Male Pseudohermaphroditism Due to 17α-Hydroxylase Deficiency

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ABSTRACT This is the first report of a male with 17α-hydroxylase deficiency resulting in male pseudohermaphroditism, ambiguous external genitalia, absence of male secondary sexual characteristics, and gynecomastia at puberty. Diagnosis was based on extensive studies of steroid metabolism including the following: low urinary excretion of 17-ketosteroids and 17-hydroxycorticoids which did not increase after ACTH; no response of very low plasma testosterone and dehydroepiandrosterone to adrenocorticotropin (ACTH) or chorionic gonadotropin; and low urinary aldosterone and plasma renin which increased after dexamethasone. Secretion rates of 17-hydroxylated steroids, cortisol (F) and 11-desoxycortisol (S), were very low while desoxycorticosterone (DOC) and corticosterone (B) secretion rates were increased sevenfold. Results expressed as milligrams per meter squared per day were as follows: F, 1.3; S, 0.023; DOC, 0.35; and B, 16 (mean normal values were F, 7.5; S, 0.26; DOC, 0.055, and B, 2.2). Plasma gonadotropins were markedly increased (FSH, 106; LH, 364 mIU/ml). Testicular biopsies revealed interstitial-cell hyperplasia and early spermatogenesis. Karyotype was 46/XY. Pedigree showed no other affected member. At laparotomy ovaries, uterus, and fallopian tubes were absent, vas deferens was incomplete, and prostate was present. External genitalia consisted of small phallus, bifid scrotum, third-degree hypospadias, and small vagina. At puberty there was no growth of body hair or phallic enlargement. Biopsy of marked gynecomastia showed both ducts and acini. Testosterone administration produced virilization. Sexual ambiguity demonstrates strong dependence of external genitalia on androgens for male differentiation. Suppression of Müllerian structures occurred despite female levels of testosterone indicating this step in male differentiation is not testosterone dependent. Pubertal breast development in this male supports the concept of femaleness during ontogeny unless counteracted by male factors. Diagnosis of other adrenocortical enzymatic deficiencies is excluded by the steroidal studies. The clinical response to testosterone excludes testicular feminization. Deficiency of 17-hydroxylation must be added to the cause of male pseudohermaphroditism.

INTRODUCTION

Since the report by Biglieri, Herron, and Brust of 17α-hydroxylase deficiency in a female (1), there have been three subsequent females described with the syndrome of hypertension, primary amenorrhea, and sexual infantilism due to defective 17-hydroxylation (2, 3) of steroids.

This is the first report of a male with 17α-hydroxylase deficiency which resulted in male pseudohermaphroditism, ambiguous external genitalia, absence of male secondary sexual characteristics, and prominent breast development at puberty. Unlike the previously reported females, this male did not manifest severe hypertension or hypokalemia. Deficiency of an enzyme necessary for synthesis of testosterone and estrogen in the female resulted in a normal phenotype while in the male the phenotype was markedly altered. The role of estrogens and androgens in embryological differentiation of the human male external and internal genitalia and in the production of secondary sexual characteristics is elucidated by this case.

METHODS

Secretion rates of cortisol (F), 11-desoxycortisol (S),[1] corticosterone (B), and 11-desoxycorticosterone (DOC)

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[1] The following compounds and their trivial names and abbreviations are used: 17,21-dihydroxy-pregn-4-ene 3, 20 dione (11-desoxycortisol; compound S); 3α,17,20-trihydroxy-5β-pregnane (pregnanetriol); and 9α-fluoro-16α-methyl-11β,17α,21-trihydroxypregn-1,4-diene-3,20-dione (dexamethasone; Decadron).

were measured by the method of New, Seaman, and Peterson (4). Urinary 17-ketosteroids, 17-hydroxycorticosteroids, pregnanetriol, aldosterone, and plasma 17-hydroxycorticoids were measured by previously reported methods (5). Plasma androgens were determined by a double isotope dilution derivative technique (6). Urinary estrogens were determined by the method of Brown, Bulbrook, and Greenwood (7), as modified by Beling (8) and urinary pregnanediol by the method of Klopper, Michie, and Brown (9). Plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were determined by a radioimmunoassay (10). The urinary 17-ketosteroids were partitioned by a single isotope dilution technique utilizing hot acid hydrolysis, separation of steroids by paper chromatography, and quantitation of the separate eluates by the Zimmermann reaction (5).

