Original articles

Male pseudohermaphroditism due to 5 α -reductase-2 deficiency in an Arab kindred

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Summary

Six Arabs subjects (three postpubertal, two prepubertal and one pubertal) from three interrelated Omani families with male pseudohermaphroditism due to 5 α -reductase-2 deficiency were evaluated. These subjects had been raised as girls since birth as they were born with a clitoral-like phallus and ambiguous external genitalia of pseudovaginal perineoscrotal hypospadias with separate urethral and vaginal orifices. They underwent variable degrees of increased muscular habitus and phallic enlargement during puberty and beyond. Gynaecomastia was absent and the body and facial hair was insignificant. After diagnosis, a transition to male social sex occurred in two cases, one of which was interventional. Two retained the female social sex, one of which was also interventional, while the other two maintained an equivocal gender status. This report provides new data on the characterisation of 5 α -reductase-2 deficiency in various clusters.

Keywords: 5 α -reductase deficiency, pseudohermaphroditism, Arabs

A deficiency of 5 α -reductase-2 leads to a characteristic form of male pseudohermaphroditism. The clinical manifestations are related to decreased conversion of testosterone to its more active metabolite dihydrotestosterone. Classically, the affected subjects are 46XY males with testes and a male ejaculatory

system, but with predominantly female external genitalia. The lack of virilization of genitalia is so severe in some patients that they are assigned the female gender in the newborn period. Various degrees of virilization, however, occur at puberty, including the development of masculine habitus, deepening of the voice and growth of phallus. Perhaps the most salient feature that accompanies the pubertal changes is a deep disturbance in the gender-related behaviour of patients raised as females, as in most cases they change to a male social sex.^{1–3} The disorder is inherited in an autosomal recessive fashion and the heterozygous obligate carriers are clinically normal.⁴ Two 5 α -reductase genes have recently been cloned. These encode different isoenzymes that can be distinguished on the basis of biochemical, pharmacological and genetic criteria. Male pseudohermaphroditism due to 5 α -reductase-2 deficiency is a consequence of mutations in the type 2 gene, located in band 23 of chromosome 2.⁵

Patients

Over a period of 10 years, six Arab individuals (three postpubertal, two prepubertal and one pubertal) with male pseudohermaphroditism have been identified. They are interrelated members of an Omani kindred. Culturally, these families are of low social and educational background, and their community favours patriarchal control. Sexual segregation between unmarried males and females is widely observed, and marriage amongst cousins is common. All affected subjects of this kindred

Figure 1 Family pedigree. ■ represents subjects with 5 α -reductase deficiency who have been examined, □ represents affected subjects who have not been examined and ● represents subjects with a short Y chromosome

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were born to consanguineous parents (figure 1). They were assigned the female gender at birth and were all raised as females.

Subject 1, was 17 years old in 1986 when he was identified as a male pseudohermaphrodite. He was seeking medical advice for sex conversion. The psychosexual evaluation at that time indicated the presence of male gender identity since puberty. The development of masculine habitus and failure to develop feminine features had enforced the male self-awareness and orientation.

In the same year, *Subject 2* was identified through screening of other family members with special attention being given to those who appeared phenotypically female. He was the eldest sibling of Subject 1. Despite the masculine habitus and absence of breast development, his self-awareness and orientation were surprisingly ambivalent. At age of 17 years, the subject had, as a woman, married a man, but was divorced after a few days. Since then and until the diagnosis was made, the subject had maintained a rather conservative female role.

Subject 3 came to our attention in 1994. The parents of this 14-year-old presumed girl had some background knowledge of the abnormal trait in the kindred. They became rather suspicious over the true gender of their eldest child who failed to reach menarche or to develop breasts. The subject seemed to have a deep-seated uncertainty over his/her gender identity, which deepened as masculinization increased and the voice thickened, yet the phallic size remained noticeably small. The Subject's appearance in society as female became increasingly problematic. Despite re-assignment to a male gender, he failed to declare himself fully as a male in the community and maintained an equivocal social sex status. Screening other family members led to the identification of other affected subjects.

Subjects 4 and 5 are the youngest siblings of Subject 3. Their recognition as being male pseudohermaphrodites brought psychological trauma to the parents. Their current social sexes, however, were ultimately determined by parental choice.

Subject 6 was 21 years old in 1991 when he presented himself for evaluation away from his own Omani community. He dressed and behaved as a woman, but had no ambiguity in his mind about the masculinized component of his gender identity since puberty. This was enhanced by his phallic adequacy for intromission (figures 1 and 2). Indeed, he became a 'man in disguise' as he began to have heterosexual activities as a male but maintained a female role in the nonsexual activities of life. He feared a stormy reaction from the community and possible problems with re-adjustment were he to be overtly re-assigned as male.

