodium supplementation. Hypotension and fever continued. Therefore the patient was referred to the division of endocrinology, and endocrinological studies were performed.

Table 2 shows the basal endocrinological data. ACTH and cortisol levels were low, and 24-hour urinary determinations of cortisol, 17-hydroxycorticosteroid (17-OHCS) and 17-ketosteroid (17-KS) were within the normal ranges but low concentrations under the stress state. GH level was slightly elevated. In addition, an increased value of thyroid stimulating hormone (TSH), and decreased levels of free triiodothyronine (T3) and free thyroxine (T4) were observed. Anti-thyroglobulin (Tg) antibody was positive. These findings were compatible with chronic thyroiditis. Immunoreactive insulin level was low. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), testosterone, plasma renin activity, and aldosterone were within the normal ranges. Autoantibody against pituitary cells was negative.

Assessment of anterior pituitary function test and its evaluation were performed, using a stimulation test as follows [2]. Corticotropin-releasing hormone (CRH) (human corticorelin 100 μg), LH-releasing hormone (LH-RH) (gonadorelin acetate 100 μg), Thyrotropin-releasing hormone (TRH) (protirelin 500 μg), and GRH (somatorelin acetate 100 μg) were intravenously administrated. Results of the stimulation test were summarized in Table 3A. Normal responses are indicated in parentheses [3–5]. CRH stimulation demonstrated a poor response of ACTH (normal response of peak ACTH ≥ 2-4-fold) and cortisol (normal response of peak cortisol ≥ 20 μg/dl). Upon LH-RH stimulation, LH and FSH showed a normal response (normal response of peak LH ≥ 2-3-fold, and normal response of peak FSH ≥ 1.5-2-fold). TRH stimulation revealed elevated basal level of TSH and a normal response of TSH (normal response of peak TSH ≥ 6 μU/ml or 2.5-fold). Prolactin response to TRH stimulation was normal (normal response of peak PRL ≥ 2.0-fold). GRH stimulation elicited elevated basal level of GH but a poor response (normal response of peak GH ≥ 15 ng/ml). Magnetic resonance imaging (MRI) revealed a normal pituitary. An ultrasonic imaging study of the thyroid gave normal results.

The patient received an intravenous replacement of hydrocortisone (300 mg/day) immediately after the stimulation tests, and his symptoms including general malaise, anorexia and fever were gradually resolved. Hypoglycemia and hyponatremia did not recur. The elevated values of CK, LDH, AST, ALT, and CRP decreased to the normal ranges.

Along with the amelioration of general malaise, hypoglycemia, hypotension, and hyponatremia, the dose of hydrocortisone was tapered to 20 mg a day. After the improvement in his general condition with hydrocortisone replacement, the patient was discharged 32 days after the admission. His endocrinological profiles had been re-evaluated in the outpatient clinic. After hydrocortisone replacement (20 mg daily), the basal levels of TSH and GH were normal, and the stimulation test (TRH and GRH) responses of TSH

Table 2 Endocrinological Findings on Admission

	Values	Normal range
ACTH (pg/ml)	3	6–36
Cortisol (μg/dl)	1.8	3.8–18.4
Urine free cortisol (μg/day)	13	11–80
Urine 17-OHCS (mg/day)	8.2	3.4–12.4
Urine 17-KS (mg/day)	6.5	4.6–18.0
GH (ng/ml)	6.93	<1.46
LH (mU/ml)	7.2	1.1–8.8
FSH (mU/ml)	2.1	1.8–13.6
Testosterone (ng/dl)	340	320–1030
PRL (ng/dl)	25.6	<30
TSH (μU/ml)	4.77	0.3–4.0
Free T3 (pg/ml)	1.59	2.50–4.50
Free T4 (ng/dl)	0.48	0.75–1.75
Tg Ab (U/ml)	451.4	<55.0
TPO Ab (U/ml)	2.7	<10.0
PRA (ng/ml/h)	2.2	0.3–2.9
Aldosterone (pg/ml)	56	30–159
IRI (μU/ml)	1.7	3.0–17.0
Anti-pituitary antibody	(-)	(-)

ACTH, adrenocorticotropic hormone; 17-OHCS, 17-hydroxycorticosteroids; 17-KS, 17-ketosteroids; GH, growth hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; PRL, prolactin; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; Tg Ab, anti-thyroglobulin antibody; TPO Ab, anti-thyroid peroxidase antibody; PRA, plasma renin activity; IRI, immunoreactive insulin.

