

Case Report

Isolated Adrenocorticotrophic Hormone (ACTH) Deficiency and Thyroid-Stimulating Hormone (TSH)-Thyroid Hormone Derangement: Report of Three Cases

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Abstract: We present three cases of isolated adrenocorticotropin (ACTH) deficiency accompanied by derangement of the thyroid-stimulating hormone (TSH)-thyroidal axis. Thyroid hormone and TSH levels were evaluated before and after cortisol replacement. Although markedly elevated levels of TSH were noted in one case, this patient also showed typical features of Hashimoto's thyroiditis. In the other two cases, basal TSH levels were increased, and replacement of cortisol reversed the values. We have previously reported that interference of thyroid hormone synthesis and/or secretion by glucocorticoid deficiency is a major cause of TSH-thyroidal axis derangement. However, it has been shown that a considerable number of reported cases exhibit severe hypothyroidism due to Hashimoto's thyroiditis, as was shown in case 2. It has been recognized that, whether the origin is the pituitary or the adrenal gland, polyglandular failure is a complex of autoimmune endocrinopathy. Alternatively, it is assumed that depletion of the physiological concentration of cortisol may worsen hypothyroidism due to Hashimoto's thyroiditis, possibly through modification of T cell function. Since transient abnormalities of the TSH-thyroidal axis and growth hormone could occur in glucocorticoid-deficient patients along with derangement of other pituitary hormones, hormonal evaluation should be carried out after a sufficiently long interval following cortisol replacement.

Keywords: adrenocorticotrophic hormone deficiency, hypothyroidism, hypocortisolism, Hashimoto's thyroiditis
J Saitama Med School 2004;31:115-120

(Received February 23, 2004)

Introduction

Isolated adrenocorticotrophic hormone (ACTH) deficiency is regarded as a rare disorder characterized by hypocortisolism. It has been reported that this disorder is often accompanied by derangement of the thyroid-stimulating hormone (TSH)-thyroidal axis¹⁻³. As a considerable number of patients with isolated ACTH deficiency have been proven to possess circulating auto-antibodies against pituitary cells⁴, this disease is presumed to be caused by an autoimmune mechanism. We have previously reported that the abnormality in the pituitary-thyroid axis is transient, and can be reversed by glucocorticoid replacement⁵. A literature survey revealed that interference of thyroid hormone synthesis and/or secretion by glucocorticoid deficiency

is the major cause of the thyroid dysfunction, rather than autoimmune thyroid disease⁵. However, we have also noticed that a considerable number of cases are accompanied by severe hypothyroidism due to Hashimoto's thyroiditis or primary hypothyroidism⁶⁻⁸. Here we describe three cases of isolated ACTH deficiency experienced recently at our hospital and discuss the possible relationship between ACTH deficiency and the TSH-thyroidal axis.

Case reports

Case 1

A 64-year-old man was admitted to Saitama Medical School Hospital because of general fatigue and weight loss. He had lost 14 kg in weight over the previous

11 months. Physical examination showed emaciation with a body weight of 40 kg and height of 160 cm. Body temperature was 36.2 °C, pulse rate was 58/min, and blood pressure was 136/74 mmHg. There was no hyperpigmentation on his skin or mucosa. The thyroid gland was normal in size and consistency. Blood chemistry revealed hypoglycemia (fasting plasma glucose (FPG): 59 mg/dl), a slightly high creatinine kinase level (234 IU/l), and hyponatremia (121 mEq/l). Hematological tests revealed a white blood cell count of 6870/ μ l with 18.1 % eosinophils. Basal endocrinological data are shown in Table 1, and the results of various hormone-stimulating tests are summarized in Table 2. Auto-antibodies against the pituitary and thyroid glands were all negative. Magnetic resonance imaging (MRI) of the head showed no specific lesion around the pituitary gland. Basal endocrinological data as well as various hormone-stimulating tests showed central hypocortisolism with mildly elevated TSH values. These data indicated that the most compatible diagnosis was isolated ACTH deficiency. The patient's symptoms gradually improved after hydrocortisone replacement. Without thyroid hormone replacement, increased levels of TSH and responses to TRH returned to the reference range, as shown in Table 3.

