Siblings of 21-Hydroxylase Deficiency (Non-Salt-Losing) with Aldosterone Hypersecretion

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We describe siblings with the non-salt-losing form of 21-hydroxylase deficiency who had hypersecretion of aldosterone and plasma renin activity (PRA). Blood pressure and serum electrolytes in both cases were normal despite the aldosterone hypersecretion. Aldosterone secretion was elevated markedly with ACTH administration and with sodium deprivation and/or volume depletion during ACTH suppression by dexamethasone. With suppression by dexamethasone, aldosterone hypersecretion was decreased with lowering of the steroids proximal to the block in the biosynthetic pathway. However, urinary sodium excretion was decreased. These results suggest that the biosynthetic pathway for aldosterone production was preserved. Furthermore, aldosterone hypersecretion and high PRA may serve to compensate for the sodium loss which results in turn from the overproduction of the sodium-losing steroids, such as progesterone and 17 α -hydroxyprogesterone which are aldosterone antagonists. (Internal Medicine 31: 690–694, 1992)

Key words: congenital adrenal hyperplasia

Introduction

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency results in a decreased synthesis of cortisol with a consequent increase in ACTH secretion. An increased ACTH secretion leads to an overproduction of steroids proximal to the site of the block in the biosynthetic pathway, and these precursor steroids are shunted into androgen synthesis that induces virilization in females (1–3). 21-hydroxylase deficiency can be classified in the salt-losing-form characterized by mineralocorticoid and glucocorticoid deficiencies, and the non-salt-losing form (simple form) is preserved in aldosterone synthesis and has usually normal secretion or hypersecretion of aldosterone (1, 4–7). In this paper, we describe two siblings with the non-salt-losing form of 21-hydroxylase deficiency whose blood pressure and serum electrolytes were normal, despite hypersecretion of aldosterone.

Methods

Plasma progesterone (8), aldosterone (9) and plasma renin activity (PRA) (10) were measured by RIA in

our hospital. Progesterone RIA kit was obtained from Daiichi Radioisotope Ltd, Tokyo, Japan, and aldosterone and PRA kit were from Dainabot Ltd, Tokyo, Japan. Plasma cortisol, testosterone and ACTH, and urinary free cortisol and aldosterone were measured by RIA at Otsuka Assay Laboratories (Tokushima, Japan). Plasma 17-hydroxyprogesterone and deoxycorticosterone, and urinary pregnanediol and pregnanetriol were measured at Kitazato Biochemical Laboratories (Kanagawa, Japan).

A dexamethasone suppression test was carried out with consecutive 4-day dexamethasone (2, 2, 8, 8 mg) administration on 10 g sodium diets. Blood samples for the measurement of hormones and electrolytes were obtained at 8 a.m. on day 1 and on day 5, and urine samples were obtained on the preceding day (day –1) and on day 4. An ACTH stimulation test was accomplished by intramuscular administration of ACTH-Z (Cortrosyn-Z, Organon, Tokyo) in dose of 0.5 mg/day for 3 consecutive days. Blood samples were obtained at 8 a.m. before the first injection and 24 hours after the third injection, and urine samples were obtained on day –1 and day 3.

The effect of sodium deprivation on hormone secretion was examined while receiving 10 g of salt for at least

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7 days, followed by 3 g of salt for 3 days. Urine samples were obtained final days of the 10 g and 3 g salt diets. PRA and aldosterone responses after 2 hours of upright (Case 1) and 2 hours of upright plus 20 mg of furosemide intracutaneous administration (Case 2) were examined during 10 g and 3 g salt diets.

Case Report

Case 1

A 16-year-old elder sister was referred to our clinic because of amenorrhea and virilization. The clitoral enlargement was pointed out in early infancy. At the age of 10, heterosexual precocity was observed. In July 1990, she consulted a gynecologist in our hospital and was found to have abnormalities of external genitalia.

Physical examination showed as follows: height 151 cm, weight 50 kg, blood pressure 100/50 mmHg. Her habitus was demonstrated to be apparently masculinization. Virilization consisted of hypertrichosis, acnes and low voice. Ambiguity of the external genitalia was revealed, such as enlargement of the clitoris, small outlet of the vagina, and urethral orifice located into the vagina. Serum electrolytes were determined on several occasions on regular diets (10 g NaCl): serum sodium 136–140 mEq/l, potassium 3.6–4.5 mEq/l and chloride 98–100 mEq/l.

Case 2

A 12-year-old younger sister was admitted together with Case 1 because of amenorrhea and virilization. Her clinical course and physical findings were similar to those of her elder sister. Serum sodium was 138–141 mEq/l,

potassium was 3.8–4.1 mEq/l, and chloride was 100–102 mEq/l on a regular diet.

