Reversibly Increased Lymphocyte Response to Mitogens in a Young Man with Isolated Adrenocorticotrophic Hormone Deficiency

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A 21-year-old man with isolated adrenocorticotrophic hormone (ACTH) deficiency complained of loss of consciousness in association with hypoglycemia. Both plasma ACTH and cortisol levels were low and failed to respond to corticotropin-releasing hormone (CRH) stimulation. The patient also showed abnormal findings in hematological examination, such as neutropenia and anemia with lymphocytosis, activity of coagulation factors, and electroencephalography (EEG). Furthermore, mitogen-induced lymphocyte proliferation was increased. After successful replacement therapy with hydrocortisone 15 mg/day, most of these abnormalities including the lymphocyte proliferation were fully restored.

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Key words: adrenocorticotrophic hormone (ACTH) deficiency, lymphocyte proliferation, glucocorticoid

Introduction

Isolated adrenocorticotrophic hormone (ACTH) deficiency has been reported to occur commonly in adult men (1). In the present study, we report a case of isolated ACTH deficiency in a young male whose lymphocyte response to mitogens was markedly increased.

Case Report

A 21-year-old man was admitted to hospital with the complaint of an episode of loss of consciousness in association with hypoglycemia (blood glucose 38 mg/dl), fever, and incontinence. Although no specific family or past medical history was identified, the patient's family mentioned that he gradually became less active from age 15 and had no work since finishing high school.

On admission, he was 169.3 cm tall and weighed 51.7 kg, blood pressure was 94/50 mmHg, pulse rate was 88/min, regular. In general status, pubic hair was sparse and bilateral testes were small. Face color and conjunctivae were normal. Thyroid gland was not swollen. There was no specific abnormal

finding in chest, abdomen, and extremities. There was no neurological abnormality. Leukocyte count was 6,000/ μ l, both neutropenia and lymphocytosis (seg 28.5%, lym 56.3%) were identified. Hematological test also revealed mild anemia (erythrocyte count 4.08×10^4 / μ l, mean corpuscular volume (MCV) 85.1 μ m³, mean corpuscular hemoglobin (MCH) 28.5 pg/cell, mean corpuscular hemoglobin concentration (MCHC) 33.5%, hemoglobin 11.9 g/dl, hematocrit 34.7%). Blood chemistries revealed a slightly increased concentration of muscle-derived enzymes (lactate dehydrogenase 533 IU/l, creatine kinase 385 IU/l). Prothrombin time (PT) and activated partial thromboplastin time (APTT) were prolonged and coagulation factors, 5th, 9th, 11th and 12th, were low (Table 1). As shown in Table 2, both plasma ACTH and cortisol were significantly decreased whereas plasma thyrotropin (TSH) and prolactin (PRL) were normal. The circadian rhythm was not identified in the levels of both ACTH and cortisol. Head-computed tomography (CT), magnetic resonance imaging (MRI), and abdominal CT revealed no abnormal finding. Electroencephalography (EEG) showed that basic rhythm was 7–8 Hz, θ - α rhythm mixed with θ wave, which has been reported in other cases with ACTH deficiency (2, 3). Thus, isolated ACTH deficiency was sus-

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Table 1. Blood Coagulation Analysis

Activities		
	before therapy	after therapy
PT (INR)	1.46	1.29
APTT (sec.)	44.9	37.9
PT: prothrombin time, APTT: activated partial thromboplastin time, INR: international normalized ratio.		
Coagulation factors		
	before therapy	after therapy
5th (%)	61.0	51.4
9th (%)	76.0	52.8
11th (%)	75.4	92.4
12th (%)	69.6	78.9

Table 2. Endocrinological Findings

	before the therapy	after the therapy
ACTH (pg/ml)	8	10
TSH (μ U/ml)	9.3	3.2
LH (mIU/ml)	4.8	3.7
FSH (mIU/ml)	2.5	2.7
GH (ng/ml)	0.28	0.47
PRL (ng/ml)	15.1	9.3
Cortisol (μ g/dl)	<1.0	11.6
Aldosterone (ng/dl)	21	30
DHEA (ng/dl)	273.0	659.0
Testosterone (ng/dl)	537	702
PRA (ng/ml/h)	1.00	3.90

ACTH: adrenocorticotrophic hormone, TSH: thyroid-stimulating hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, GH: growth hormone, PRL: prolactin, DHEA: dehydroepiandrosterone, PRA: plasma renin activity.