Case 2

A 58-year-old woman was referred to Saitama Medical

School Hospital for evaluation and treatment of hypoglycemia. She had been suffering from generalized edema and loss of appetite. Due to loss of consciousness, she was treated at an emergency unit and found to have bradycardia (48/min) and pericardial effusion. Since laboratory tests showed positive anti-thyroid antibodies and decreased thyroid hormone levels, she had been treated as having hypothyroidism due to Hashimoto's thyroiditis. Replacement of L-thyroxine had improved her general condition, but hypoglycemia was observed (32 mg/dl). To examine further the pathogenesis of the fasting hypoglycemia, she was referred to our hospital. Her condition was relatively good with a body weight of 47 kg and height of 148 cm. Blood pressure was 128/96 mmHg and heart rate was 64/min. No hyperpigmentation was observed on her skin and mucosa. The thyroid gland was mildly enlarged. Blood chemistry showed elevation of the total cholesterol (243 mg/dl) and creatinine kinase (387 IU/ml) levels. The serum sodium concentration was 136 mEq/l and FPG was 38 mg/dl. Basal endocrinological data and results of various hormonal tests under L-thyroxine replacement (50 μ g/day) are summarized in Tables 1 and 2, respectively. Anti-pituitary auto-antibodies were negative and thyroid-related antibodies were positive: the titer of thyroperoxidase antibody was higher than 30 U/ml and that of thyroglobulin antibody was more than 100 U/ml. Along with the decreased levels of ACTH

Table 1. Basal endocrinological data

	case 1	case 2	case 3	Reference range
GH	4.9	1	2.2	<5.0 ng/ml
LH	5.6	9.6	8.7	1.8-8.3 mIU/ml
FSH	4.1	46.6	8	1.6-11.0 mIU/ml
ACTH	<5.0	<3.0	<5.0	6.0-36.0 pg/ml
Prolactin	-	29.1	17.5	2.7-16.8 ng/ml
TSH	7.35	55.8	8.5	0.43-3.94 μ U/ml
Free tri-iodothyronine	3.43	2.12	3.1	3.14-4.93 pg/ml
Free thyroxine	1.14	0.35	1.52	0.82-1.59 ng/dl
Thyroperoxidase antibody	<0.3	>100	<0.3	<0.3 U/ml
Thyroglobulin antibody	<0.3	>30	<0.3	<0.3 U/ml
Serum cortisol	0.7	0.6	1	3.0-15.2 mg/dl
Urine 17-KS	0.9	0.6	1.5	4.2-12.4 mg/day
Urine 17-OHCS	3	1	0.5	3.1-8.7 mg/dl
Urine cortisol	<2	<2	<2	35-160 μ g/day

GH: growth hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; ACTH: adrenocorticotropin; TSH: thyroid-stimulating hormone; KS: ketosteroids; OHCS: hydroxycorticosteroids

and cortisol, it was found that growth hormone (GH) did not respond well against GH-releasing hormone (GRH) and insulin-induced hypoglycemia. MRI did not reveal any lesions around the pituitary. Findings of thyroid sonography, i.e. decreased and non-homogeneous echogenicity, were compatible with the diagnosis of Hashimoto's thyroiditis. These data indicated that the case was most compatible with a diagnosis of partial hypopituitarism with hypothyroidism due to Hashimoto's thyroiditis. However, as Hashimoto et al.⁹⁾ had noted that the low or absent response of GH in cases of isolated ACTH deficiency would recover after cortisol replacement, the GH response was re-evaluated after replacement of hydrocortisone (20 µg/day) and L-thyroxine (100 µg/day). Three months later, basal pituitary hormonal levels as well as the GH response were studied, and it was found that the diminished response of GH against GRH had improved (Table 3).

Table 2. Hormone-stimulating tests (before replacement)

			Time		
			0	30	60
Case 1	CRH test				
	ACTH	pg/ml	8	5	4
	Cortisol	mg/dl	0.4	0.3	0.4
	TRH test				
	TSH	µU/ml	7.4	41	35.6
	GRH test				
	GH	ng/ml	4.9	19.8	20.5
Case 2	CRH test				
	ACTH	pg/ml	4	4	3
	Cortisol	mg/dl	0.3	0.3	0.3
	TRH test				
	TSH	µU/ml	74.9	335	273
	prolactin	ng/ml	28.7	197.3	129.5
	GRH test				
	GH	ng/ml	1	2.3	2.3
	Insulin tolerance test				
GH	ng/ml	1	1	2.5	
Case 3	CRH test				
	ACTH	pg/ml	5	5	5
	Cortisol	mg/dl	1	1	1
	TRH test				
	TSH	µU/ml	6.9	26.3	22.9
	GRH test				
	GH	ng/ml	1	2	6.2
	<i>l</i> -arginine test				
GH	ng/ml	1	1	2.3	

Anterior pituitary hormones and cortisol responses were assessed by administration of CRH (100 mg), TRH (500 mg), GRH (100 mg), *l*-arginine (30 g), and insulin (0.05 U/kg). CRH: corticotropin-releasing hormone; GRH: growth hormone-releasing hormone; TRH: thyrotropin-releasing hormone. Response of these pituitary hormones was described in ref. 16.