The various periods of study described in the results were as follows: base line—no medications; i.v. ACTH—40 U of ACTH intravenously daily; metyrapone—3 g of metyrapone p.o. daily for 3 days; Decadron—8 mg of dexamethasone p.o. daily for 3 days; Decadron + CGT—8 mg of dexamethasone p.o. + human chorionic gonadotropin, 5000 U intramuscularly, daily for 3 days; and testosterone—injection of 400 mg of testosterone enanthate intramuscularly once.

Case report. This 24 yr old male pseudohermaphrodite was admitted for mastectomy. He was born with ambiguous genitalia and the sex assignment was uncertain until his first medical investigation at age 20 months when he was definitely considered male. At that age his height (90 cm) and weight (14.5 kg) and blood pressure were normal. His genitalia were described as follows: "the labia majora or bifid scrotum contain oval shaped bodies (testes); that on the right is descended and on the left is at the upper pole of labium. There is a large prepuce and rudimentary penis. A urethral groove is visible on the under surface which is divided into two halves. At the posterior end of this groove is an opening leading to the bladder." His bone age and urinary 17-ketosteroid excretion were normal. Upon cystoscopy at 21 months, a 1.5 cm vagina was visualized. The urethral meatus was located in the vagina. No cervix was observed. The urethra was described as female in type. Exploratory laparotomy at 22 months reported "no female adnexa." The diagnosis was male pseudohermaphroditism. He was thereafter reared as a male.

At 3½ yr of age he weighed 18.7 kg and his height was 103 cm. A biopsy of the right testicle revealed an infantile testis and a normal epididymis. Exploration of the left inguinal canal did not locate the left testicle. Microscopic examination of the right testicular biopsy showed tubules lined by columnar epithelium which appeared to be inactive. There were no mitotic figures, spermatocytes, or sperm seen. The interstitial tissue was minimally increased and consisted of closely packed fibrous tissue but no increase in Leydig cells. At the age of 3½ he was treated with methyl testosterone 5 mg p.o. daily and 5 mg/g of testosterone ointment by inunction to the genital area for 2 months. The penis increased from 2.5 to 3.2 cm in length. An intravenous pyelogram at this time demonstrated normal renal function but an unusual bladder neck. Over the next 5 yr he had multiple urologic operations to release the chordee, lengthen the penis, and bring the urethra to the mid-shaft of the penis. He next presented himself at the age of 16 because he had developed marked gynecomastia over the previous 2 yr. At that time he manifested no secondary sex characteristics except gynecomastia. He had no pubic, axillary, or facial hair. A prostate was palpated. A small right testis was in the scrotum and a mass was felt in the left inguinal canal. Urinary 17-ketosteroid excretion was 14 mg/24 hr (normal for outside laboratory 15–20); 17-hydroxycorticoid excretion was 2.3 mg/24 hr (normal for outside laboratory 2–4). Karyotype was reported as 46/XY and a male chromatin pattern was observed on buccal smear. Serum electrolytes were normal (K, 4.1 mEq/liter). Repeat testicular biopsies were performed at age 16 which revealed the same microscopic findings bilaterally. There was mild tubular atrophy with increased space between tubules and basement membrane thickening. Tubules showed decreased spermatozoa and were lined almost completely with Sertoli cells. There was a relative increase in Leydig cells. The microscopic diagnosis was atrophy of the right and left testes. When the patient was 20 yr of age, a prostate was palpated and the patient claimed to have normal libido but no ejaculation or orgasm. His voice was high-pitched, he still had no facial, axillary, or body hair, no temporal hair recession, and gynecomastia was marked. Height was 68 inches (pubis to crown, 31¼ inches, and pubis to floor, 36¼ inches). A bone age was normal and the proximal epiphyses of the fibulae were fused.

He was admitted for the first time to The New York Hospital at 24 yr of age for mastectomy. At this time he had marked gynecomastia (see Fig. 1), hypospadias, chordee, hypoplasia of the scrotum, empty left scrotum, and a small right gonad. His height was 68 inches and weight 206 lb. The blood pressure was only slightly elevated (150–130/90–60). He was markedly obese and had a eunuchoid habitus. He claimed to have erections and sexual intercourse but no ejaculation. Enuresis was common. His voice was high-pitched, there was no recession of temporal hair line, skin was very smooth, and there was no facial hair, seborrhea, or acne. He never had shaved. Repeated cystoscopy confirmed the presence of a vaginal utricle 1.5 cm from the bladder neck in the floor of the urethra. The 2 × 3 cm utricle could be filled with water and readily emptied with pressure via a 2 mm opening into the surgically constructed urethra. A retrograde and voiding cystogram demonstrated an irregular distal urethra and a bulbous dilation of the mid-portion of the urethra. Bone age was normal (Fig. 2).

