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Occurrence of Male Phenotype in Genotypic Females With Congenital Virilizing Adrenal Hyperplasia

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We report on two genotypic females with complete masculinization of the external genitalia secondary to congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency. One patient had the salt-losing variant, and the other had the simple virilizing or nonsalt-losing variant. One was evaluated neonatally during an adrenal crisis and misidentified as male; the second was unrecognized. Both were being reared as males when the true genotype was recognized during evaluation for cryptorchidism. The female internal genitalia were subsequently removed and testicular implants placed. These cases demonstrate the need to exclude congenital virilizing adrenal hyperplasia in any phenotypic male infant with bilateral cryptorchidism. When this condition is diagnosed, early and genotypically appropriate sex assignment is important if reproductive function is to be preserved and subsequent emotional and social complications avoided.

KEY WORDS: 11-hydroxylase deficiency, 21-hydroxylase deficiency, virilization or masculinization of external genitalia, bilateral cryptorchidism, salt-losing, nonsalt-losing, autosomal recessive inheritance

INTRODUCTION

The virilizing forms of congenital adrenal hyperplasia (CVAH) are autosomal recessive disorders produced by a deficiency of either of two enzymes necessary for cortisol but not for androgen biosynthesis. If untreated, they result in excessive androgen secretion and produce varying degrees of virilization of female external genitalia in utero and may lead to precocious sexual development in affected males. Deficiency of the 21-hydroxylase enzyme is the most common cause of CVAH, accounting for approximately 95% of all cases; the remainder result from defective 11-hydroxylation [Brook et al., 1974; Rösler and Leiberman, 1984].

The most extensive virilization produces complete labial fusion, a phallic urethra, and an external meatus at the tip of the glans penis. This type of presentation has been reported to occur in 1–7% of female infants with CVAH [Prader, 1958; Verkauf and Jones, 1970; Wyatt et al., 1987]. To date, 43 cases of this "complete" masculinization have been reported (Table I). In several of these reports histologic evaluation documented the presence of prostatic tissue [Matheson and Ward, 1954; Rosenberg et al., 1969; Kiviat and Leonard, 1978].

Here we describe two genotypic females with 21-hydroxylase deficiency. Both had an empty scrotum but otherwise normal male genitalia. They were considered to be cryptorchid males until other developments led to the discovery of their correct genotype later in childhood.

CLINICAL REPORTS

Patient 1

M.B. (DOB: 9-19-67), was born at term after a normal pregnancy and delivery; at birth he was described as a normal male without palpable testes. Persistent vomiting, diarrhea, and abnormal electrolyte levels led to a diagnosis of congenital adrenal hyperplasia at age 1 month; treatment with glucocorticoids was followed by a prompt recovery. Early care during infancy was erratic, with historical reports of salt-craving and the development of cushinoid manifestations. Because of concern about cryptorchidism, the child was given intramuscular human chorionic gonadotropin (4,000 U × 5 doses) at age $6^{9}/_{12}$ years with no evidence of descent of testes. A buccal smear did not show any X-chromatin bodies. At age $7^{9}/_{12}$ years the child was first noted to have pubic hair, and the left inguinal canal was explored for a testicular tumor. Failure to discover a testis prompted a more extensive search, which located fallopian tubes, gonads, and a uterus. A gonadal biopsy confirmed primordial follicles consistent with a preadolescent ovary.

