A Case of Male Pseudohermaphroditism due to 17 α -Hydroxylase Deficiency

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A case of male pseudohermaphroditism due to 17 α -hydroxylase deficiency is described. A 24-year-old woman with a quadriplegic attack exhibited primary amenorrhea, lack of secondary sexual characteristics, hypertension, hypokalemic alkalosis and hyporeninemia. She had female external genitalia together with a 46 XY karyotype and intraabdominal testes. No uterus was found. Endocrinological studies showed low levels of urinary pregnanetriol, plasma cortisol and urinary 17-OHCS, high level of urinary pregnanediol, and markedly elevated plasma levels of deoxycorticosterone, corticosterone and 18-hydroxycorticosterone with a low level of plasma and urinary aldosterone. Plasma ACTH was high. Plasma and urinary androgens and estrogens were low in the presence of a high level of plasma and urinary gonadotropins. Treatment with 2-0.5 mg/day of dexamethasone improved the abnormal plasma levels of the corticosteroids and normalized the blood pressure, serum potassium and PRA. The addition of estrogen (ethinylestradiol, 0.05 mg daily) to dexamethasone treatment produced only poor development of the breasts six months later.

Key Words: Hypertension, Male pseudohermaphroditism, 17 α -hydroxylase deficiency.

17 α -hydroxylase deficiency, which was first described in a female by Biglieri et al.¹⁾, is a rare type of congenital adrenal hyperplasia associated with hypertension. In genetical males this enzyme deficiency induces pseudohermaphroditism. Since the report of a male by New²⁾ only about 17 male patients with this enzyme deficiency have been reported³⁻¹⁶⁾.

Recently, we had a patient with female appearance who showed hypertension, hypokalemic paralytic attack and lack of secondary sexual characteristics. On further investigation, male pseudohermaphroditism due to 17 α -hydroxylase deficiency was confirmed. The present paper deals with this rare case and the investigation into the pathogenesis of this syndrome.

PATIENT REPORT

A 24-year-old patient with female appearance was admitted to the Koseiren Takaoka Hospital on January 27, 1981 because of progressive muscular weakness of the extremities lasting 3 days prior to admission. The patient, who complained of primary amenorrhea and lack of secondary sexual characteristics, was pointed out to have infantile female external genitalia with no palpable uterus at 18 years of age and to have high blood pressure (systolic blood pressure 160-180 mmHg) at 19 years of age. The patient was not taking any antihypertensive drugs until the present time. The marriage of the patient's parents was consanguineous (uncle and niece).

On physical examination the patient was

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Fig. 1. Photograph of the patient at 24 years of age before treatment.

170 cm tall and weighed 53 kg. Skin pigmentation was unremarkable. The blood pressure was 160/106 mmHg and pulse rate 80/min. She had a slightly enlarged, diffuse, soft thyroid. No abnormalities of the lung, heart and abdomen were noted. There was no breast development and no axillary and pubic hair (Fig. 1 and 2). The external genitalia appeared female and infantile (Fig. 2). The vagina was a blind pouch of about 7 cm and the uterus was not palpable. The muscle strength of the extremities was moderately weak and the tendon reflexes were normal. The bone age was normal. The optic fundi showed vascular changes, comparable to a grade 1 of Keith-Wagener-Barker classification. The electrocardiogram showed U-waves compatible with hypokalemia. The Karyotype was 46 XY (Fig. 3).

Fig. 2. External genitalia of the patient.

Fig. 3. Karyotype analysis of the patient.

Fig. 4. Histological examination of the testis (magnification $\times 400$).

After completion of the endocrinological examinations, laparotomy was performed on March 30, 1981 and the testes were removed. No uterus was found. Histological examination (Fig. 4) showed atrophied seminiferous tubules with various degrees of Sertoli cell degeneration without evidence of spermatogenesis. Islets of Leydig cells were found in the slightly fibrotic interstitial tissue with numerous dilated veins and hemorrhage. However, various degrees of Leydig cell degeneration were observed. Routine laboratory examinations showed a red blood cell count of $300 \times 10^4/\text{mm}^3$, hemoglobin of 11.0 g/dl, and white blood cell count of $7,000/\text{mm}^3$ with a normal differential. The serum sodium was 148 mEq/l, potassium 1.7 mEq/l, chloride 99 mEq/l, bicarbonate 34 mEq/l, blood urea nitrogen 6.3 mg/dl, creatinine 0.9 mg/dl, uric acid 2.8 mg/dl, total protein 0.7 g/dl and total cholesterol 158 mg/dl. Blood pH was 7.49. Urinalysis showed no protein and no glucose. Urinary potassium excretion was 40 mEq/24 h. Other routine laboratory data were normal. Renal blood flow was 678, renal plasma flow was 451, and glomerular filtration rate was 120 ml/m²/min. The thyroid function studies revealed normal thyroid function including a basal metabolic rate of +10%, serum total thyroxine of 8.0 $\mu\text{g}/\text{dl}$, serum triiodothyronine of 114 ng/dl and radioiodine uptake at 24 hrs of 32%.

