LESSON OF THE WEEK

Sexual precocity in a 4 year old boy

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Caution men treated with testosterone gel to wear clothing when in close contact with children

A boy aged 4.8 years was referred by his general practitioner with a year's history of progressive pubic hair development and increase in length and width of the penis (figure). Parents had also noticed a growth spurt in the previous year; the boy was now wearing age 6-7 clothes and his shoe size had increased during the past six months. There was no axillary hair, acne, or body odour.

The mother was aged 43 years and in good health. The father, aged 50, had undergone pituitary surgery and radiotherapy followed by bilateral adrenalectomy for Cushing's disease at the age of 19 and was receiving hormone replacement therapy for adrenal insufficiency and central hypogonadism.

On examination the boy measured 115.1 cm and weighed 23.8 kg. Both these measurements are above the 97th centile, according to current UK growth standards, with height well above the range expected for the parents' heights (mother 3rd-10th centile, father 10th centile). The penis was 5.5 cm long and 6.5 cm in circumference, equivalent to Tanner stage G4[1] (see box); pubic hair Tanner stage 3-4; axillary hair Tanner stage 1. Testes were prepubertal, measuring 2 cm long and 1.2 cm wide (volume 1.5 ml).

Tanner stages of puberty in boys[1]

Genital staging

G1 Prepubertal penis, scrotum, and testes (volume ≤3 ml)

G2 Testes ≥4 ml with scrotal laxity, but no penile enlargement

G3 Penile lengthening with further development of testes and scrotum

G4 Penile lengthening and broadening, further development of the testes (volume usually 10-12 ml)

G5 Adult genitalia, testes 15-25 ml

Pubic hair staging

P1 No pubic hair

P2 Fine hair over mons or scrotum

P3 Adult type hair (coarse, curly) but distribution confined to pubis

P4 Extension to near adult distribution

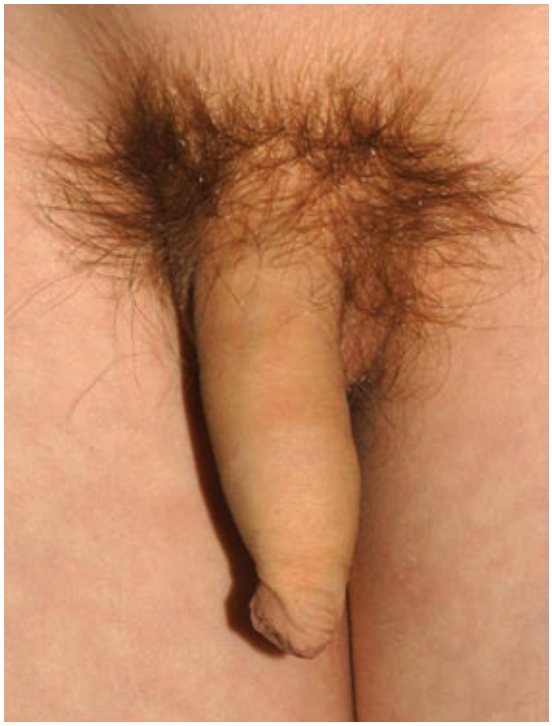
P5 Adult

Axillary hair staging

A1 No axillary hair

A2 Hair present but not adult amount

A3 Adult



Genitalia of 4 year old boy exposed to testosterone gel showing penile enlargement (Tanner stage G4) and pubic hair development (Tanner stage P4)

We made a clinical diagnosis of simple virilising congenital adrenal hyperplasia and gave a small dose of hydrocortisone, pending the results of blood and urine tests. Bone age, assessed by the TW2 system of Tanner and Whitehouse,[2] showed a relatively modest advance at 7.3 years (chronological age 4.8 years). Serum 17-hydroxyprogesterone and cortisol concentrations before and after stimulation with synthetic adrenocorticotrophic hormone were 6/13 and 131/717 nmol/l respectively, excluding classic 21-hydroxylase deficient congenital adrenal hyperplasia. Serum androgens showed androstenedione <1.4 nmol/l (normal range <2 nmol/l), dehydroepiandrosterone sulphate (DHAS) <0.8 µmol/l (<2 µmol/l), testosterone 6.4 nmol/l (<0.7 nmol/l). The luteinising hormone and follicle stimulating hormone response to luteinising hormone releasing hormone (LHRH) stimulation was prepubertal, with all values below 1.4 U/l. Urine steroid profile was unremarkable.