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TABLE I. Review of Cases in Females With CVAH and Male Phenotype

Author (No. of cases)	Age of diagnosis	Sex of Rearing	Chief complaint	Clinical and postmortem data
Salt-losing form				
Krokiewicz [1896] (1)	5 days, postmortem	M	Salt-losing crisis?	Penile urethra and empty scrotum; female internal genitalia and large adrenal glands
Benda [1914] (1)	2 months, postmortem	M	Salt-losing crisis?	Male external genitalia, female internal genitalia, and large adrenal glands
Marie et al. [1952] (1)	1 month, postmortem	M	Vomiting	Enlarged adrenal glands and female internal organs
Allibone et al. [1947] (1)	<3 months	M	Vomiting	Normal male external genitalia, enlarged adrenal glands
Perloff et al. [1953] (1)	3 months, postmortem	M	Recurrent vomiting and dehydration at 2 weeks	Normal penis without palpable testes; bilateral adrenal hyperplasia with female internal genitalia
Matheson and Ward [1954] (1)	1 month	M	Persistent vomiting and weight loss since birth	Large adrenal glands, female internal genitalia and prostate
Prader [1958] (1)	4 years	M	Sexual development at 4 years	Severe symptoms of salt loss during first year of life; diagnosis of CVAH and identification of genetic sex at 4 years
Ainger et al. [1958] (1)	3 years	M to F	Advanced sexual and somatic development beginning at 1½ yrs	Salt-craving; amputation of the phallus; a younger sister with female pseudohermaphroditism
Rook et al. [1961] (1)	2 weeks, postmortem	M	Fever, dehydration, and dyspnea at day 9	Female internal genitalia and enlarged adrenal glands
Platt and Becker [1963] (1)	Birth	F	Virilization and salt wasting	Dark skin, pigmented nipples, micropenis, and empty scrotum; uterus by rectal palpation; buccal smear: chromatin (+); low serum sodium; an older sib with postmortem finding of adrenal hyperplasia
Wiedemann [1965] (1)	14 months	M to F	Vomiting	Completely developed penis with female karyotype and internal genitalia
Weldon et al [1966] (3)[a]	1. 2½ years	M	Undescended testes, phallic enlargement, and pubic hair	Buccal smear: chromatin (+); high urinary pregnanetriol; female internal genitalia
	2. 3 weeks	M to F	Dehydration and increased pigmentation found at 3 weeks	Two buccal smears: chromatin (−); third buccal smear (+); correct sex identified at 2 months
	3. 1 month	M to F	Recurrent vomiting and dehydration at 3 days	Initial buccal smear: (−); repeat smear: (+); correct sex identified at 11½ months
Rosenberg et al. [1969] (3)[b]	1. 3 weeks	M to F	Vomiting and dehydration at 3 weeks	Female karyotype; normal uterus, ovaries, and prostate; clitorectomy and vaginoplasty performed
	2. 2 weeks	F	Vomiting and dehydration at 2 weeks	Buccal smear: chromatin (+); clitorectomy and vaginoplasty performed
	3. birth	F	Virilized genitalia	Buccal smear: chromatin (+); vaginoplasty performed
Verkauf and Jones [1970] (6)	?	M?	Salt-losing crisis?	Six of 89 patients with CVAH had completely masculinized external genitalia associated with salt wasting
Redman and Gould [1972] (1)	Birth	M	Undescended testes at 6 years	Sex misidentified at birth based on two (−) buccal smears; at 6 years, had karyotype 46,XX; internal genitalia removed
Money and Daléry [1976] (2)	1. 6 days	F	Salt-losing	Had corrective surgery of external genitalia
	2. 11 days	M	Salt-losing	Genetic sex determined at 1 month; no gender change; at age 3½ years, removal of female internal genitalia

(*continued*)

TABLE I. (continued)

