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5 α -Reductase deficiency without hypospadias

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Abstract

A boy aged 4 with penoscrotal hypospadias and his brother aged 12 with micropenis had typical changes of homozygous 5 α -reductase deficiency. After three injections of chorionic gonadotrophin there was a trivial rise in plasma dihydrotestosterone with a normal increase in plasma testosterone. Urine steroid chromatography showed abnormally high 5 β :5 α ratios and 5 α -reductase activity was appreciably reduced in genital skin fibroblasts. The results indicate that 5 α -reductase deficiency is not invariably associated with genital ambiguity.

5 α -Reductase deficiency is a well recognised but uncommon cause of male pseudohermaphroditism.¹ Published cases have been characterised by pronounced underdevelopment of the male external genitalia with microphallus and incomplete fusion of the labioscrotal folds.² Many of the reported cases have been initially raised as girls because of the female appearance of the genitalia at birth but cases with more pronounced virilisation have been described.³

All previously reported males with 5 α -reductase deficiency have had some degree of genital ambiguity with hypospadias. We describe two brothers with the condition, one of whom had micropenis without hypospadias while the other had penoscrotal hypospadias.

Patients and methods

The propositus and his older brother had consanguineous parents who come from Pakistan. At birth, the younger boy was found to have abnormal external genitalia with a small phallus and hypospadias. When he was 4 years old he was referred for evaluation of his genital anomaly. At that time he was noted to have a small penis (stretched length 1.9 cm) with noticeable chordee and penoscrotal hypospadias. The scrotum was normal but only the right testis was palpable.

Initial investigations showed a 46XY karyotype. A sinogram showed a normal bladder; the proximal urethra had a male configuration with a prominent verumontanum and well developed utricle.

After initial evaluation he was given one injection of depot testosterone (50 mg) to improve the size of his penis and hypospadias

repair was carried out. A skin biopsy specimen for fibroblast culture was taken at that time.

The older brother was noted to have a small penis at birth. He was seen at the age of 12 years, at the same time as his brother. His external genitalia were normal, apart from the size of his penis, which had a stretched length of 4 cm. There was no chordee and the urethra opened at the tip of the penis. Both testes were in the scrotum and were 6 ml in volume.

Investigation showed a 46XY karyotype. After initial investigation a skin biopsy specimen was obtained from the scrotum.

Plasma testosterone and dihydrotestosterone concentrations were measured by radioimmunoassay before and after three daily injections of 1000 units of human chorionic gonadotrophin. Urine steroid concentrations were measured by gas chromatography as previously described,⁴ and the results expressed in terms of 5 β : α ratios for different steroid metabolites.

Fibroblasts were established in culture from genital skin to determine 5 α -reductase activity and androgen receptor concentrations. The activity of 5 α -reductase was measured after incubation of fibroblasts with serum free medium containing 2 nM of tritiated testosterone. The medium was extracted with ethyl acetate and analysed by single step thin layer chromatography. Areas corresponding to dihydrotestosterone, 5 α -androstanedione, androsterone, epiandrosterone, and the 5 α -androstanediols were cut out and counted for tritium. Enzyme activity was expressed in pmol/mg protein/hour of 5 α -reduced products. The concentration of androgen receptors, receptor binding affinity, presence or absence of heat labile receptors, and effect of preincubation

Table 1 Results of endocrine investigations

	Propositus	Brother
Before human chorionic gonadotrophin:		
Testosterone (nmol/l)	0.4	3.1
Dihydrotestosterone (nmol/l)	0.1	0.2
Testosterone:dihydrotestosterone ratio	4.0	1.5
After human chorionic gonadotrophin:		
Testosterone (nmol/l)	4.2	21.9
Dihydrotestosterone (nmol/l)	0.1	0.3
Testosterone:dihydrotestosterone ratio	42.0*	73.0*
Urinary 5 β :5 α ratios:		
THF:alloTHF†	24.7	14.3
Aetiocholanolone:androsterone‡	0.6	4.7
THB:alloTHB§	0.8	4.3

*Normal range in prepubertal boys: 2-25.¹
Mean (SD) results in normal subjects: †1.1 (1.7), ‡0.8 (1.7), §0.7 (1.6).

