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A CASE OF AN ISOLATED ADRENOCORTICOTROPIN (ACTH) DEFICIENCY : RESOLVED AND DELIVERED A CHILD AFTER 8 YEARS OF TREATMENT

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Abstract: We describe a 19-year-old Japanese woman with isolated ACTH deficiency who improved and delivered a child after 8 years hydrocortisone replacement therapy. Menarche was at the age of 13 y, and menstruation continued regularly. At the age of 16 y general fatigue and amenorrhea developed, and she was referred to our hospital. Her plasma ACTH and cortisol levels were low, and ACTH provocation tests revealed no response. Although the plasma ACTH and cortisol levels were low, dexamethasone suppressed them. Results of other pituitary function tests were normal. Autoantibodies against ACTH-producing cells were identified. She was diagnosed with isolated ACTH deficiency, and we initiated hydrocortisone replacement therapy. Her general condition and anemia were improved, but the amenorrhea persisted. Seven years later, the hydrocortisone was tapered off and menstruation started again. At that time, the test for pituitary autoantibody was negative. One year after fisishing hydrocortisone replacement therapy, she gave birth to a healthy child by natural delivery. This was an atypical case of isolated ACTH deficiency because the ACTH levels were not responsive to provocation tests but were suppressed by dexamethasone. We suggest that the deficiency of ACTH secretion was functional and transient due to the autoimmune mechanism.

Index Terms

isolated adrenocorticotropin deficiency, isolated ACTH deficiency, pituitary autoantibody

Isolated ACTH deficiency is characterized by selected deficiency in ACTH secretion associated with secondary adrenal insufficiency without abnormalities in other pituitary functions. Some reported cases have been recognized to have an autoimmune cause because of positive tests for autoantibodies to ACTH-producing cells[1-4]. Although most patients need hydrocortisone replacement throughout their lives[5], some patients have been reported to have experienced remission[6-7]. We discuss here an interesting ACTH response to the provocation test and the dexamethasone suppression test.

ASSAY METHODS

The concentration of ACTH was measured with radio-immuno-assay (RIA) kit, (ACTH Kit -II, DPC Co., Los Angeles, USA) and immuno-radio-metric assay (IRMA) kit, (ACTH IRMA KIT, Euro-Diagnostics BV, Netherlands). The concentration of cortisol was measured with radio-immuno-assay (RIA) kit, (Gamma Coat™ Cortisol, INCSTER Co., Stillwater, USA). The concentration of growth hormone (GH) was measured with immuno-radio-metric assay

(IRMA) kit, (Daiichi GH Kit, Daiichi RI Lab., Tokyo, Japan), The concentrations of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured with immunoradiometric assay (IRMA) kit (SPAC-S LH Kit and SPACS-FSH Kit, Daiichi RI Lab., Tokyo, Japan). The concentration of estradiol (E_2) was measured with radio-immuno-assay (RIA) kit, (Oestradiol-COATRIA, CIS DIAGNOSTICS K. K., France)

CASE REPORT

The patient was a 19-year-old Japanese woman who was referred to our hospital in June 1989 for evaluation of amenorrhea, hair loss and general fatigue. She was born at full term and after a normal delivery. Her growth and development were normal. Menarche was at 13 y and menstruation continued regularqy after that. At the age of 15 y, following a high fever that persisted for 10 d, iron deficiency anemia developed. She was given iron per os intermittently. From the age of 17 y she suffered amenorrhea accompanied by general fatigue and hair loss. She was admitted to our department for evaluation of pituitary function.

She was 159 cm tall and weighed 40.5 kg. Her body temperature was 35.7 ℃, and her blood pressure was 96/40 mmHg. The hair on her head was thin and yellow-brown in color. Axillar and pubic hair were absent. Her skin was pale and anemic. No abnormalities were found in her heart, lung and abdomen.