At this point he was studied extensively from an endocrine viewpoint as indicated below. Random fasting growth hormone level was 1.9 mμg/ml (normal 0–8). A mastectomy was performed and the microscopic sections showed an unusual lobular pattern of acini (Fig. 3). He had a smooth operative and postoperative course without steroid treatment. Postoperatively he was treated with testosterone enanthate 400 mg intramuscularly and subsequently testosterone propionate 25 mg intramuscularly every 2 wk. Within 6 wk he manifested the following signs of virilization: deepening of voice, seborrhea and very slight acne, pubic hair and facial hair requiring him to shave weekly. He claimed improved muscular strength. In addition body hair on arms and legs increased. The size of the phallus after 2 months of treatment with testosterone had not changed. Family history revealed no other affected member.

Review of testicular biopsies confirmed histological diagnosis of infantile testes at age 2. At age 16 the presence of spermatocytes and marked interstitial-cell hyperplasia was confirmed (Fig. 4). A repeat karyotype was 46/XY.

RESULTS

Urinary excretion of metabolites of steroidal hormones (*Table I*). The daily urinary 17-ketosteroid excretion was low for an adult male and the response to ACTH was minimal. The 17-hydroxycorticoid excretion doubled with ACTH but showed no greater increase with metyrapone. At no period before treatment with testosterone did the urinary 17-ketosteroid excretion or the 17-hydroxycorticoid excretion rise to adult male levels. Although the urinary 17-hydroxycorticoids suppressed briskly with 2 mg of dexamethasone, the 17-ketosteroid values decreased only slightly. With the maintenance of adrenal suppression, chorionic gonadotropin did not increase the 17-ketosteroid excretion. Treatment with testosterone increased 17-ketosteroid excretion while 17-hydroxycorticoid excretion remained low. A partition of the urinary 17-ketosteroid on the day of ACTH administration showed an etiocholanolone excretion of 2.1 mg,