Author (No. of cases)	Age of diagnosis	Sex of Rearing	Chief complaint	Clinical and postmortem data
Nonsalt-losing form				
Peris [1960] (1)	18 years	M	Micropenis and cyclic "hematuria" at 18 years	Microphallus and empty scrotum; at age 12 years, inguinal exploration disclosed no testes; ↑ urinary pregnanetriol; normal electrolytes; chromatin (+); hysterectomy and bilateral salpingo-oophorectomy
Madsen [1963] (2)	1. 35 years[c]	M	"Wanted to be changed to a woman"	Penile urethra and empty scrotum; pubic and axillary hair at age 5 years; at 26 years, started to have cyclic bleeding; had hypertension, normal electrolytes, elevated etiocholanolone; 46xx karyotype; enlarged adrenal glands, female internal genitalia
	2. 30 years[dc]	M	Marked hypertension	"Brother" of previous case; cyclic "hematuria" at age 22 years
Maxted et al. [1965] (2)	1. 21 years	M	Cyclic hematuria at 21 years	No palpable gonads; bilateral gynecomastia; buccal smear: chromatin (+); normal electrolytes
	2. 10 months[c]	M	Empty scrotum	Normal electrolytes; high urinary 11-deoxycorticoids
Gillenwater et al. [1970] (1)	4 years[c]	M	Marked masculinization with sexual hair at 4 years	Chromatin (−); genetic sex identified at 7 years when intermittent "hematuria" occurred; BP = 150/90; enlarged adrenal glands; female internal genitalia
Money and Daléry [1976] (1)	3½ years[c]	M	Sexual development at age 2½ years	Correct genotype identification at age 12 years when breast development began
Kiviat and Leonard [1978] (1)	17 years	M	Undescended testes and short stature at 17 years	Younger sister with CVAH and five phenotypic male siblings died during infancy; buccal smear: chromatin (+); karyotype 46,XX; ↑ plasma 17-OHP; normal electrolytes; had prostate; female internal genitalia removed
Wyatt et al. [1987] (1)	3 7/12 years	M	Undescended testes with phallic enlargement and pubic hair since 3 years	↑ 17-OHP; female internal genitalia removed at 3 9/12 years
Rösler and Leiberman [1984] (5)[d]	1 11/12 years[c]	M	Hypertension and virilization	Hypertensive before age 2 years, controlled with medication
	1 year[c]	M	Hypetension and virilization	Hypertension responded to treatment
	1 7/12 years[c]	M	Hypertension and virilization	Developed hypertensive encephalopathy with vascular accident that caused death at age 6 years
	2 years[c]	M	Virilization	Refused treatment initially and had hypertension and breast development at age 8 years
	Birth[c]	F	Virilization	Diagnosed and treated at birth and remained normotensive
Gross and Meeker [1955] (1)	Infancy?	M?	Vomiting?	46xx Karyotype
Bentinck et al [1956] (1)	2 years	M	Empty scrotum, phallic enlargement since age 15 months	Bilateral adrenal hyperplasia, female internal genitalia
Jeune and Bertrand [1959] (1)	Infancy?	?	Vomiting	Micropenis

[a] Reported two additional cases with first degree hypospadias.
[b] Reported an additional case with urethral opening at the base of the glans.
[c] These cases had 11-hydroxylase deficiency.
[d] Reported four additional genotypic females with chordees, three reared as males and one as female.

The patient was first evaluated in our clinic at age 8 2/12 years. Family history showed that an older female sib had died at age 26 days and had postmortem findings consistent with congenital adrenal hyperplasia. On physical examination, the blood pressure was 90/60; weight 25.4 kg (50th centile for female); and height, 127 cm (50th centile for female). The patient was normal except for approximately 50 dark pubic hairs at the base of the penis. The stretched phallus measured 6 cm, and the urethral meatus was at the tip of the glans. The scrotum was rugate and empty with no gonads palpable in the sac or inguinal canals (Fig. 1).