Table 1. Laboratory datas on admission

Urine			*Immunological examination*		
Protein	(−)		Micosome test	(−)	
glucose	(−)		Thyroid test	(−)	
Peripheral Blood			Anti-DNA antibody	(−)	
RBC	456×10^4/mm³		LE test	(−)	
Ht	34.4	%	ANA	(−)	
Hb	10.3	g/dl	*Basal Hormone values*		normal range
WBC	6,600/mm³		ACTH	<10.0 pg/ml	(<60)
Plt	21.3×10^4/mm³		GH	0.7 ng/ml	(<2.3)
Blood Chemistry			Prolactin	5.4 ng/ml	(<15)
T. Bil	0.4	mg/dl	LH	16.2 mIU/ml	(1.8~34.9)
ZTT	1.1	KU	FSH	7.4 mIU/ml	(5.2~14.8)
ALP	98	IU/L	TSH	0.4 μU/ml	(0.4~5.0)
GOT	20	IU/L	T_3	136.1 ng/dl	(80~200)
GPT	11	IU/L	T_4	13.7 μg/dl	(4.5~12.0)
LDH	338	IU/L	free T_4	1.4 ng/dl	(0.9~1.8)
ChE	286	IU/L	cortisol	5.6 μg/dl	(4.3~10.7)
LAP	62	IU/L	Aldosterone	110.4 pg/ml	(47~131)
γGTP	7	IU/L	E_2	32 pg/ml	(25~220)
S-Amy	279	IU/L	Progesterone	1.6 ng/ml	(0.1~28)
T Chol	186	mg/dl	U-17OHCS	3.3 mg/day	(2.6~7.8)
TG	141	mg/dl	U-17KS	2.8 mg/day	(1.9~8.5)
BUN	14	mg/dl			
Cr	0.6	mg/dl			
Na	140	mEq/L			
K	4.1	mEq/L			
Cl	103	mEq/L			
Fe	11	μg/dl			
TIBC	328	μg/dl			
CRP	(−)				

1) Urinalysis and peripheral blood examination (Table 1)

Trace positive proteinuria was found, but glucoseuria was negative. The red blood cell count was $456\times10^4/\mu l$ and Hb was 10.3 g/dl. Iron deficiency (Fe 11 μg/dl and total iron binding capacity 328 μg/dl) was found. No other abnormalities were found. Thyroid autoantibody, anti-nuclear antibody and anti-DNA antibody tests were negative.

2) Basal hormone values (Table 1)

Plasma GH (0.7 ng/ml), thyroid stimulating hormone (TSH) (0.4 μU/ml), luteinizing hormone (LH) (16.2 mIU/ml), follicle stimulating hormone (FSH) (7.4 mIU/ml) and prolactin (PRL) (5.4 ng/ml) revealed normal ranges. The plasma ACTH level (<10.0 pg/ml) was undetectable, and cortisol (5.6 μg/dl) was on the low end of the normal range. Urinary 17-hydroxy steroids and 17-ketosteroids were also slightly low but within normal levels at 3.3 mg/d and 2.8 mg/d, respectively. Plasma estradiol (E_2) (<25 pg/ml) was undetectable.

These data indicated partial pituitary insufficiency; therefore, pituitary function tests were performed.

3) Pituitary function test (Table 2, 3)

①GH provocation tests: Arginine test (4.6 to 14.3 ng/ml), glucagon-propranolol test (2.2 to 14.7 ng/ml) and growth hormone releasing hormone (GRH) test (0.6 to 37.5 ng/ml) showed normal responses, but the insulin tolerance test (0.5 to 1.3 ng/ml) showed a low response.

②LH and FSH provocation test: The LH-RH test showed normal LH response (11.2 to 74.2 mIU/ml) but a low FSH response (6.6 to 10.2 mIU/ml).

③TSH and PRL provocation test: The TRH test showed a low but normal TSH response (0.6 to 5.8 μU/ml) and a normal PRL response (10.5 to 62.8 ng/ml).

④ACTH and cortisol provocation tests: In the insulin tolerance test, ACTH (<10.0 to <10.0 pg/ml as measured by ACTH RIA Kit, DPC Co., USA) and cortisol (5.6 to 5.2 μg/dl) showed no response, but the basal levels were within the normal ranges. For the corticotropin releasing hormone (CRH) test, ACTH was measured by RIA and immunoradiometric assay (IRMA). With RIA, ACTH (<10.0 to <10.0 pg/ml) showed no response and was below the detectable levels; with IRMA, ACTH (24 to 31 pg/ml) showed no effective response but was within the detectable levels.

⑤ACTH test: $^{1-24}$ACTH 0.25 mg was administered intravenously and cortisol, aldosterone, and dehydroepiandrosterone sulfate (DHEAS) levels were measured. Cortisol (8.2 to 31.6 μg/dl), aldosterone (25.2 to 107.2 pg/ml) and DHEAS (1.0 to 3.8 ng/ml) showed normal responses.

⑥Overnight dexamethasone suppression test: 1.0 mg of dexamethasone was administered at 9 : 00 pm and ACTH (measured by RIA and IRMA) and cortisol were measured. IRMA results demonstrated that ACTH was suppressed from 37.0 pg/ml to below detectable level. Cortisol also suppressed from 9.0 μg/dl to 1.2 μg/dl. ACTH was not detectable by RIA.

