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Early diagnosis and management of 5α-reductase deficiency

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Abstract

Two siblings of Pakistani origin, karyotype 46 XY, were born with predominantly female external genitalia with minute phallus, bifid scrotum, urogenital sinus, and palpable gonads. The older sibling at the age of 8 days showed an adequate testosterone response to human chorionic gonadotrophin (hCG) stimulation. The diagnosis of 5α-reductase deficiency was made at age 6 years when no 5α-reduced glucocorticoid metabolites were detectable in urine even after tetracosactrin (Synacthen) stimulation. In the younger sibling the diagnosis of 5α-reductase deficiency was provisionally made at the early age of 3 days on the basis of high urinary tetrahydrocortisol (THF)/allotetrahydrocortisol (5α-THF) ratio and this ratio increased with age confirming the diagnosis. Plasma testosterone: dihydrotestosterone (DHT) ratio before and after hCG stimulation was within normal limits at age 3 days but was raised at age 9 months. Topical DHT cream application to the external genitalia promoted significant phallic growth in both siblings and in the older sibling corrective surgery was facilitated. In prepubertal male pseudohermaphrodites with normal or raised testosterone concentrations, phallic growth in response to DHT cream treatment could be an indirect confirmation of 5α-reductase deficiency.

Deficiency of 5α-reductase was described as a distinct biochemical entity in 1974.[1 2] The condition is inherited as an autosomal recessive disorder and is characterised by external female phenotype at birth, presence of bilateral testes and normally developed internal male genitalia, including seminal vesicles and ejaculatory duct, while at puberty there is variable virilisation of the external genitalia accompanied by the development of pubic and axillary hair.[1–4]

The biochemical abnormalities characteristic of 5α-reductase deficiency are clearly described in adults and older children but it is only recently that the diagnosis has been made in infancy, the critical period for sex determination in the newborn with ambiguous genitalia.[3 5–7] The typical pattern is that of normal or raised concentration of plasma testosterone with decreased dihydrotestosterone (DHT) and increased testosterone: DHT ratio especially after human chorionic gonadotrophin (hCG) stimulation.[5 6 8] Additional abnormalities include reduced levels of 5α-reduced urinary glucocorticoid and androgen metabolites, for example, allotetrahydrocortisol (5α-THF) and androsterone.[9 10] In infancy measurement of these steroid metabolites can be difficult as they are present at low concentrations in the presence of high concentrations of steroid metabolites of similar structure. Sensitive detection methods of high specificity (for example, gas chromatography/mass spectrometry) are therefore required.[7] Decreased 5α-reductase activity in fibroblasts cultured from genital skin may also aid diagnosis.[11 12]

We describe two siblings with 5α-reductase deficiency, the younger of whom was diagnosed shortly after birth. In both siblings DHT treatment was of value in increasing phallic size.

Methods

hCG stimulation was performed by giving 1000 IU of hCG daily for three days. Plasma samples for testosterone and DHT measurements were taken on days 0 and 4.[13] The tetracosactrin (Synacthen, Ciba) stimulation test was performed by administering tetracosactrin 250 μg as a six hour infusion. Twenty four hour urine samples were collected before and after the infusion for the measurement of THF and 5α-THF. Plasma testosterone and DHT were measured with a specific radioimmunoassay after ether extraction and celite column chromatography.[14]

Urinary steroid metabolites were measured by a method based on that of Shackleton and Honour using capillary column chromatography linked either to a flame ionisation detector (patient 1) or to a mass spectrometer (patient 2). Selective measurement of THF and 5α-THF was performed by monitoring ion m/z 652 (M-31) of the methyloxime-trimethysilyl ether derivative.[15]

Case reports

PATIENT 1

This child, born in 1983, was the second child of Pakistani parents who were first cousins and practising Muslims. The pregnancy was normal and the child weighed 3100 g at 40 weeks' gestation. Examination at birth revealed micropenis with bifid scrotum, penoscrotal hypospadias, and palpable gonads in the labioscrotal folds. Karyotype was normal male, and no mullerian structures were seen on abdominal ultrasound.