A chromosome analysis confirmed the suspected 46,XX genotype, and the bone age was advanced at 13 years (chronological age was 8 3/12 years). Results of pretreatment laboratory studies included: urinary 17-ketosteroids, 25.9 mg/24 hr (<1.0–3.2 mg/24 hr)[1]; urinary pregnanetriol, 39 mg/24 hr (<4 mg/24 hr); plasma testosterone, 148 ng/dl (<10 ng/dl); and androstenedione, >519.4 ng/dl (<50 ng/dl). Later, 17-hydroxyprogesterone levels were found to be elevated. After 5 days of suppression with intramuscular cortisone acetate, the urinary 17-keto-steroid levels were 5.1 mg/24 hr. Following 3 months of maintenance doses of cortisone acetate and fludrocortisone acetate, no further progression of pubic hair was noted, but early breast development did occur. The patient has been reared as a boy since birth, with a strongly established male gender identity and behavior. The significance of the clinical findings, as well as the consequences of surgery and alternative gender assignment, were thoroughly discussed with the family, and they were resolute about his continued male gender identity. When this decision was made, surgical removal of the ovaries and Müllerian structures and insertion of bilateral testicular prostheses were carried out. His subsequent physical and psychological development was satisfactory and uneventful. Iatrogenic puberty was induced at the time of adolescence.

Patient 2

D.G. (DOB: 9-20-80) was referred at age 4 4/12 years for evaluation of cryptorchidism and early pubertal development. Born at term to nonconsanguineous parents following an uncomplicated pregnancy, the child had an uneventful neonatal course. At age 2 1/2 years, the child was noted to be cryptorchid and underwent surgical exploration of the right inguinal canal; no testis was found, and no further investigation was done. At age 3 10/12 years, the patient developed pubic hair and phallic enlargement, prompting referral to our clinic. Additional history identified three older brothers and an older sister who were healthy and without genital anomalies. There was no other family history of precocious puberty, cryptorchidism, or ambiguous genitalia.

On physical examination, this Hispanic child had a height of 109.2 cm (90th centile for female) and a weight of 20.3 kg (90th centile for female). The blood pressure was 94/50. There was some facial acne but no axillary hair or apocrine sweating. Approximately 20 dark, straight pubic hairs were present at the base of an uncircumcised phallus, which measured 6 cm when stretched. The urethral opening was at the tip of the glans, and the scrotum was fused normally and rugate, but no testes were palpable (Fig. 2).

The initial laboratory findings were compatible with a nonsalt-losing form of 21-hydroxylase deficiency and included the following results: plasma 17-hydroxyprogesterone, 6,350 ng/dl (<150 ng/dl)[2]; 11-deoxycortisol, 1.3 μg/dl (<1 μg/dl); testosterone, 55.3 ng/dl (<10 ng/dl); plasma renin activity (PRA), 10.7 ng/ml/min (<6 ng/ml/min), and normal electrolyte levels. The skeletal age was advanced at 11 3/12 years (chronological age was 5 years), and ultrasonography of the pelvis visualized a uterus. A suspected female genotype was confirmed with a 46,XX chromosome constitution. Following suppression with 5 days of intramuscular cortisone acetate, 17-hydroxyprogesterone decreased to 370 ng/dl, testosterone to 9.1 ng/dl, and PRA to 6.6 ng/ml/min.

The patient perceived himself as being male since he has been reared as a boy by the family. The activities and behavior pattern conformed to that of average boys. The child's condition was extensively discussed among the consultant group, with agreement that a male gender identity was strongly established and should continue. This concurred with the wishes of the family. At age 6 4/12 years, he underwent surgical removal of a small uterus, tubes, and cystic ovaries; testicular prostheses were placed. His postoperative recovery was unremarkable, and he has continued to have normal and physical and emotional development.

DISCUSSION

In this report we have described two genotypic females with CVAH. Both had extreme masculinization *in utero* because of 21-hydroxylase deficiency resulting in a completely normal male phenotype except for cryptorchidism. Both of these children were incorrectly identified at birth as males and reared as such, despite the recognition of salt-losing CVAH in one.