Table 3. Hormone-stimulating tests (after replacement)

			Time		
			0	30	60
Case 1	TRH test				
	TSH	µU/ml	3.4	14.2	15.8
Case 2	GRH test				
	GH	ng/ml	0.1	13.3	15.1
Case 3	TRH test				
	TSH	µU/ml	3	10.3	12.3
	GRH test				
	GH	ng/ml	2.1	8.6	7.2

TSH and GH responses were re-assessed by administration of TRH (500 mg) and GRH (100 mg) after hormone replacement

Case 3

A 64-year-old man was referred to Saitama Medical School Hospital for evaluation and treatment of hematological abnormalities. He had been well until 18 months before, when he noticed general fatigue and persistent cramp in the lower extremities. He had lost 6 kg in weight over the previous year. His weight was 48 kg and height was 159 cm. Body temperature was 36.6 °C, pulse rate was 78/min, and blood pressure was 150/96 mmHg. No hyperpigmentation was observed on his skin or mucosa. His thyroid gland was normal in size and consistency. Hematological examination showed hypochromic and hypovolemic anemia (Hb 10.9 g/dl, MCV 89.4 fl, MCH 28.1 pg, MCHC 31.4 %) and thrombocytopenia (75,000 /µl). Blood chemistry revealed hyponatremia (126 mEq/l) and mild elevation of the creatinine kinase level (243 IU/l). His fasting plasma glucose level was 52 mg/dl. To examine the hyponatremia and low plasma glucose, we evaluated his hormonal status. Basal endocrinological data and results of hormone-stimulating tests are shown in Tables 1 and 2. In addition to the decreased levels of ACTH and cortisol, it was found that GH responded to neither GRH nor *L*-arginine. Auto-antibodies against pituitary and thyroid were negative. MRI of the head showed no specific lesion around the pituitary gland. Anemia and thrombocytopenia improved 3 months after cortisol replacement. As in case 2, we re-evaluated the patient's hormonal status and found that the low response of GH against GRH was improved.

Discussion

Several hormonal abnormalities have been reported in cases of isolated ACTH deficiency^{5, 7, 9)}. We and others have demonstrated increased basal TSH or

TSH hyper-responsiveness to TRH in about half of all reported cases; increased basal TSH levels were observed even in patients with normal thyroid hormone values. To date, several interactions between glucocorticoid and the pituitary-thyroid axis have been reported^{9, 10}. It is suggested that the physiological concentration of glucocorticoid has a suppressive effect on TSH secretion. Glucocorticoid deficiency may therefore be one of the causes of the increased basal TSH level in isolated ACTH deficiency. Similarly, the cases presented also showed increased values of basal TSH. Hyper-responsiveness of TSH to TRH was diminished after hydrocortisone replacement, although the values of TSH were only observed until 60 min after TRH administration. It is likely that glucocorticoid affects thyroid hormone synthesis and/or secretion more easily in patients with intrinsic thyroid disease. TSH secretion can be impaired not only quantitatively, but also qualitatively¹¹: TSH secreted in response to TRH is biologically inactive in some cases of hypothalamic hypothyroidism. It is therefore possible that elevated levels of TSH in isolated ACTH deficiency would have no stimulatory effect on the thyroid gland.

In a review of 103 reported cases with isolated ACTH deficiency, we found that 12.6 % of the patients were positive for anti-thyroid antibodies⁵. Autoimmune thyroiditis is common in both female and male Japanese individuals, and the prevalence of autoimmune thyroid disease among patients with isolated ACTH deficiency was almost the same in the general Japanese population. However, we also noticed that a considerable number of the patients had severe hypothyroidism due to Hashimoto's thyroiditis, as seen in the second of the present cases⁶⁻⁸. There must be a unique relationship between hypocortisolism and Hashimoto's thyroiditis; primary adrenal insufficiency accompanied by Hashimoto's thyroiditis was a well-known complex of polyglandular autoimmune syndrome¹². It is mostly recognized that, whether the origin is the pituitary or the adrenal gland, polyglandular failure is a complex of autoimmune endocrinopathy. Furthermore, there may be an additional explanation that a depleted physiological concentration of cortisol may worsen hypothyroidism due to Hashimoto's thyroiditis possibly through modification of T-cell function. It has been reported that codon 17 polymorphism of the cytotoxic T lymphocyte antigen 4 (CTLA4) gene is related to Hashimoto's thyroiditis and Addison's disease¹³. An alanine residue at CTLA4 codon 17 confers genetic susceptibility to Hashimoto's thyroiditis, and this was