At age 8 days basal plasma testosterone concentration was 6·3 nmol/l and an increase to 16·0 nmol/l was demonstrated after hCG stimulation. A diagnosis of incomplete androgen insensitivity was made, having excluded a biosynthetic defect of testosterone, but the parents

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forcibly expressed their commitment to raising this baby as a male in accordance with the chromosomal sex. They were averse to the alternative of gonadectomy followed by raising in the female gender with the certainty of sterility. Parents defaulted from follow up until the child was 22 months old, at which time the basal plasma testosterone concentration was less than 0·7 nmol/l with an increase to 18·4 nmol/l after hCG stimulation. The child was then not seen until the age of 6 years when phallic length was only 2 cm. A diagnosis of 5α-reductase deficiency was made based on urinary steroid analysis. Basal THF was 320 μg/24 hours, increasing to 1310 μg/24 hours after tetracosactrin stimulation. However, 5α-THF was below detectable concentrations (<50 μg/24 hours) before and after tetracosactrin stimulation. Basal urinary THF: 5α-THF ratio was greater than 6·4 (normal range for adult males: 0·61–1·43[7]) and this ratio was greater than 26·2 after tetracosactrin.

In an attempt to facilitate surgery and to improve his phenotypic appearance by increasing phallic size this boy was given a trial of DHT cream (Andractim, Laboratories Besins Iscovesco, Paris), 2·5 g applied twice daily to the phallus for three months. Phallic length and circumference before treatment were 2·5 cm and 3 cm respectively, increasing after three months to 4·5 cm and 6 cm (fig 1A and B). A stage 1 Cecil-Culp repair of the penoscrotal hypospadias was performed three months after cessation of DHT cream application, and to date there has been no reduction in phallic size despite cessation of treatment.

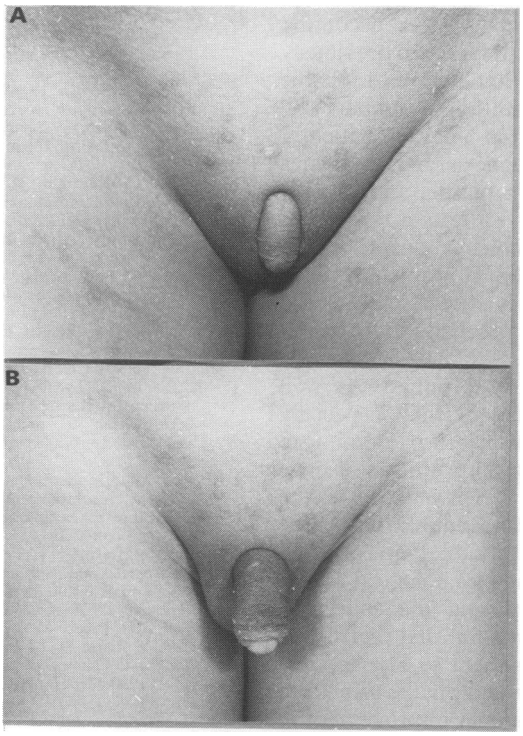

Figure 1 Patient 1 at age 6 years (A) before DHT treatment and (B) three months after DHT treatment.

Plasma steroid analysis in patient 2

	Age 3 days		*Age 9 months*		*Controls after hCG*[*16]
	Basal	*After hCG*	*Basal*	*After hCG*	
Testosterone (nmol/l)	1·20	14·06	0·20	16·93	23·12 (8·60)
DHT (nmol)	0·50	1·17	0·21	0·60	1·88 (0·68)
Testosterone: DHT ratio	2·34	12·02	0·95	28·22	11·4 (1·30)

*Mean (SD) with protocol of seven injections (1500 IU/48 hours×7) in prepubertal boys (6 months–10 years).