4) Anti-pituitary antibody

Antibodies against pituitary cells were examined by cultured rat GH-producing cell (GH_3 cell) and ACTH-producing cell (AtT-20 cell) incubated with patient sera. Furthermore,

Table 2. Pituitary function tests

GH provocation tests

Arginin test (30 g iv)	Bf.	30'	60'	90'	120'	
GH (ng/ml)	4.6	7.0	14.1	14.3	4.9	
Glucagone-propranolol	Bf.	30'	60'	90'	120'	
GH (ng/ml)	2.2	0.6	0.6	0.7	14.7	
GRH test (100 μg iv)	Bf.	15'	30'	60'	90'	120'
GH (ng/ml)	0.6	2.6	2.6	3.7	7.2	37.5
ITT (0.1 U/kg iv)	Bf.	10'	20'	30'	40'	
GH (ng/ml)	0.5	0.5	0.6	0.6	1.3	

LH-RH test

LH-RH (100 μg iv)	Bf.	15'	30'	60'	90'	120'
LH (mIU/ml)	11.2	40.4	74.2	71.3	68.6	52.1
FSH (mIU/ml)	6.6	8.0	9.5	10.2	10.6	10.9

TRH test

TRH (500 μg iv)	Bf.	15'	30'	60'	90'	120'
TSH (μU/ml)	0.6	4.5	5.8	4.7	3.7	3.0
PRL (ng/ml)	10.5	62.8	53.8	36.7	24.8	18.5

Table 3. Pituitary-adrenal function tests

ITT

regular insulin (0.1 U/kg iv)	Bf.	10'	20'	30'	40'	
B. glucose (mg/dl)	72	53	41	low	low	
ACTH (pg/ml) (RIA : DPC)	<10	<10	<10	<10	<10	
cortisol (μg/dl)	5.6	5.1	4.8	4.7	5.2	

CRH test

CRH (100 μg iv)	Bf.	15'	30'	60'	90'	120'
ACTH (pg/ml) (RIA : <60 pg/ml)	<10	<10	<10	<10	<10	<10
ACTH (pg/ml) (IRMA : 30~60 pg/ml)	24	22	24	27	28	31
cortisol (μg/dl)	9.3	7.4	6.3	7.5	7.3	11.5

Dexamethasone suppression test

Dexamethasone 1.0 mg overnight	Bf.	Af.
ACTH (pg/ml) (RIA : <60 pg/ml)	<10	<10
ACTH (pg/ml) (IRMA : 30~60 pg/ml)	37	<10
cortisol (μg/dl)	9.0	1.2

autoantibodies to rat pituitary tissues were examined. The autoantibody to AtT-20 cell was positive, but the other two were negative.

In summary, this patients had an ACTH secretion deficiency accompanied by low plasma cortisol level. The GH response to the insuln tolerance test was low, but results from the other provocation tests were normal. However, this case was atypical compared with other reported cases because our patient's plasma cortisol levels were low but within the normal range and ACTH and cortisol secretions were suppressed by dexamethasone. We recognize this case as an atypical case of isolated ACTH deficiency, and therefore diagnosed "isolated insufficiency of ACTH secretion".

5) Clinical course and therapy (Fig. 1)

After treatment with hydrocortisone, 15 to 20 mg daily, the patient's general fatigue and anemia improved markedly after 5 mo but her amenorrhea and thin hair persisted. Cyclic female hormone therapy and gonadotropin therapy were started. In April 1995, menstruation resumed, and ACTH levels responded slightly to CRH administration. The hydrocortisone dose was reduced gradually and could be stopped in March 1996. Hydrocortisone withdrawal syndrome was not observed, and the menstrual cycle was regular. In September 1996, the ACTH response (24.9 to 75.0 pg/ml) to CRH was normal, and the basal ACTH and cortisol levels were normal. She married in December 1996 and delivered a healthy child in December 1997.