Methods

All affected individuals and the parents of subjects 3, 4, and 5 had a careful clinical assessment. The children were additionally evaluated by a paediatric physician and surgeon. Cytogenetic studies of all subjects and

Figure 2 The general appearance of external genitalia of patient 6 who had asymmetrical inguinal and scrotal testes, and an adequate size phallus

Figure 3 Typical ambiguous genitalia of pseudovaginal perineoscrotal hypospadias of the same patient

the parents of subjects 3, 4, and 5 were carried out locally. Assays of serum cortisol, androstenedione, dehydroepiandrosterone (DHEA)-sulphate, 17 α -hydroxyprogesterone, and other relevant hormones were determined locally by radioimmunoassay. Simultaneous assays for serum testosterone and dihydrotestosterone were initially performed in laboratories in UK, and more recently in the laboratory of Professor J Imperato-McGinley in the US. In the same laboratory, blood samples from subjects 1, 2, 3, 4, and 5, and those of the parents of subjects 3, 4, and 5 were analysed by polymerase chain reaction–single stranded DNA conformational polymorphism (PCR–SSCP) for the 5 α -reductase-2 gene. Analysis with denaturing gradient gel electrophoresis (DGGE) following PCR amplification of exon II and exon V of the 5 α -reductase-2 gene was also carried out.

Due to financial constraints, lack of cooperation and the reluctance of some of the patients and their relatives to provide samples for further laboratory investigations, the urinary chromatography for C19 and C21 steroid metabolites was performed (in Northwick Park Hospital and JSPS Laboratories, UK) only for patients 1 and 4. The assay included: aetiocholanolone/androsterone (E/A), 11 β -hydroxyandrosterone/11 β -hydroxyaetiocholanolone (11OHE/11OHA), tetrahydrocorticosterone / 5 α -tetrahydrocorticosterone (THB / 5 α -THB) and tetrahydrocortisol / 5 α -tetrahydrocortisol (THF/5 α -THF).

Facilities for genital fibroblast enzyme and

receptor studies are also not available in local laboratories in the UAE. All subjects had pelvic ultrasonographic examination, and three subjects (1, 2, and 6) also underwent cystoscopic examination and testicular biopsy. Only subjects 1 and 2 agreed to be interviewed by a psychiatrist. Relevant data on pre- and post-pubertal perception and the analytic conclusion of each case was based on direct interviewing of the subjects and parents.

Results

All affected subjects had normal 46-XY karyotype and buccal smear showed a negative chromatin body. The Y chromosome appeared short yet without aberrations on fluorescence G-banding in the karyotype of siblings 3, 4, and 5, and in that of their father. External genitalia of pseudovaginal perineo-scrotal hypospadias (PPHS) phenotype, separate urethral and vaginal orifices and fully regressed mullerian structures were identical in these patients. Other phenotypic features are shown in table 1. The plasma hormone values are given in table 2. Plasma testosterone values were within normal limits, as were those of luteinising hormone and follicle-stimulating hormone. Plasma dihydrotestosterone levels were low and the testosterone/dihydrotestosterone ratios were elevated in five out of the six patients, ranging from 22.8 to 40. Values of androstenedione, DHEA-sulphate, 17 α -hydroxyprogesterone and cortisol were all normal. The parents of siblings 3,

Table 1 Phenotypic presentation of Arabs with male pseudohermaphroditism due to 5 α -reductase-2 deficiency

Subject	Age at diagnosis (years)	Present age (years)	Presentation	Testes, phallus & prostate	Habitus	Facial and body hair	Progress
1	17	27	amenorrhoea, seeking change of sex at age 17	scrotal testes, small phallus, rudimentary prostate, oligospermia	masculine, no gynaecomastia	scanty, few acne spots	reared formally to male social sex, correction of hypospadias, married since 1990, seeking remedies for phallic enlargement and oligospermia
2	18	28	identified through screening the family, was briefly married to a man, then divorced	identical to subject 1	identical to subject 1	scanty	maintained female identity and role, bilateral orchiectomy, oestrogen therapy with full breast development, seeking to be remarried
3	14	16	amenorrhoea, failure to develop female secondary characters, screening for ambiguous genitalia	scrotal, very small phallus	masculine, no gynaecomastia	scanty facial, moderate amount of body hair including linea alba; few acne spots	in deep psychological conflict, reared as male, failed to declare himself to the community, resuming conservative female role (equivocal gender status)
4	4	5	screening for ambiguous genitalia	high scrotal	prepubertal		reared as male (interventional), receiving supervised androgen therapy
5	2 1/2	3 1/2	screening for ambiguous genitalia	inguinal	prepubertal		parents refused to rear 'her' as male, unwilling to subject 'her' to orchiectomy, remains as female
6	21	25	voluntarily presented himself for clinical evaluation, full realization of male gender	asymmetrical left (scrotal), right (inguinal), adequate size phallus, rudimentary prostate	masculine, no gynaecomastia	scanty	unwilling to disclose his male identity to the community, dichotomy of gender role, maintained female role only in non-sexual activities, (equivocal gender status)