PATIENT 2

This child, a younger sibling of patient 1, was born in 1990 just when patient 1 was being diagnosed. The pregnancy was normal and the child weighed 3400 g at 40 weeks' gestation. Ambiguous genitalia were noted at birth with minute phallus, bifid scrotum, palpable gonads, and single urogenital sinus. Chromosomal analysis showed normal male karyotype with no mullerian structures on abdominal ultrasound. The diagnosis of 5α-reductase deficiency was made on the basis of an elevated urinary THF: 5α-THF ratio of 1·78 (normal range for young infants 0·3–0·6[7]). This ratio increased with age to 5·0 at age 2 months (fig 2) and 14·1 at 10 months. Plasma analysis after hCG stimulation showed a testosterone: DHT ratio of 12·02 at

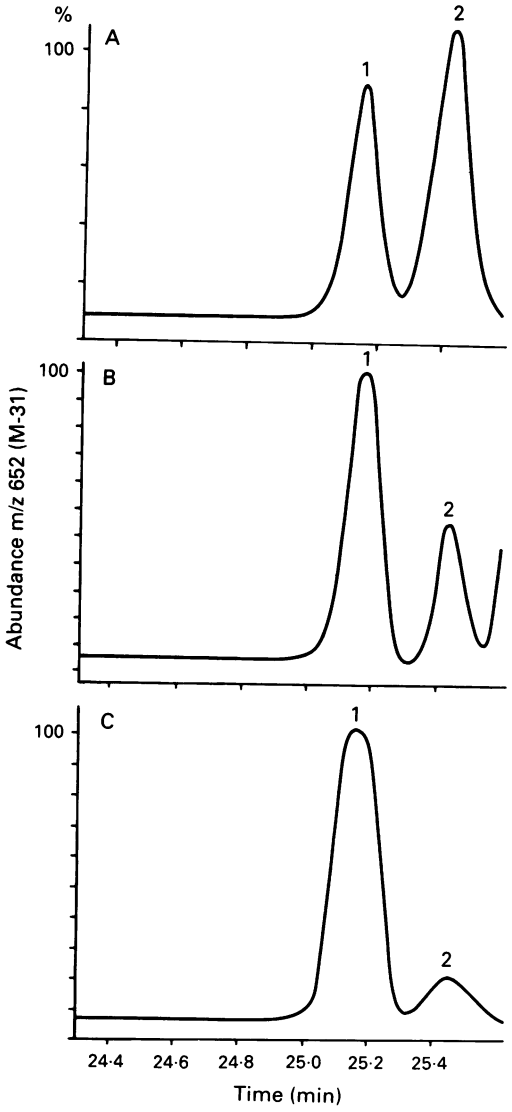

Figure 2 Urinary steroid analysis by gas capillary column chromatography/mass spectrometry. Selective analysis of ion m/z 652 (M-31) specific for THF (1) and 5α-THF (2). (A) Normal male at 3 days, THF: 5α-THF ratio=0·84; (B) patient 2 at 3 days, THF: 5α-THF ratio=1·78; (C) patient 2 aged 2 months, THF: 5α-THF ratio=5·0.

age 3 days and this ratio increased to 28·22 at age 9 months (table).

The child received a six months' course of DHT cream applied to the phallus twice daily, and an increase in phallic length from 0·5 cm to 2·6 cm was observed.

Discussion

The birth of a baby with ambiguous genitalia is extremely distressing for the parents, and the clinician needs to establish the correct diagnosis and the appropriate decision regarding gender assignment as quickly as possible, taking into account the cultural and religious beliefs of the parents. In this family, the parents were practising Muslims and the rearing of the first son as a castrated female was unacceptable. Fortunately this proved to be the correct decision but it was not until the child was 6 years old that the correct diagnosis was made. Even with the knowledge that the elder brother had 5α-reductase deficiency the initial decision regarding the gender in the younger sibling was difficult. The external genitalia were extremely poorly virilised even when compared with the older brother at a similar age. An early clinical decision to advise the parents to raise as a male was taken after the diagnosis of 5α-reductase deficiency based on the urine steroid metabolite abnormality detected at day 3. By contrast, plasma DHT and testosterone:DHT ratio at 3 days were within normal range, becoming abnormal with age (table). It has been previously suggested that the hCG stimulation is a reliable diagnostic test for the condition in infancy,[1 5 8] however the normal result at 3 days in patient 2 could have led to misdiagnosis and illustrates the need to measure both plasma and urinary steroids, and to repeat these tests a few weeks later when studying neonates suspected of suffering from this disorder. It is apparent from our experience that urinary steroid analysis is a more sensitive diagnostic test than hCG stimulation in neonates.