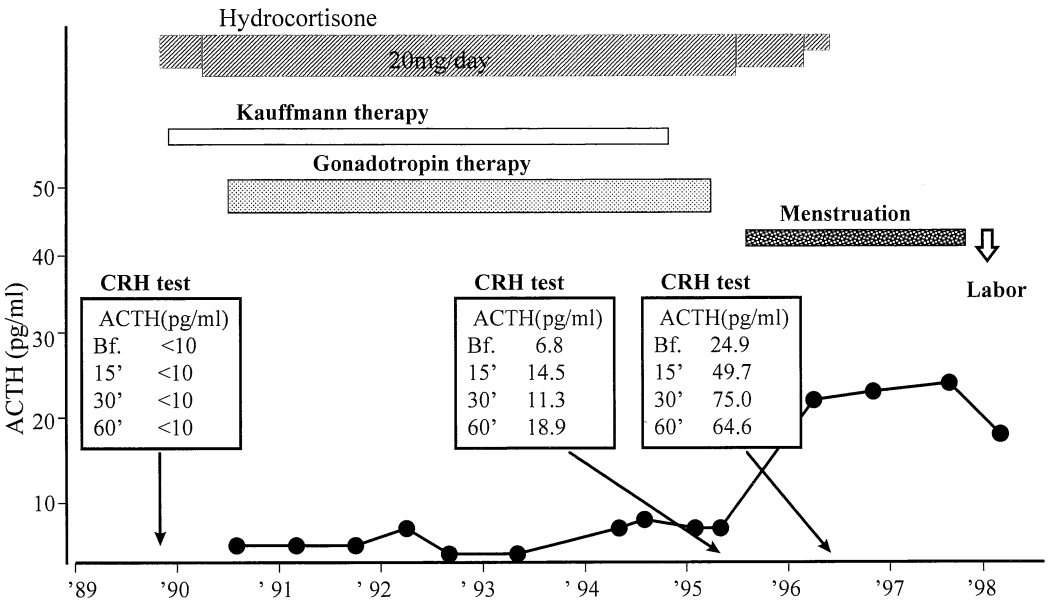

Fig. 1. Clinical course during and after hydrocortisone replacement therapy. The patient delivered a normal, healthy child after 8 years of therapy.

DISCUSSION

Isolated ACTH deficiency is a heterogeneous syndrome with secondary adrenocortical insufficiency due to corticotropin deficiency without abnormalities in secretion of other pituitary hormones. The etiology of this disease is not clear, but some cases are thought to result from autoimmune attacks on pituitary cells[1-4] or infiltration of lymphocytes in the pituitary or hypothalamus[8-9].

The patient reported here had symptoms of fatigability, anemia, hair loss, and amenorrhea. Although these symptoms were thought to result from secondary adrenal insufficiency[5,10], the amenorrhea persisted over 6 years, even with hydrocortisone replacement therapy. The LH-RH provocation test showed normal LH and FSH responses before treatment. The amenorrhea might have had a hypothalamic origin. During gonadotropin therapy together with Kauffmann therapy, cyclic genital bleeding was observed, but spontaneous menstruation did not occur by skipping these treatments. Six years after the start of treatment, menstruation resumed spontaneously. After menstruation resumed, the hydrocortisone replacement therapy was tapered rapidly. Concerning these episodes, the amenorrhea was most likely not due to the hydrocortisone deficiency but due to the same etiology as the isolated ACTH deficiency.

In most reported cases, plasma ACTH and cortisol levels were both undetectable or below the lower limits of the normal ranges[5]. In our patient, ACTH level was not detectable by RIA. IRMA (level detectable) was much more sensitive than RIA (level detectable)[11]. By IRMA, the patient's ACTH levels were detected. Although this patient had low but detectable levels of ACTH and low to normal levels of cortisol, we diagnosed this case as isolated ACTH deficiency because the ACTH and cortisol levels did not respond to CRH provocation test. Another interesting observation is that the plasma ACTH and cortisol levels were suppressed by dexamethasone administration. How do we resolve that ACTH and cortisol levels do not respond to CRH but are suppressed by dexamethasone? We speculated that the patient's ACTH producing-cells were not damaged completely. The ACTH secreting cells produced basal ACTH levels but could not respond to stresses such as hypoglycemia or CRH stimulation. We hypothesized that the CRH response of ACTH-producing cells was blocked by autoimmune mechanisms but that the intracellular steroid receptor was intact, and therefore dexamethasone could suppress basal ACTH secretion. During hydrocortisone replacement therapy, the CRH test improved after 6 y, and no replacement therapy was needed after 7 y. Based on this clinical course, we hypothesized that the isolated ACTH deficiency remission was due to the disappearance of the ACTH-producing cell autoantibody.

Some cases of isolated ACTH deficiency with remission have been reported[6,7]. Many of these cases were due to autommune disease with isolated ACTH deficiency. There are two groups of patients, those with spontaneous remission and those with no remission who need permanent hydrocortisone replacement.

We conclude that cases of isolated ACTH deficiency thought to be due to autommune disease have a possibility of remission, and that therefore we must observe carefully the remission status during hydrocortisone replacement therapy.

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