Hormone studies

Urinary and plasma hormone levels are shown in Table 1. In both cases, hormonal and electrolyte levels in serum and urine were similar before and after various procedures. Plasma and urinary steroids proximal to the site of the block by 21-hydroxylase in the biosynthetic pathway and C19 steroids were elevated, and the precursor steroids were decreased to normal by 4-day of dexamethasone administration (Table 1). On the other hand, they had normal cortisol and increased aldosterone levels in plasma and urine, which were decreased by dexamethasone. However, the aldosterone levels were not completely suppressed. PRA was elevated despite aldosterone oversecretion before and during ACTH suppression. Urinary excretion of sodium was decreased with the dexamethasone administration in both cases.

After consecutive 3-day ACTH-Z administration (0.5 mg/day), all urinary and plasma steroids including cortisol and aldosterone were elevated and urinary sodium excretion was decreased in both cases (Table 2). Blood pressure and serum electrolytes were normal among these procedures.

In Case 1, the effect of sodium deprivation on aldosterone secretion and PRA was examined during a maintenance therapy of 0.75 mg dexamethasone (Table 3). Plasma and urinary aldosterone levels were elevated after sodium deprivation, and urinary sodium excretion decreased. PRA did not change. Furthermore, PRA and plasma aldosterone levels increased with 2 hour

Table 1. Urinary and Plasma Hormone Levels after 4 Days of Dexamethasone (2, 2, 8, 8 mg); Suppression Test on 10 g Salt Diet

	Normal range	Case 1		Case 2	
		before	after	before	after
Serum					
Progesterone	(0.67> ng/ml)*	0.71	0.63	2.6	0.73
17OH-progesterone	(0.3–0.85 ng/ml)*	95.6	1.40	163.0	1.71
Testosterone	(10–60 ng/d)	190.0	24.7	210.0	16.0
Cortisol	(2.7–15.5 µg/dl)	6.20	1.00>	8.8	1.00>
DOC	(0.03–0.33 ng/ml)	2.04	0.09	2.60	0.10
Aldosterone	(52–175 pg/ml)	324.9	189.40	331.0	156.6
PRA	(0.5–2.0 ng/ml/h)	9.20	12.40	4.90	12.40
ACTH	(4.4–48.0 pg/ml)	79.80	4.00>	52.10	4.00>
Urine					
17OHCS	(1.9–6.1 mg/day)	2.5	1.3	2.0	0.5
Pregnanediol	(0.03–0.16 mg/day)*	1.47	0.25	1.64	0.17
Pregnanetriol	(1.5> mg/day)	3.29	0.28	9.68	0.21
Free cortisol	(35–150 µg/day)	61	15	46	10>
Aldosterone	(10> µg/day)	29.9	19.0	20.0	12.0
Na	(mEq/day)	161	133	180	128
K	(mEq/day)	63	53	63	49
Cl	(mEq/day)	157	115	119	129

17OH progesterone: 17α-hydroxyprogesterone, DOC: 11-deoxycorticosterone

* Normal range of follicular phase

Table 2. Urinary and Plasma Hormonal Levels before and after 3-Day ACTH-Z (0.5 mg) Administration on 10 g Salt Diets

Normal range		Case 1		Case 2	
		before	after	before	after
Plasma					
Progesterone	(0.67> ng/ml)*	2.90	8.10	6.10	12.10
17OH progesterone	(0.3–0.85 ng/ml)*	91	348	131	522
Testosterone	(10–60 ng/dl)	360	470	324	487
DOC	(0.03–0.33 ng/ml)	1.74	3.84	3.42	6.61
Cortisol	(2.7–15.5 µg/dl)	11.5	45.0	13.3	38.7
Urine					
17-OHCS	(1.9–6.1 mg/day)	4.5	20.6	2.6	18.1
Pregnanediol	(0.03–0.16 mg/day)	2.86	8.51	2.15	4.79
Pregnactriol	(1.5> mg/day)	17.0	116.0	19.5	92.1
Free cortisol	(35–160 µg/day)	83	1,940	39	1,520
Aldosterone	(10> µg/day)	32.0	96.0	20.0	77.0
Na	(mEq/day)	129	59	150	109
K	(mEq/day)	58	49	46	44
Cl	(mEq/day)	125	88	119	122

17OH-progesterone: 17 α -hydroxyprogesterone, DOC: 11-deoxycorticosterone

* Normal range of follicular phase

Table 3. Effect of Sodium Deprivation on Plasma and Urinary Hormone Levels and Urinary Electrolytes during 0.75 mg of Dexamethasone for Maintenance Therapy in Case 1

		10 g Salt	3 g Salt*
Plasma			
Progesterone	(ng/ml)	7.6	2.1
17OH-progesterone	(ng/ml)	118.0	60.4
PRA	(ng/ml/h)	5.3	5.4
ACTH	(pg/ml)	93.6	32.4
Urine			
Aldosterone	(µg/dl)	11.0	23.0
Na	(mEq/day)	121	69
K	(mEq/day)	31	32
Cl	(mEq/day)	136	62

PRA: plasma renin activity, 17OH-progesterone: 17-hydroxyprogesterone

* 3 g salt diet for 3 days

upright posture on both regular and low sodium diets (Table 4). However, those responses were significantly greater with sodium deprivation than those with 10 g sodium diet. The effect of upright posture plus 20 mg of furosemide administration on low sodium diet without suppression with dexamethasone was examined in Case 2. PRA increased 8.7 to more than 22 ng/ml/h and plasma aldosterone level was from 624 to 1,491 pg/ml.