These findings did not support the initial diagnosis of simple virilising congenital adrenal hyperplasia, and hydrocortisone treatment was stopped. At follow-up the child's mother volunteered the information that the father had been receiving testosterone gel 50 mg daily and that the child had been sleeping in the parents' bed for the past six months while major structural repair to the house, involving the child's bedroom, was being carried out. Contact with the

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Recent lesson of the week articles

- Copper deficiency as a treatable cause of poor balance (*BMJ* 2010;340:c508)
- Treatment for lymph node tuberculosis (*BMJ* 2010;340:c63)
- Tachycardia due to atrial flutter with rapid 1:1 conduction following treatment of atrial fibrillation with flecainide (*BMJ* 2010;340:b4684)
- Protein and creatine supplements and misdiagnosis of kidney disease (*BMJ* 2010;340:b5027)
- Reduced level of consciousness from baclofen in people with low kidney function (*BMJ* 2009;339:b4559)

testosterone gel was discontinued. When the boy was reassessed at 5.1 years, the penis was 7 cm long and 7.5 cm in circumference, testes were unchanged in volume, and height velocity was 10 cm/year. Basal testosterone had fallen to 0.7 nmol/l; other serum androgens were low or unrecordable. At 5.5 years the boy's pubic hair had regressed to Tanner stage 2, penile length was 6 cm and circumference was 7 cm, and height velocity was 5.3 cm/year. Testes were 2 ml in volume.

Discussion

Testosterone gels are approved for use in men with congenital or acquired primary and secondary hypogonadism who need substitution therapy and have the advantage of avoiding the need for painful intramuscular injections. Passive hormone transfer from skin to skin contact is a recognised adverse event in children[3-5] and female partners,[6] but the risk is greatly reduced by washing the skin within 10 minutes after application[7] and by wearing clothing (sleeping in pyjamas, for example). Current label instructions advise patients to apply testosterone gel topically to the shoulders, upper arms, or abdomen and then to wash their hands and cover the treated area with clothing.

Despite the new label precautions imposed by the US Food and Drug Administration (FDA) in May 2008, eight new reports of children being exposed to testosterone were received in the following six months.[8] Most cases were attributable to patients failing to follow the label instructions, and being unaware of the risk.[4] Although symptoms regressed when testosterone exposure was stopped in most of the eight cases reported to the FDA, residual genital enlargement and advanced bone age were recorded in a few.[3] In their publication of five cases, Kunz et al reported two children as having an advanced bone age at the time of initial presentation.[4] Among the three children in whom clinical examination after discontinuation of exposure to androgens was documented, one girl showed regression of virilisation, and one boy and the other girl showed no change two and four months after contact with androgen had been discontinued. Moreover, many children had undergone invasive procedures to determine the cause of their symptoms before the correct diagnosis was made.

Our case highlights the serious clinical consequences of contamination by transdermal testosterone in a child. The clinical presentation resembled simple virilising congenital adrenal hyperplasia. However, the normal serum 17-hydroxyprogesterone and absence of extreme bone age advance were not consistent with the diagnosis, and the absence of raised serum adrenal steroids or urinary steroid metabolites also pointed to a non-adrenal cause. In the context of normal prepubertal testes, the raised concentration of testosterone was initially hard to explain, although testotoxicosis or a very small Leydig cell tumour were possible diagnoses. Until the mother volunteered the information about the father's medication we were considering more invasive investigation, including selective venous sampling from the testicular veins.

In the light of increased use of transdermal testosterone products to influence libido, muscle strength, and behaviour,[9] we advise extra vigilance in counselling patients as to unwanted side effects. This case underlines the importance of taking a careful drug history from the family members of children presenting with sexual precocity.

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Guinea pigs for the "developed" countries

I was listening to a guest lecture by an acclaimed professor on groundbreaking research—work that is probably going to save a whole generation of currently unsalvageable patients. The research seemed well founded and is going to be implemented soon. It has got huge funding and seems to have ticked all the necessary boxes. The only slight hitch is that it is still undergoing a randomised control trial in a remote village in India. Everyone in the audience sat mesmerised, while my thoughts went miles away.

As a graduate from a state run medical college in India, I have seen the hardships that the peasants endure. With sparse medical knowledge and sparser money but abundant respect for life for their loved ones, they treat doctors as gods and hang on to any ray of hope offered. They are unassuming and do not doubt or question the treatment being offered. In such situations "ethical approval" may not be stringent and in some cases may not be needed at all.

As I sat viewing the slides of this village in India and the recruits (nurses and patients), I was struck by their naivety and innocence. They will have unquestioning faith in a professor from a top university in England.

If the research is good enough to be implemented in our hospitals, I am sure it is more sensible to do a clinical trial here, under pretty much similar conditions and cohort of patients. This is a common short cut employed by many. Do you think it's right?

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