Diurnal rhythm of cortisol and ACTH

	06:00	16:00	24:00
Cortisol (μ g/dl)	<1.0	<1.0	<1.0
ACTH (pg/ml)	8	7	6

pected in this case. The results of various endocrinological stimulation tests are shown in Table 3: plasma cortisol did not respond in the rapid ACTH test, and both plasma ACTH and cortisol did not increase in response to the corticotropin-releasing hormone (CRH) stimulation. However, plasma corti-

Table 3. Results of Stimulation Tests

1. Rapid ACTH test (tetracosactide acetate 250 μ g i.v.)

Time (min)	0	30	60
Cortisol (μ g/dl)	<1.0	<1.0	<1.0

2. CRH test (human corticorelin 100 μ g i.v.)

Time (min)	0	15	30	45	60	90	120
Cortisol (μ g/dl)	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
ACTH (pg/ml)	7	<5	6	<5	<5	<5	<5

3. Standard ACTH test (tetracosactide acetate 1 mg i.m. for 3 days)

	0 day	1 day	2 day	3 day
Urine 17-OHCS (mg/day)	<0.02	0.53	3.52	9.05
Urine cortisol (μ g/day)	11.53	14.6	—	81.9
Plasma cortisol (μ g/dl)	<1.0	2.6	9.1	18.4

4. TRH, LH-RH test (protirelin 500 μ g i.v. and gonadorelin acetate 100 μ g i.v.)

Time (min)	0	15	30	60	90	120	180
LH (mIU/ml)	6.0	14.6	17.9	16.8	15.2	12.8	11.2
FSH (mIU/ml)	2.7	3.9	4.1	4.3	4.2	4.1	3.8
TSH (μ U/ml)	4.5	19.9	23.9	19.8	16.0	12.4	—
PRL (ng/ml)	9.8	41.8	35.2	28.4	20.4	15.3	—

sol, and urinary excretion of cortisol and 17-hydroxycorticosteroid (17-OHCS) increased in the 3-day ACTH test. Plasma TSH and plasma PRL responses in the TRH test and LH response in the LH-RH test were all normal whereas plasma FSH response in the LH-RH test was low. Plasma testosterone level was normal (Table 2).

This case was, thus, diagnosed as isolated ACTH deficiency, and treated with glucocorticoid (hydrocortisone 15 mg/day). In response to the replacement therapy, neutropenia, lymphocytosis, and anemia were all restored and normalized. PT and APTT were also normalized. Among coagulation factors reduced at baseline, 11th and 12th factors were restored, whereas 5th and 9th were still low (Table 1). As shown in Fig. 1, mitogen-induced lymphocyte proliferation, which was increased at baseline, was decreased after replacement therapy. Both plasma glucose and insulin response in 75g oral glucose tolerance test (OGTT) were also normalized (Fig. 2). As for the endocrine abnormalities, basal plasma TSH and PRL levels were normalized, and PRA was increased (Table 2). The results of LH-RH test and TRH test were not changed after the treatment. EEG was normalized with 9–10 Hz basic rhythm slightly mixed

Figure 1. Mitogen-induced lymphocyte proliferation. Open bar and closed bar represent ^3H -thymidine uptake of lymphocytes before and after glucocorticoid replacement therapy, respectively. ConA: concanavalin A, PHA: phytohemagglutinin, PWM: pokeweed mitogen.

with θ wave. The patient is currently followed up with hydrocortisone 15 mg/day.

Discussion

We report on a case of isolated ACTH deficiency in a young man. Successful glucocorticoid replacement therapy restored both his daily activities and laboratory findings. It is known that isolated ACTH deficiency is often associated with many abnormal findings other than those of pituitary-adrenal axis: anemia (4), elongation of PT and APTT (5), neutropenia, lymphocytosis (6), and abnormal EEG (2). This case also showed such findings as neutropenia, lymphocytosis, mild anemia, increased levels of muscle-derived enzymes, and abnormal EEG. However, there have been no reports on an abnormality of immunological function in isolated ACTH deficiency. In this study, we examined cellular immunity and demonstrated that mitogen-induced lymphocyte proliferation was increased in the patient. These enhancements were normalized after successful glucocorticoid replacement therapy, suggesting that these abnormal lymphocyte function may be attributable to chronic cortisol deficiency. Glucocorticoids have been reported to have suppressive effects on lymphocyte functions (7). For example, although the mechanism is not well understood, glucocorticoids alter the circulating population of white blood cell resulting in monocytopenia and lymphocytopenia (8–10). Glucocorticoids are also known to inhibit the production of IL-2, which is an

Figure 2. 75 g OGTT. Solid square (■) and open square (□) represent blood glucose concentrations before and after glucocorticoid replacement therapy, respectively. Solid circle (●) and open circle (○) represent plasma insulin levels (IRI) before and after glucocorticoid replacement therapy, respectively.

important T cell growth factor (11–13). Recently, it was suggested that nuclear factor kappa B (NF- κ B), a regulator of immune system and inflammation, may be a target for glucocorticoid-mediated immunosuppression (14, 15). In this context, the increased lymphocyte proliferation reported here may be attributable to long-term deficiency of glucocorticoid.

In this case, prothrombin time and activated partial thromboplastin time were prolonged, and 5th, 9th, 11th and 12th coagulation factors were low. After replacement therapy, however, 11th and 12th factors were restored whereas 5th and 9th were still low. There was a recent report on abnormality of coagulation factors in isolated ACTH deficiency (16).

In summary, we reported a case of isolated ACTH deficiency in a young man whose mitogen-induced lymphocyte proliferation was increased and decreased with successful glucocorticoid replacement therapy.

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