shown to apply to the subgroup with the susceptibility marker, human leukocyte antigen DQA1*0501+, in patients with adrenal hypocortisolism¹³. It would therefore be intriguing to investigate T-cell function and CTLA4 gene in cases of isolated ACTH deficiency as well.

It has been shown that serum GH levels change little or not at all in response to GRH, insulin-induced hypoglycemia, glucagon and *l*-arginine in patients with isolated ACTH deficiency; GH secretion is more responsive than before hydrocortisone replacement in 78.9 % of cases⁹. These results suggest that the impaired GH response in ACTH-deficient patients is due mostly to hypocortisolism. It is well known that an excess dosage of hydrocortisone suppresses GH secretion in patients with Cushing syndrome and patients treated with high-dose glucocorticoids¹⁴. It has also been shown that cortisol replacement in physiological daily doses increases GH output in patients with Addison's disease by augmenting GH pulse amplitude and interpulse levels¹⁵. This is likely due to attenuation of hypothalamic somatostatin secretion by physiological levels of cortisol, implying that hypocortisolism leads to diminution of GH output with a low GH pulse amplitude. Therefore, it is suggested that a physiological dosage of glucocorticoid is indispensable for normal GH secretion.

The patients presented here were diagnosed as having isolated ACTH deficiency, according to the typical endocrinological findings as well as hormonal re-evaluation after a sufficient time interval on replacement therapy. In case 2, the patient had been supplemented with L-thyroxine before hypocortisolism replacement. It is generally recognized that thyroxine therapy should be carried out after evaluation of ACTH-cortisol axis, which might contribute to earlier diagnosis of this rare complex of isolated ACTH deficiency and severe hypothyroidism. Forster et al. reported that polyglandular autoimmune syndrome occurred relatively often among patients visiting a core medical center, with a 3:1 female to male ratio¹². Although the etiology of severe hypothyroidism due to Hashimoto's thyroiditis seen in isolated ACTH syndrome is uncertain, depletion of the physiological concentration of cortisol may worsen the thyroid destruction through an autoimmune mechanism. Since transient abnormalities of pituitary hormones could occur in glucocorticoid-deficient patients, hormonal evaluation should be carried out after a sufficient period of cortisol replacement.

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症例報告

副腎皮質刺激ホルモン (ACTH) 単独欠損症における甲状腺刺激ホルモン-甲状腺ホルモン値異常：3 例報告 安田重光, 和田誠基, 鈴木美穂, 皆川晃伸, 北濱真司, 飯高誠, 片山茂裕

ACTH単独欠損症では、しばしば甲状腺ホルモン異常が合併するとの報告がある。本論文では副腎皮質刺激ホルモン (ACTH) 単独欠損症における甲状腺刺激ホルモン (TSH)-甲状腺ホルモン値異常に関して、コルチゾール補充前および補充後に評価し得た3例に関して報告した。1例ではTSH値の顕著な上昇を認めるとともに甲状腺自己抗体の存在および特徴的な超音波所見から橋本病の合併と診断し得たが、その他の2例ではコルチゾール補充のみでTSH値上昇は低下し、橋本病の合併は否定された。我々は以前、本症のTSH高値がコルチゾール欠乏による分泌異常であり、生物学的活性を示さない可能性に関して言及したが、その後も本症に自己免疫性甲状腺疾患の橋本病による高度な甲状腺機能低下症を合併したとの報告は多い。本症での甲状腺機能異常は多腺性内分泌障害の可能性も考えられるが、コルチゾール欠乏が免疫応答に異常を来している可能性も否定できない。ACTH単独欠損症のみならずコルチゾール欠乏状態ではTSHや成長ホルモン値の高値を認める場合も多く、初診時に的確な診断は困難であり、それらはコルチゾール補充後に再評価し診断を導く必要があると考えられた。