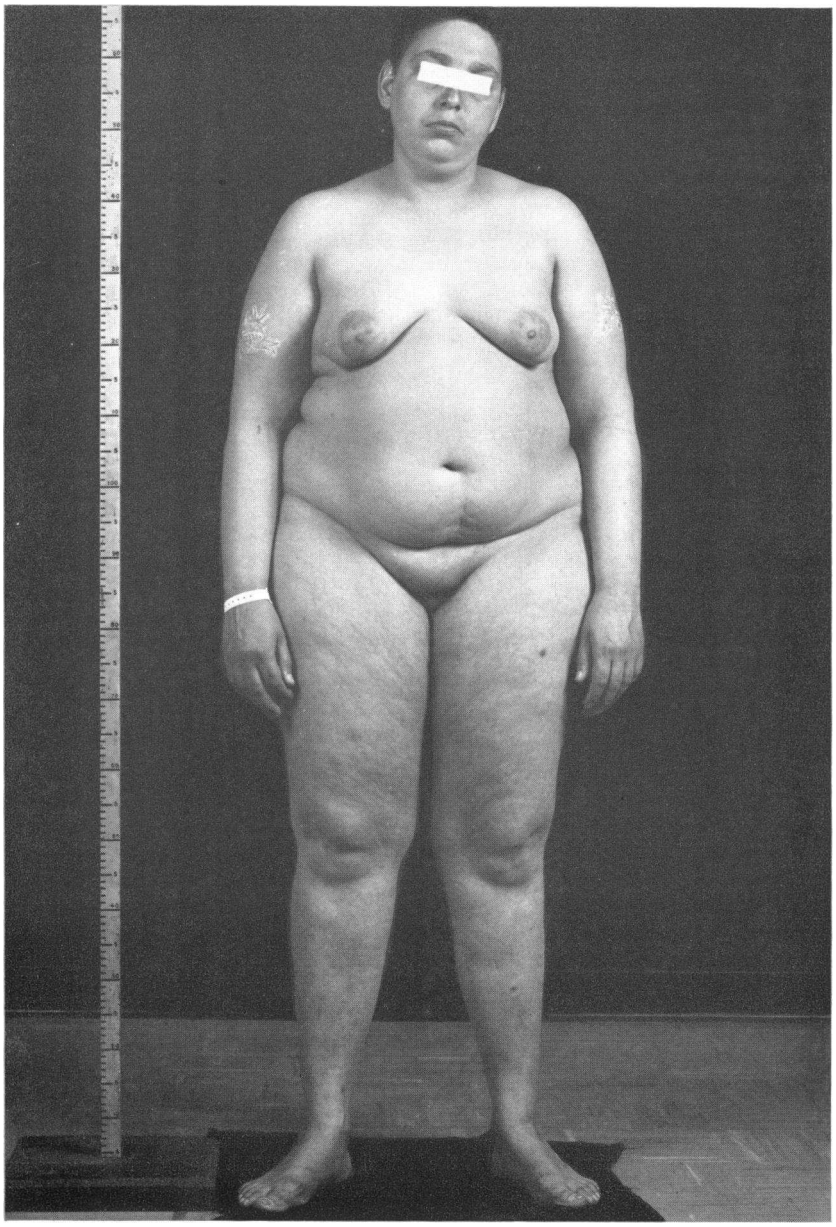

FIGURE 1 17-Hydroxylase defect resulting in male pseudohermaphroditism with prominent breast development and absence of virilizing signs at puberty. Note eunuchoid habitus, absence of recession of hairline, and hairlessness.

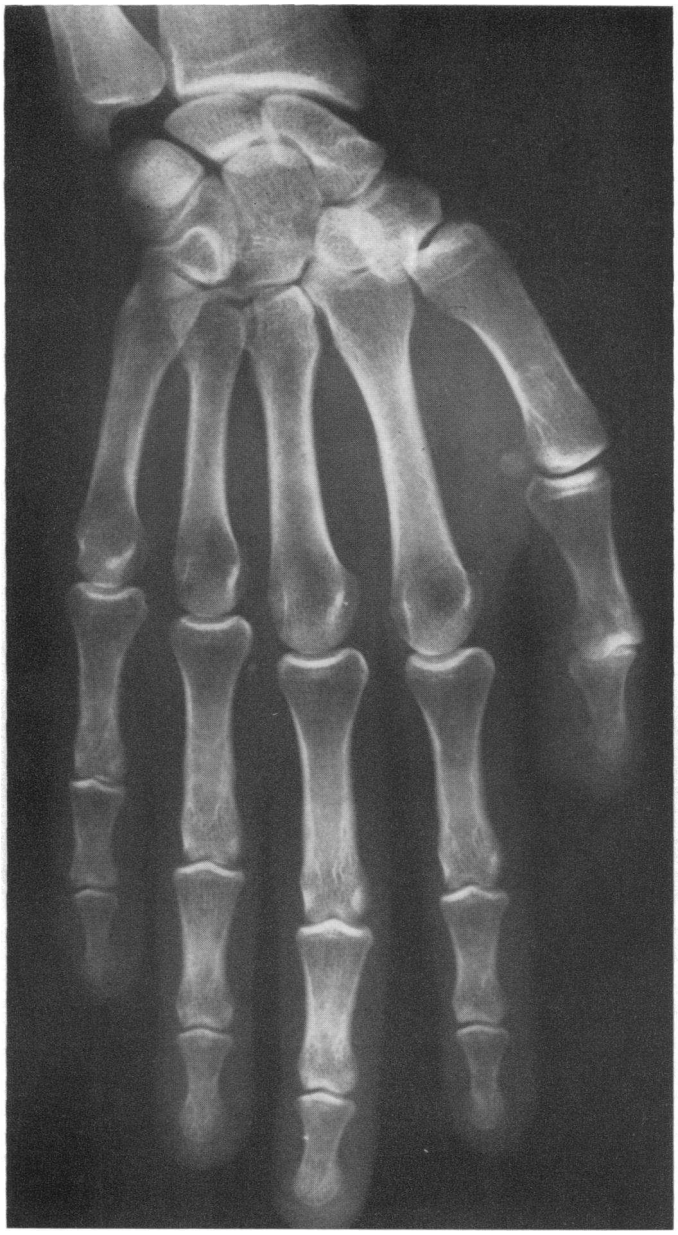

FIGURE 2 Wrist film demonstrating fusion of all epiphyses of metacarpals and distal ulna and radius, despite marked deficiency of androgens and estrogens.

androsterone 2.5 mg, and dehydroepiandrosterone of 1.9 mg. The total 17-ketosteroid excretion on that day was 6.6 mg.

Pregnanetriol excretion was slightly increased. This was determined by an unpublished single isotope dilution technique and then rechecked by a double isotope dilution derivative technique (11). The level of pregnanetriol excretion varied very little with either stimulation by ACTH or chorionic gonadotropin or with suppression by dexamethasone or testosterone (see Table I).

By the method used, the total excretion of estrone (E_1), estradiol (E_2), and estriol (E_3) is 5–10 μg in normal males. Estrogen excretion in this patient was very low. E_2 was 1.1 μg/day. E_1 and E_3 were undetectable.