Complete masculinization can be produced by deficiency of either the 21-hydroxylase or 11-hydroxylase exzymes. In 21-hydroxylase deficiency, it has been suggested that more severe virilization occurs in individuals with the salt-losing defect [Verkauf and Jones, 1970; Qazi and Thompson, 1972]; however, there have been several reports of male phenotypes occurring in genotypic females with the nonsalt-losing form of 21-hydroxylase deficiency [Peris, 1960; Gillenwater et al., 1970; Kiviat and Leonard, 1978; Wyatt et al., 1987]. These individuals are frequently mistaken as males with bilateral cryptorchidism, and the diagnosis of CVAH is delayed until signs of precocious puberty occur, as evidenced by phallic enlargement and increased growth with appearance of pubic and axillary hair [Lebovitz et al., 1984]. As reported by Wyatt et al. [1987], in several early reports of cases of complete virilization of genotypic females, the patients were not defin-

[1]Normal values for age are given in parentheses.

[2]See footnote 1.

Fig. 1. The external genitalia of patient 1 (M.B.) at age $8^{2}/_{12}$ years. Note the presence of pubic hair, the circumcised phallus, and empty scrotum.

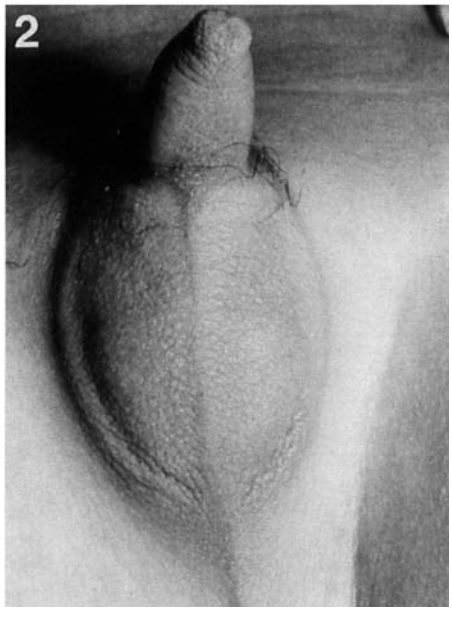

Fig. 2. The external genitalia of patient 2 (D.G.) at age $3^{10}/_{12}$ years. Note the presence of pubic hair, the circumcised phallus with the urethral opening at the tip of the glans, and normally fused scrotum.

itively studied, but, by clinical criteria, were not salt-losers. Though one of our patients with the salt-losing variant was misidentified as male on the basis of a buccal smear, we suspect that this would not have happened with the current availability and use of chromosome studies. In individuals with the nonsalt-losing variant, delayed diagnosis is more likely. For example, in genotypic males with nonsalt-losing CVAH, the average age at diagnosis is 61.5 months [Lebovitz et al., 1984], which is close to the 52 months of our second patient who had no clinical evidence of salt wasting in spite of slight elevated PRA.

The development of normal or near normal male genitalia in genotypic females with 11-hydroxylase deficiency probably occurs with greater frequency than in the more common 21-hydroxylase deficiency. In the 14 genotypic females reported by Rösler and Leiberman [1984], nine had a phallic structure, penile urethra, and fused labia; seven were reared as males and were ritually circumcised. This is important to note because, in our experience, infants with ambiguous genitalia or absent testes are often not tested for deficiency of this enzyme.

The real incidence of this phenomenon is unclear. From the report of Pang et al. [1988], based on the screening of 1,093,310 newborn infants in six countries from 1980 to 1988, the identification of 77 with 21-hydroxylase deficiency yields an incidence of 1:14,199. The phenomenon of complete masculinization has been previously reported to occur in 1–7% of genotypic females with CVAH [Prader, 1958; Verkauf and Jones, 1970; Wyatt et al., 1987]. Given these data one could predict 17,607 cases in the United States (2.5×10^8 population) with 88–616 fully virilized females. Our review of the literature (summarized in Table II) found 45 cases, or many fewer than the number predicted for the United States alone. This suggests that 1–7% is an overestimate or that extremely virilized CVAH females are underreported.