Table 2 Plasma hormone levels in male pseudohermaphrodites

Subject	Age (years)	Testosterone (T) (nmol/l)	Dihydro-testosterone (DHT) (nmol/l)	T/DHT ratio	Androstene-dione (nmol/l)	DHEA-sulphate (μmol/l)	17α-Hydroxyprogesterone (nmol/l)	LH (mU/mol)	FSH (mU/mol)	Cortisol (nmol/l)
1	17	12.36	0.54	22.8	3.04	3.00	1.63	8	3	380
2	18	17.7	0.7	25.3	4.62	3.40	2.16	13	4	350
3	14	17.5	0.45	39	4.5	3.02	3.93	3	8.2	355
4	4	1.35	0.034	40	0.173	1.2	0.60	1.2	1	150
5	2½	0.034	0.0135	3	0.169	1.3	0.60	1	0.8	148
6	21	19	0.55	34	5.5	11.3	4.6	5.0	15.8	408
Normal for adult male		12–32.2	1.04–2.6	12.3±3.1	1.7–7.1	2.3–11.7	0.9–6.6	2–12	1–10	50–650

Table 3 Ratio of urinary 5β/5α steroid metabolites

Subject	Age (years)	E/A	11 OHE/11 OHA	THB/5α THB	THF/5α THF
1	17	7.82	0.88	4.75	124.90
4	4	NM	3.2	NM	>11
Normal range		0.93±0.37	0.38±0.23	0.50±0.22	1.07±0.36

NM: unmeasurable levels

4, and 5 appeared phenotypically normal and exhibited normal values of testosterone, dihydrotestosterone and testosterone/dihydrotestosterone ratios. The elevated levels of urinary 5β/5α C19 and C21 metabolites are shown in table 3. No mutation has yet been detected in samples subjected to molecular studies. The more sensitive method of DNA sequencing of the entire 5α-reductase-2 gene is currently being performed.

The testes, epididymis and vas deferens were well developed in patients 1, 2, and 6. Good maturation to the spermatid stage and a few sperm were seen in the testicular biopsy of subject 1, while less developed features resembling those of undescended testicles were present in subjects 2 and 6.

Discussion

Affected individuals with 5α-reductase-2 deficiency exhibit a wide range of phenotypic variability, varying from being genetic males with a female phenotype at birth, through males with hypospadias, to occasional boys with a normal penile urethra.⁶ Others with severe hypospadias and microphallus without

pseudovaginal pouch have also been described.⁷ Some individuals have separate vaginal and urethral orifices, while others have a common urogenital sinus; some subjects have azoospermia, while others have a near-normal sperm count; some undergo profound virilization at the time of expected puberty, and in others virilization remains limited. Some of those raised as girls make the change to a male social sex, while others retain a female role and identity.^{1–4,8–10}

The clinical presentation of ambiguity of genitalia with virilization of adults around puberty in this group was similar to the phenotype of previously described individuals with inherited 5α-reductase-2 deficiency. PPHS and perineoscrotal hypospadias are the most common genital defects in this disorder.^{1,2,9–11} In contrast to other reported clusters, PPHS and separate urogenital orifices were present in all subjects of this group, while the presence of a pseudovaginal pouch had led to their assignment as girls at birth. Their different testicular locations and the histopathological findings were as anticipated. Apart from subject 3, the other adults had scanty facial and body hair. A similar pattern has been observed in affected Dominican males,¹ and in a number of Brazilian adults,¹⁰ while those in the Papua New Guinean⁹ and Turkish¹¹ kindreds appeared to have more abundant facial hair. Neither severe acne nor baldness were described in any group including the present. Mild acne, however, was reported in a few affected Dominican and Papua New Guinean males.^{1,9}

Variability of features can occur among affected individuals of the same family as well as in different families with the same mutation.^{10,12} The different severity of the mutations themselves or the variable expression of steroid 5α-reductase-1 enzyme may be responsible for the variability of the manifestations.^{13,14} The isoenzyme of 5α-reductase-1 is normal in

Diagnosis of ‘classical’ 5α-reductase-2 deficiency

- 46 XY with ambiguous genitalia
- masculinization at puberty
- normal plasma testosterone for male
- decreased plasma dihydrotestosterone levels
- abnormal testosterone/dihydrotestosterone ratios pre- and post human chorionic gonadotropin
- increased 5β/5α ratios of C19 and C21 steroid metabolites of testosterone
- decreased or abnormal 5α-reductase activity in genital skin *in vitro*
- autosomal recessive pattern of inheritance

individuals with 5 α -reductase-2 deficiency and it is believed to be responsible for virilization at the time of expected puberty in this disorder.¹⁵