Gene analysis of the family

In 21-hydroxylase B gene of both siblings and parents neither deletion nor gene conversion was revealed by PCR analysis which was previously described by Kinoshita et al (11).

Clinical course after treatment of dexamethasone

Both patients were treated with 1 mg of dexamethasone, followed by 0.75 mg as a maintenance dose.

Table 4. Effect of 2 Hour Upright Posture and 2 Hour Upright Posture Plus 20 mg of Furosemide Administration during a 10 g and a 3 g Salt Diets

		10 g Salt		3 g Salt*	
		before	after**	before	after**
Case 1					
PRA	(ng/ml/h)	6.0	11.7	5.9	23.6
Aldosterone	(pg/ml)	111	473	176	702
Case 2					
PRA	(ng/ml/h)			8.7	22<
Aldosterone	(pg/ml)			624	1,491

PRA: plasma renin activity, * 3 g salt diet for 3 days, ** values after upright posture or upright plus furosemide administration

Plasma ACTH levels were suppressed, and plasma levels of precursor steroids blocked by 21-hydroxylation became normal and levels of aldosterone decreased to reach the upper normal level in both cases. Blood pressure and serum electrolytes remained normal level on regular diets in both cases. In both cases virilization was improved along with the lowering of plasma testosterone levels in both cases.

Discussion

Adrenal 21-hydroxylase acts on the conversions of progesterone to deoxycorticosterone and 17 α -hydroxyprogesterone to cortisol. In patients with the non-salt-losing form of 21-hydroxylase deficiency, defective C21-hydroxylation results in a block in the conversion of 17 α -hydroxyprogesterone to 11-deoxycortisol and cortisol, and resultant increased ACTH secretion (1–3). Despite blockade in the pathway of glucocorticoid, plasma and urinary cortisol levels in the present cases were preserved to normal levels by the excess ACTH secretion because 21-hydroxylation was not completely blocked. It was also suggested by the further secretion of cortisol with the administration of ACTH-Z administration.

On the other hand, 21-hydroxylation in the mineralocorticoid biosynthesis in the adrenal gland is preserved in patients with the non-salt-losing form (5–7). Previous studies (5–7) demonstrate that untreated patients with 21-hydroxylase deficiency usually have normal secretion or hypersecretion of aldosterone. Pardini et al (12) and Fiet et al (13) observed impaired mineralocorticoid hormone responses to ACTH stimulation in subjects with the non-salt-losing form of 21-hydroxylase deficiency, and suggested the presence of a mild defect of the mineralocorticoid biosynthetic pathway in that form. The present cases had higher levels of aldosterone in urine and blood. Aldosterone and deoxycorticosterone secretions were elevated along with the steroids proximal to the block in the mineralocorticoid pathway by ACTH administration. Furthermore, aldosterone secretion was elevated markedly with the stimulus of sodium deprivation and volume depletion during ACTH suppression by dexamethasone. These results suggest that the biosynthetic pathway for aldosterone production is preserved in the present patients.

Despite the increases of plasma and urinary aldosterone and PRA, blood pressure and serum electrolytes were normal in the present cases. It seems that the overproduction of aldosterone is secondary to a relative sodium depletion. Excess ACTH secretion leads to the overproduction of progesterone and 17 α -hydroxyprogesterone which might cause a loss of sodium by antagonizing the effect of aldosterone (14–19). Kowarski et al (6) and Bartter et al (7) have reported cases of the non-salt-losing form of 21-hydroxylase deficiency who did not have hypertension or hypokalemia despite aldosterone

hypersecretion, and suggest that the overproduction of aldosterone represents an attempt to compensate for the sodium loss which results in turn from the overproduction of weak sodium-losing steroids such as progesterone and 17 α -hydroxyprogesterone. We do not know whether the plasma levels of progesterone and 17 α -hydroxyprogesterone observed in the present cases were high enough to lead to a loss of sodium. However, with lowering of ACTH secretion by dexamethasone, the secretion of antagonistic hormones decreased, and urinary sodium excretion decreased despite the lowering of aldosterone secretion in both cases at the same time. These results suggest that an increased production of antagonistic factors might be the primary cause for a compensatory increase in the aldosterone secretion. The renin-aldosterone system plays an important role in the aldosterone hypersecretion in the present patients. Furthermore, the aldosterone hypersecretion in these patients decreased to normal without changes of serum electrolytes or blood pressure with the long-term treatment of dexamethasone.

The abnormality of this disorder is due to an autosomal recessive gene (20). Predictions of carrier status can be made by kinship by gene analysis (11, 13, 21). However, we could not reveal the deletion or gene conversion in the 21-hydroxylase B gene in the siblings or parents. Therefore, gene abnormality in the present patients may be a point mutation in the 17 α -hydroxylase B gene that leads to a mild enzymatic deficiency, resulting in the non-salt-losing form.

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