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Table 2 5 α -Reductase activity and androgen receptor concentrations in genital skin fibroblasts. Values in 22 normal subjects are also given

	Propositus	Brother	Normal subjects
5 α -Reductase activity (pmol/mg protein/hour)	0.5	0.6	12.8 (range 3.3–42.3)
Androgen receptor concentration ($\times 10^{-18}$ M/ μ gDNA)	815	939	775 (SD 185)
Receptor binding affinity ($\times 10^{-10}$ M)	0.82	1.09	0.88 (SD 0.35)
Thermolabile	No	No	No
Augmentation	$\times 2.6$	$\times 1.8$	$\times 1.4$

with androgen on receptor concentrations (termed 'augmentation') were determined as described previously.^{5,6}

Results

The results of endocrine investigations are summarised in the tables.

PLASMA ANDROGENS

Both boys showed a rise in plasma testosterone after stimulation with human chorionic gonadotrophin, which was appropriate for their ages. There was a trivial increase in dihydrotestosterone and this resulted in extremely high testosterone:dihydrotestosterone ratios in both boys after human chorionic gonadotrophin (table 1).

URINE STEROIDS

Both brothers showed an abnormal pattern of urinary steroid metabolites, with high ratios for 5 β : α reduced steroids (table 1). This was most striking in the tetrahydrocortisol:allotetrahydrocortisol (THF:alloTHF) ratio, which was 24.7 in the propositus and 14.3 in his older brother. In normal adult males the mean (SD) ratio is 1.1 (1.7). The ratios for aetiocholanalone:androsterone (4.7) and tetrahydrocorticosterone:allotetrahydrocorticosterone (THB:alloTHB) (4.3) were also raised in the propositus. In his brother the aetiocholanalone:androsterone and THB:alloTHB ratios were normal and this is probably related to the low concentrations of these metabolites before puberty.

SKIN FIBROBLAST STUDIES

Fibroblast 5 α -reductase activity in both brothers was extremely low at 0.5 and 0.6 pmol/mg protein/hour, as compared with a mean of 12.8 pmol/mg protein/hour (range 3.3–42.3) in eight normal males (table 2).

Androgen receptor concentration was normal in both brothers at 815 and 939 $\times 10^{-18}$ M. There was no evidence of receptor thermolability, and receptor augmentation after preincubation with androgen was normal.

Discussion

The biochemical findings described above indicate that both brothers are homozygous for 5 α -reductase deficiency. Not only was there no

significant rise in plasma dihydrotestosterone after human chorionic gonadotrophin stimulation but very abnormal THF:alloTHF ratios were obtained on urine chromatography. 5 α -Reductase activity in fibroblasts grown from genital skin was extremely low, findings which are typical of homozygous 5 α -reductase deficiency.

5 α -Reductase deficiency usually produces severe male genital ambiguity with bifid scrotum, urogenital sinus, and a clitoris like phallus,^{1,2} but three brothers with labioscrotal fusion and hypospadias have been described.³ The absence of hypospadias in our older patient is very much in contrast with all previously reported cases of 5 α -reductase deficiency, and it is very difficult to account for the absence of hypospadias in the light of current views on male external genital development. During early fetal development testosterone is thought to act as a prohormone in the urogenital tissues where it is converted to dihydrotestosterone by intracellular 5 α -reductase, thus effecting virilisation of the external genitalia. Penile growth is at least partly dependent on intracellular 5 α -reductase as micropenis has been a cardinal feature of all reported cases of 5 α -reductase deficiency.

Our findings indicate that there may be considerable heterogeneity in the clinical manifestations of 5 α -reductase deficiency. In the older case, sufficient local dihydrotestosterone must have been produced to allow early virilisation of the genitalia with fusion of the labioscrotal folds to produce a normal urethra and scrotum. In the younger boy, virilisation was slightly less complete leading to penoscrotal hypospadias and chordee. Reduced 5 α -reductase activity in the second half of gestation probably accounts for the presence of microphallus at birth.

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