This patient excreted 0.29 mg of pregnanediol in 24 hr. Although few determinations of pregnanediol in

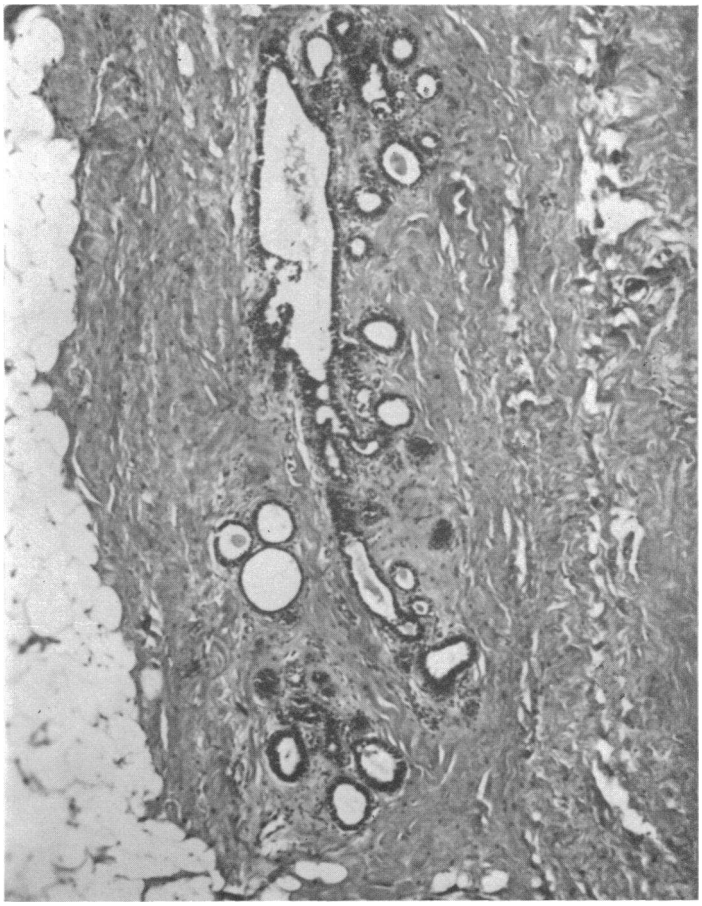

FIGURE 3 Histology of breast tissue demonstrating both ductal and acinar development.

male urine have been reported, this level does not appear to be elevated. Excretion rates in males have been previously reported as 0.32–0.88 mg/day (12); 1.1 mg/day (13), and 0.7 mg/day (14).

Plasma hormones (*Table I*). The plasma 17-hydroxycorticoids were initially at the lower limit of normal and showed no diurnal variation. There was no rise of plasma 17-hydroxycorticoids with ACTH administration; however, the pre-ACTH concentration was higher than previous values. The plasma testosterone levels were repeatedly in the female range and below the normal adult male range (6). Neither ACTH nor chorionic gonadotropin administration caused an increase in the plasma testosterone. Dexamethasone did not suppress the already low levels of testosterone. The plasma dehydroepiandrosterone (DEA) was below normal female or male levels (6). Plasma gonadotropins were very high (FSH 106, LH 364). Normals for this laboratory are FSH 3.9–42, LH 2.5–32 mIU/ml (10). Plasma renin initially was very low, 0.1 mμg/ml per hr. Normal values in this laboratory are 2–7 mμg of angiotensin generated per ml per hr. Plasma progesterone was 0.020 μg/100 ml.[2] Normal values for a female in the follicular phase are 0.020–0.100 μg/100 ml. Normal male levels are very low. Plasma 17-hydroxyprogesterone was 0.091 μg/100 ml[2] and 17-hydroxy-Δ-5-pregnenolone was 0.200 μg/100 ml.[2] Both values were considered to be within the normal range.

Secretion rates of cortisol (*F*), *corticosterone* (*B*), *desoxycorticosterone* (*DOC*), *desoxycortisol* (*S*), *and aldosterone* (*aldo*) (*Table II*). The secretion rates of F, S, and aldo were very low whereas the secretion rates of B and DOC were 7–8 times normal (4).

Metabolic balance studies (*Fig. 5*). The sodium and potassium balance as determined by dietary intake and urinary excretion are depicted in Fig. 5. The blood pressure was never very elevated. The highest diastolic blood pressure was 100 mm. No single period of study produced a consistent change in blood pressure; rather the values

[2] We are grateful to Dr. Mortimer Lipsett for carrying out these determinations. Normal values are those given by Dr. Lipsett for his laboratory.

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