The diagnosis of CVAH must be considered by all physicians who see and evaluate children with cryptorchidism. This is a common problem since in term boys with a weight of >2,500 g, the incidence of cryptorchidism is 3–4%, while in premature boys it approximates 30% [Scorer and Farrington, 1971]. In individuals with cryptorchidism, both testes fail to descend in 10–35% [Gross and Jewett, 1956; Benson and Lofti, 1967; Hortling et al., 1967; Sudmann, 1971]. True congenital absence of both testes must also be considered in the differential diagnosis, though it is less common than cryptorchidism, occurring in only 1% of children operated for cryptorchidism [Gross and Jewett, 1956; Abeyaratne et al., 1969].

The consequences of erroneous and/or delayed diagnosis of CVAH are serious and far-reaching for the genotypic female with a male phenotype. Having been assigned a male gender identity, the child may face a late gender change with phallic amputation and reconstructive surgery. Alternatively, preservation of a male gender identity requires surgical removal of the female internal genitalia and results in infertility and a requirement for male hormone replacement at puberty. The information from previous studies [Rösler and Leiberman, 1984; Money and Daléry, 1976] suggests that virilized females reared as males can and do function normally in that role with proper medical therapy and counseling. Late attempts to change gender identity generally have not produced adult women who are

TABLE II. Summary of Pertinent Data in Reported Cases* of Females With CVAH Male Phenotypes

	No.	Percentage
A. Form of CVAH		
1. Salt-losing	27	60.0
2. Nonsalt-losing	15	33.3
3. Indeterminate[a]	3	6.7
Total	45	100.0
B. Enzyme deficiency		
1. 21-Hydroxylase	35	77.8
a. Presumptive[b]	(9)	
b. Confirmed[c]	(26)	
2. 11-hydroxylase confirmed[d]	10	22.2
Total	45	100.0
C. Final sex of rearing		
1. Male	27	60.0
2. Female	10	22.0
3. Unspecified	8	17.8
Total	45	100.0
D. Determination of genetic sex		
1. Karyotype	8	33
2. Buccal smear[e]	16	67
a. False negative	(5)	
b. True positive	(11)	
Total	24	100.0

* Collected from the references in Table I and including the two patients reported here.
[a] Data insufficient to determine salt-losing status.
[b] Presumptive diagnosis was based on the clinical history of virilization, precocious puberty, salt-losing crisis, and autopsy or operative findings of female internal genitalia.
[c] Diagnosis was confirmed by elevated urinary 17-ketosteroids, 17-pregnanetriol, or 17-hydroxyprogesterone.
[d] Diagnosis of 11-hydroxylase deficiency was made on the basis of hypertension in addition to virilization, precocious puberty, and confirmed by elevated urinary 17-ketosteroids, 11-deoxycortisol, and/or elevated etiocholanolone.
[e] Three patients had more than one buccal smear.

judged to be well adapted socially and sexually [Money and Daléry, 1976; Rösler and Leiberman, 1984]; therefore, decisions to follow this course must be made cautiously. On the other hand, early diagnosis combined with surgical correction and medical therapy in females with genital ambiguity is generally associated with successful female gender identity, normal female physical and psychosocial development, and potential fertility [Hochberg et al., 1987]. If neonatal screening for this disorder becomes more widely available, early intervention should be more easily implemented.

It is clear from these cases and previous ones that males without identifiable testes need careful evaluation. One should pursue the presence of Müllerian structures by palpating rectally for a uterus and/or by pelvic ultrsonographic examination. Genetic sex must be determined since the lack of reliability of a buccal smear is established [Weldon et al., 1966; Gillenwater et al., 1970; Redman and Gould, 1972] and demonstrated again in our first case. If a discrepancy between the genotype and apparent phenotype is documented, the infant should be evaluated immediately for 21-hydroxylase and 11-hydroxylase deficiencies and treated if either is confirmed. When the diagnosis has been delayed until a male gender identity is established, the question of continuation or change of this identity must be carefully and thoroughly discussed with the family as well as with all physicians and health care workers concerned with the child's care. Our experience in these two cases suggests that the choice for maintenance of male gender identity is preferred.

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