Although the phenotype of PPHS due to 5 α -reductase-2 deficiency is distinctive, it is not essential for the condition and the terms should not be used synonymously. The normal values of plasma testosterone, 17 α -hydroxyprogesterone, DHEA-sulphate and androstenedione, argue against a pre-testosterone biosynthetic enzyme deficiency as the cause of male pseudohermaphroditism in this group. The diagnosis, however, has customarily been supported by a combination of most of the criteria proposed,^{16,17} in association with the similar features of these subjects. Except the youngest child, they exhibited reduced plasma dihydrotestosterone levels and elevated testosterone/dihydrotestosterone ratios of at least twice the normal level. These results are compatible with the diagnosis and the available data on urinary 5 β /5 α steroid metabolites of subjects 1 and 4 were confirmatory of 5 α -reductase-2 deficiency. The markedly elevated ratio of THF/5 α -THF was found to be the most sensitive indicator of diminished 5 α -reductase-2 activity, with the greatest index of discrimination.¹⁷ Markedly elevated THF/5 α -THF and THB/5 α -THB ratios differentiate individuals with this condition from those with complete and partial forms of androgen insensitivity.^{18,19} Moreover, a moderately raised THF/5 α -THF ratio has the highest index of discrimination of carrier status in men, whereas the E/A ratio is more discriminatory in women.²⁰

Although the plasma testosterone and dihydrotestosterone levels and their ratio for subject 5 were not impressive, this boy was less than three years old when he was endocrinologically evaluated. The diagnosis is often made in children by measurement of urinary steroid metabolite ratios and the testosterone/dihydrotestosterone ratio after human chorionic gonadotropin stimulation.^{17,21} Even though these tests must still be done for this child, this report provides other clinical and biochemical data which are sufficient for us to make the same diagnosis in his case. Higher values of plasma testosterone, luteinising hormone and follicle-stimulating hormone and their respective mean values have been observed in the Dominican, Papua New Guinean and Turkish affected individuals,^{1,9,11} compared with the normal values observed in affected Brazilians¹⁰ and in the adults of this group. The sensitivity of PCR-SSCP and DGGE in detecting mutation is approximately 70–90%, thus false-negative results of this family remain a possibility. Results of DNA sequencing of the entire gene are not available as yet.

The human Y chromosome is known for its variable size in the general population.²²

Azoospermia, oligospermia, short stature, small penis and small testes have been described in patients with deletion of Yq,^{23,24} whereas features of Ullrich-Turner syndrome, especially lymphoedema, have been associated with the deletion of Yp.²⁵ Given that the short Y chromosome of the subjects 3, 4, and 5 was structurally intact, and their 'fertile' father (whose karyotype also contains a short Y chromosome) is clinically normal, it seemed less likely that the presence of the short chromosome had contributed to the phenotypic presentation of these subjects. Unfortunately, genetic counselling has not been accepted by these families and in-breeding is still practised. Therefore, given a probable autosomal recessive gene defect, further cases of 5 α -reductase-2 deficiency are likely to emerge in generations to come in this kindred.

Most of the reported females with male pseudohermaphroditism due to 5 α -reductase-2 deficiency worldwide^{2,9–11,15} changed to male social sex at puberty or beyond, ie, coinciding with the rise of serum testosterone. The process suggested an overriding effect of male androgenization over the sex of upbringing. It also raises the concept of so-called testosterone imprinting and the influence of androgen on the gender role and identity.² This phenomenon of change to male social sex is not, however, exclusive to this disorder. It has been described in male pseudohermaphroditism of uncertain aetiology¹⁰ and occurs in individuals with 17 β -hydroxysteroid dehydrogenase deficiency,^{26,27} and 3 β -hydroxysteroid dehydrogenase deficiency.²⁸ The variability in psychosexual make-up was a striking feature in the present subjects and occurred also among members of their family. Although they were a rather homogenous group in terms of their sex of rearing, phenotypic appearance, hormonal profile and socio-cultural background, yet the development of their gender identities and roles was not uniform. It was closely related to the transaction of their different life experiences. Male sexual behaviour is a rather complex, multifactorial, phenomenon. The gender-related behaviour of this group clearly emphasizes this and demonstrates the potentially significant influence of socio-cultural, biological and psychological factors on sexual development.

Finally, when improved facilities become available and logistic problems can be overcome, more studies need to be performed on the affected and carrier subjects in order to provide further demarcation of the disorder in this kindred.

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