Spontaneous virilisation at puberty is well described in 5α-reductase deficiency, especially in affected persons from the Dominican Republic in whom successful evolution of male gender identity occurs.[17 18] However, with the exception of the Dominican Republic where the condition is socially acceptable, an affected person is vulnerable to the psychological effects of ambiguous genitalia during the childhood period. It is for this reason that corrective surgery was required in patient 1. The application of DHT cream promoted phallic growth in patient 1 sufficient to cause an improvement in male appearance as well as greatly facilitating surgery. In patient 2 DHT cream caused sufficient phallic growth to relieve parental anxiety and provided some assurance that the diagnosis and prognosis were correct.

We suggest that in the context of male pseudohermaphroditism with normal or raised concentrations of testosterone, phallic growth in response to DHT cream application could be an indirect confirmation of 5α-reductase deficiency. DHT cream treatment is certainly of benefit in improving the phenotypic appearance in affected individuals as well as facilitating reconstructive surgery.

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Addendum

Since submission of this paper additional relevant information has been published.[1] This research confirms the presence of two functional 5α-reductase genes in man but only one of the genes was abnormal in two related individuals with pseudohermaphroditism due to 5α-reductase deficiency. An explanation for the difficulties we encountered in diagnosing 5α-reductase deficiency in early infancy is now possible. If there is high activity of the unaffeced

5α-reductase during the neonatal period this could result in normal production of DHT. The activity of this enzyme may decrease rapidly with age but residual activity could account for the fact that even in older patients with 5α-reductase deficiency low but detectable concentrations of dihydrotestosterone are present. At all times the affected enzyme causes a decrease in hepatic 5α-reductase leading to low excretion of 5α-THF allowing biochemical detection of the abnormality. More studies on the 5α-reductase activities during the first few weeks of life are now required to further establish this hypothesis.

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When is a haemangioma not a haemangioma?

Many congenital dysmorphic syndromes are said to have vascular anomalies of the skin as a feature and these anomalies are often referred to as haemangiomas. A recent article from Harvard Medical School (A Jay Burns and colleagues, *Pediatrics* 1991;**88**: 1257–67) points out that these lesions are rarely true haemangiomas. The authors classify vascular birthmarks into three types: haemangiomas, vascular malformations, and macular stains. Haemangiomas as they define them seem identical with what most of us know as strawberry marks. Their main characteristic is their rapid early growth and their bulk and they differ histologically from other types of vascular anomaly. Vascular malformations grow only in pace with the child and are permanent. They may be capillary (port wine stain), venous, arteriovenous, lymphatic, or mixed. Macular stains are those lesions which are commonly found over the glabellar region, the upper eyelids, and the nape of the neck and are referred to as stork beak marks or nevus flammeus. These authors reviewed the main textbook descriptions and papers concerning congenital dysmorphic syndromes and associated vascular anomalies. Such anomalies are often described in dsymorphic syndromes and are frequently described as angiomas or haemangiomas but most of them are really either macular stains or vascular malformations. Macular stains are seen in 30 to 40% of normal children and the significance of their association with rare dysmorphic syndromes is open to question. The list of syndromes in which they are said to occur includes fetal alcohol syndrome, Rubinstein-Taybi, Beckwith-Wiedemann, Edwards, Patau, and several others.

Capillary malformations are, of course, seen in the Sturge-Weber syndrome and lymphatic malformations in Turner's and Noonan's syndromes. A list of 20 syndromes is given in which complex vascular malformations, venous malformations, and telangiectases (a variety of capillary malformations) are described.

Very few syndromes have true haemangiomas as a feature. They give a list of three: coarctation of a right sided aortic arch, cleft sternum or upper mid-line abdominal wall defect, and sacral defects, tethered spinal cord, and various genitourinary defects.

It seems that the writers of textbooks will need to be more precise in their classification of vascular birthmarks in future.

ARCHIVIST