The serum TSH was normal (4.2 $\mu\text{U}/\text{ml}$) and its response to TRH was normal (24.2 $\mu\text{U}/\text{ml}$ at 15 min). Antithyroglobulin and antimicrosomal antibodies were undetectable. The thyroid biopsy specimen showed some degree of focal infiltrations without any follicular cell damages.

Following completion of the routine laboratory examinations, the patient received 72 mEq of potassium daily, given both intravenously and orally in addition to a regular diet. One week later the muscular weakness disappeared completely with an increase in serum potassium to 4.2 mEq/l. The supplemental potassium, thereafter, was discontinued because of the endocrinological examinations.

After the endocrinological examinations were completed, treatment with 2 mg of dexamethasone daily was initiated. This treatment resulted in a prompt fall in blood pressure from 164/102 to 130/70 mmHg and a rise in serum potassium from 2.1 to 4.3 mEq/l. The dose was reduced to 1 mg daily after 2 weeks and to 0.5 mg daily after 6 weeks of the treatment. The blood pressure and serum potassium remained normal. Estrogen therapy (ethinylestradiol, 0.05 mg daily) was started 1 month after beginning of the dexamethasone treatment. Only poor development of the breasts occurred 6 months after the estrogen therapy.

METHODS

Two weeks after the cessation of potassium supplement the patient was studied under a daily diet containing 200 mEq of sodium and about 60 mEq of potassium.

The furosemide stimulation test was started at 0800 h after an overnight fast and with the patient supine. 80 mg of furosemide was given orally as a single dose and then 4 h of ambulation was permitted. Blood samples for the measurements of plasma renin activity (PRA) and plasma aldosterone were obtained before and after the furosemide stimulation test. PRA was determined by the method of Skinner¹⁷⁾. Plasma cortisol, plasma deoxycorticosterone, plasma corticosterone and plasma aldosterone were measured by RIA as described previously^{18,19)}. Urinary aldosterone was determined by RIA as the acid-labile conjugate of aldosterone²⁰⁾.

Plasma 18-hydroxycorticosterone (18-OHB) was determined by the method of Ojima and Kambe²¹⁾. Plasma ACTH was determined by RIA (Kitazato Biochem. Lab., Sagamihara). Plasma and urinary androgens and estrogens were measured by RIA (Kitazato Biocem. Lab., Sagamihara, and SRL, Tokyo), urinary pregnanetriol and pregnanediol by gaschromatography (Kitazato Biochem. Lab., Sagamihara), plasma LH and FSH by RIA and urinary gonadotropins by bioassay (SRL, Tokyo). Urinary 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS) were measured by conventional methods^{22,23)}.

RESULTS

Levels of PRA, ACTH, gonadotropins and steroids before and after dexamethasone treatment for a month are shown in Table 1.

Before treatment urinary pregnanediol

Table 1. Endocrinological data before and after dexamethasone treatment for a month in the patient.

	Patient		Normals
	Before treatment	After treatment	
Urinary pregnanediol (mg/24 h)	5.5	0.3	0.2 - 1.2*
Plasma DOC (ng/dl)	118.0	10.0	8.6 $\pm$ 2.5 (15)
Plasma corticosterone (μ g/dl)	10.8	0.9	0.65 $\pm$ 0.18 (16)
plasma 18-OHB (ng/dl)	78	16.2	6.4 - 31.3 (8)
plasma aldosterone (ng/dl)	4.7	8.4	8.7 $\pm$ 2.6 (19)
After furosemide stimulation	5.3	20.6	19.8 $\pm$ 7.5 (19)
Urinary aldosterone (μ g/24 h)	4.4	6.7	8.9 $\pm$ 2.8 (15)
Plasma renin activity (ng/ml/h)	0.1	1.3	1.2 $\pm$ 0.6 (52)
After furosemide stimulation	0.1	3.2	3.9 $\pm$ 1.9 (19)
Urinary pregnanetriol (mg/24 h)	0.10	0.10	0.13 - 1.60*
Plasma cortisol (μ g/dl) 0800 h	1.3	0.3	12.8 $\pm$ 3.5 (12)
Urinary 17-OHCS (mg/24 h)	1.2	0.4	6 - 10
Plasma ACTH (pg/ml)	200	25	15 - 85
Plasma DHEA (ng/ml)	0.6		1.2 - 7.5
Plasma androstenedione (ng/ml)	0.2		0.5 - 1.5
Plasma testosterone (ng/ml)	30.3		300 - 850*
Urinary testosterone (μ g/24 h)	3.8		12 - 60*
Urinary 17-KS (mg/24 h)	3.7	1.8	6 - 10*
Plasma estrone (pg/ml)	4		28 - 102*
Plasma estradiol (pg/ml)	12		20 - 64*
Plasma estriol (pg/ml)	undetectable		less than 10*
Urinary estrogens (μ g/24 h)	2.5		2 - 20*
Plasma LH (mIU/ml)	62.5		6.5 - 34.5*
Plasma FSH (mIU/ml)	127.0		1.9 - 21.8*
Urinary gonadotropins (MUU/24 h)	more than 32		12 - 20

Values given are the baseline levels unless otherwise indicated.