Table 3A Responses of anterior pituitary hormone to stimulation tests (CRH, LH-RH, TRH, and GRH) before hydrocortisone replacement

	Basal	30 min	60 min	90 min	120 min
ACTH (pg/ml)	<3	5	5	5	6
Cortisol (μg/dl)	0.7	0.9	1.1	1.0	0.9
LH (m U/ml)	8.1	26.1	28.0	24.5	21.8
FSH (m U/ml)	2.4	3.3	3.6	3.7	3.6
TSH (μ U/ml)	19.90	36.34	32.96	29.13	25.23
Prolactin (ng/dl)	25.6	52.7	47.0	40.3	33.3
GH (ng/ml)	4.26	3.92	5.22	5.46	4.24

Table 3B Responses of anterior pituitary hormone to stimulation tests (TRH and GRH) after hydrocortisone replacement

	Basal	30 min	60 min	90 min	120 min
TSH (μ U/ml)	2.78	15.79	12.55	8.89	6.69
Prolactin (ng/dl)	13.5	44.0	28.9	17.1	12.3
GH (ng/ml)	0.93	27.83	12.50	9.62	7.81

CRH, corticotrophin-releasing hormone; LH-RH, luteinizing hormone-releasing hormone; TRH, thyrotropin-releasing hormone; GRH, growth hormone-releasing hormone; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid stimulating hormone; GH, growth hormone.

Table 4 Thyroid function and titers of anti-thyroid antibody

	A/D	3 mo after D/C	normal range
TSH (μU/ml)	4.77	2.908	0.3–4.0
Free T3 (pg/ml)	1.59	3.52	2.50–4.50
Free T4 (ng/dl)	0.48	1.04	0.75–1.75
Tg Ab (U/ml)	451.4	48.3	<55.0
TPO Ab (U/ml)	2.7	4.4	<10.0

A/D, admission; mo, month; D/C, discharge; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; Tg Ab, anti-thyroglobulin antibody; TPO Ab, anti-thyroid peroxidase antibody.

and GH improved three months after the discharge (Table 3B). Thyroid function improved and the titer of anti-Tg antibody gradually decreased to the normal range (Table 4). This case was, therefore, diagnosed as isolated ACTH deficiency accompanied by reversible chronic thyroiditis. The patient has been doing well as

an outpatient for the last six years.

DISCUSSION

We have reported a patient with isolated ACTH deficiency, chronic thyroiditis with anti-Tg antibody, and a poor response of GH to GRH stimulation test. After a maintenance dose of hydrocortisone, the chronic thyroiditis and poor GH response were improved. The patient showed that immunoreactive insulin level was low. It was suggested that hypoglycemia induced suppressed immunoreactive insulin level to increase blood glucose in the patient.

Isolated ACTH deficiency is a heterogeneous disorder with several etiologies reported including a congenital defect [6], incomplete pituitary infarction associated with pregnancy [7], hypothalamic damage due to birth trauma [8], acute intermittent porphyria [9], and lymphocytic hypophysitis [10]. It is also reported that isolated ACTH deficiency is caused by extremely rare genetic disorders, pro-opiomelanocortin gene disorders [11], congenital impaired function of pro-hormone convertase 1 [12], and TPIT gene mutations found in neonatal isolated ACTH deficiency [13]. These genetic disorders are congenital or the onset is neonatal. But, the majority of cases are most likely due to an autoimmune disorder. It was reported that anti-pituitary antibody in the serum of 10 of 21 patients (48% positive) [14], and the presence of anti-corticotropic antibody in the serum of at least one patient [15]. This patient did not show positive titer of the anti-pituitary antibody. But, findings of brain CT and pituitary MRI showed no abnormality, such as tumor, infarction, trauma, and inflammation. Furthermore, the patient had neither past medical history nor family history of adrenal insufficiency. Thus, it was suggested that autoimmune mechanism might cause destruction of ACTH producing cells of the pituitary in the patient.

In the present case, measurement of anti-Tg antibody detected an autoimmune mechanism, and the improvement of thyroid function after hydrocortisone replacement was accompanied by a decrease in the anti-Tg antibody titer. There have been reports of adrenal insufficiency (isolated ACTH deficiency and Addison's disease) accompanied by reversible hypothyroidism, in which two theories to explain the mechanisms of thyroid dysfunction have been proposed [16, 17]. The first possibility is chronic thyroiditis associated with isolated ACTH deficiency, which may affect thyroid function with cortisol deficiency. It is reported that administration of glucocorticoid replacement can clinically improve thyroid function in chronic thyroiditis [18, 19]. This improvement of thyroid function may be associated with resolution of intrathyroidal autoimmune processes inhibiting thyroid hormone synthesis. The second possibility is that chronic cortisol deficiency in isolated ACTH deficiency may directly impair the thyroid response to TSH, synthesis and/or secretion of the thyroid hormone [20, 21].

Abnormal responses of anterior pituitary hormone to stimulation tests were sometimes observed [1]. It is reported that glucocorticoid affects secretion of GH from the pituitary in vitro [22, 23], and that an abnormal GH response to stimulation in cortisol deficiency is improved by cortisol replacement [24]. In our patient, GH responsiveness to GRH was improved. Thus it is suggested that cortisol is responsible for normal secretion of GH in response to GRH stimulation.

In conclusion, the findings in the present case indicate that chronic cortisol deficiency may impair the response of GH to GRH stimulation and thyroid function with anti-thyroid antibody. A follow-up re-evaluation of the anterior lobe of the pituitary and thyroid function a few months after hydrocortisone replacement is recommended for diagnosis of isolated ACTH deficiency in order to avoid unnecessary replacement of thyroid hormone.

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