ACTH = Adrenocorticotropin, DOC = Deoxycorticosterone, 18-OHB = 18-hydroxycorticosterone, DHEA = Dehydroepiandrosterone. * = Value in males. The number of normal subjects is in parentheses.

was high, and plasma deoxycorticosterone, corticosterone and 18-hydroxycorticosterone were markedly elevated. PRA and plasma aldosterone were low and did not respond to furosemide stimulation. Urinary aldosterone also was low. Urinary pregnanetriol, plasma cortisol and urinary 17-OHCS were low. Plasma ACTH was high. Plasma DHEA, androstenedione and testosterone, and urinary testosterone, urinary 17-KS, plasma estrone, estradiol and estriol, and urinary estrogens were low. Plasma LH and FSH, and urinary gonadotropins were high.

After dexamethasone treatment for a month the urinary pregnanediol, and plasma deoxycorticosterone, corticosterone and 18-hydroxycorticosterone were normalized. The PRA and plasma aldosterone increased to normal level and responded normally to furosemide stimulation. The urinary aldosterone also was normalized. The plasma ACTH decreased to normal level. The plasma cortisol, urinary 17-OHCS and urinary 17-KS remained very low.

DISCUSSION

Our patient with a quadriplegic attack showed the physical and laboratory findings suggestive of 17 α -hydroxylase deficiency, i. e. primary amenorrhea, lack of secondary sexual characteristics, hypertension, hypokalemic alkalosis and hyporeninemia¹⁷. However, the patient had female external genitalia together with a 46 XY karyotype and intraabdominal testes. In this patient with male pseudohermaphroditism the diagnosis of 17 α -hydroxylase deficiency was confirmed by the endocrinological examinations which showed low levels of urinary pregnanetriol, plasma cortisol and urinary 17-OHCS, high level of urinary pregnanediol, and markedly elevated plasma levels of deoxycorticosterone, corticosterone and 18-hydroxycorticosterone.

Low plasma and urinary levels of androgens and estrogens in the presence of a high level of plasma and urinary gonadotropins suggest that the enzyme defect occurs in both the adrenal and testis and may have

been responsible for the failure of masculinization in utero. Lack of the uterus in our patient also suggest that the testicular gland was producing the Müllerian duct inhibiting factor. In patients with male pseudohermaphroditism due to 17 α -hydroxylase deficiency the development of breasts at puberty has been reported to be either present^{2, 6, 11, 14, 15} or absent^{3-5, 7, 8, 10, 13, 16}. In addition, estrogen treatment has been shown to be either effective⁹ or ineffective¹⁶ in the development of breasts. In our patient who had a lack of secondary sexual characteristics the addition of estrogen to dexamethasone treatment produced only poor development of the breasts six months later.

In our patient the plasma and urinary levels of aldosterone were low in the presence of the high levels of its precursor steroids, deoxycorticosterone, corticosterone and 18-hydroxycorticosterone. Excessive amounts of deoxycorticosterone and corticosterone may cause sodium retention and renal potassium loss leading to hypertension, hypokalemic alkalosis and hyporeninemia¹⁷. Regarding the low aldosterone production two possible explanation have been proposed. First, some investigators suggest an additional deficiency of 18-ol-dehydrogenase^{1, 5}. This hypothesis is based on an excessive production of 18-hydroxycorticosterone before treatment and continuation of the low production of aldosterone during the treatment with dexamethasone. Second, other investigators suggest a low aldosterone production secondary to the suppression of the renin-angiotensin system^{2, 11, 15, 24-26}. This is supported by the normalization of both renin and aldosterone production during dexamethasone treatment. In some patients prolonged suppression of aldosterone production, which has caused suppression of the adrenal zona glomerulosa, may take some time periods for the zona glomerulosa to resume the ability to secrete normally aldosterone^{2, 11, 15, 24}. In addition, an excessive production of 18-hydroxycorticosterone before treatment has been explained by the reversible inhibition of 18-ol-dehydrogenase

activity due to the lack of angiotensin II²⁵⁾ or potassium depletion²⁶⁾. In our patient a normalization of the aldosterone production in association with a return to normal levels of serum potassium and PRA occurred within a month after the dexamethasone treatment, supporting the second hypothesis.

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