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Topical dihydrotestosterone to treat micropenis secondary to partial androgen insensitivity syndrome (PAIS) before, during, and after puberty – a case series

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Abstract

Aim: X-linked partial androgen insensitivity syndrome (PAIS) causes under-virilization at all stages of development. In two thirds of males, this results in micropenis. Dihydrotestosterone (DHT) is a potent androgen that is critical for male genital development, which when applied topically, has been shown to increase penile length with micropenis of varying etiologies. We present the first case series using topical DHT gel to treat micropenis in 46,XY males with PAIS, before, during, and after puberty.

Methods: Three related 46,XY males with confirmed p.L712F androgen receptor mutations exhibited varying degrees of micropenis post-surgical correction. They were of pre-pubertal, peri-pubertal and adult ages, respectively. Following baseline clinical and laboratory assessments all completed a 4-month course of daily DHT gel 2.5% (androstanolone) topically to penis (0.3 mg/kg body weight), with monitoring for adverse effects. Primary outcome was change in stretched penile length (SPL) following treatment.

Results: Mixed results were obtained following topical DHT therapy. In the pre- and peri- pubertal patients, SPL changed from 2.5 cm to 3.5 cm (+40%), and 3.5 cm to 5.7 cm (+63%), respectively. In the adult patient with 1 year of prior high-dose weekly testosterone therapy, no additional change in SPL was seen. No adverse effects of topical DHT were reported or observed throughout the 4 months of treatment.

Conclusion: Topical DHT treatment appears to be a safe and well-tolerated method of virilising micropenis both prior to and during puberty in children with PAIS. Questions remain about long-term outcomes into adulthood, and efficacy in adults with prior lengthy exposure to high-dose testosterone.

Keywords: androgen; dihydrotestosterone; disorders of sexual differentiation; micropenis; partial androgen insensitivity syndrome.

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Background

Penile development and growth is an androgen-dependent process. Disruption of this androgen signaling pathway can lead to attenuated penile growth that, at the extreme spectrum, is known as micropenis, which affect up to 0.7% of newborn males (1, 2).

Androgen insensitivity syndrome (AIS) is the most common cause of micropenis. It is caused by loss-of-function mutations in the androgen receptor (AR) (3), with over 1000 such mutations described, including point mutations, partial or complete deletions, and small insertions (4, 5). This results in a spectrum of virilization phenotypes, ranging from various states of under-virilization of male genitalia in partial androgen insensitivity syndrome (PAIS), to a female phenotype from complete androgen insensitivity syndrome (CAIS) (5).

High-dose testosterone treatment can overcome the androgen resistance in some mutations of PAIS, resulting in increased penile length and/or other secondary sexual characteristics (6, 7). This treatment is limited by adverse effects of high-dose testosterone, including triggering precocious puberty, and aromatization of excess testosterone leading to gynecomastia from raised estradiol levels (8, 9).

Dihydrotestosterone (DHT) is a potent end metabolite of testosterone with avid affinity to AR, and is essential for the adequate development of the male external genitalia (1). DHT administered topically to the penis had been reported to promote penile growth in children with micropenis of various etiologies (10–12), and in some instance as adjunctive therapy to testosterone (6). Topical DHT is an attractive alternative to high-dose testosterone therapy as it is thought not to trigger central precocious puberty, and cannot be aromatized to estradiol (10, 13).

The use of topical DHT as a single agent, specifically for micropenis in patients with PAIS, has not been reported to date. We present a clinical case series of a therapeutic administration of topical DHT in three related males across the pubertal spectrum with the same AR gene mutation, as well as report efficacious and safe outcomes for the non-adult males.

Methods

Three related males (Figure 1) were diagnosed with PAIS involving the same L712F mutation of their AR. They were medically managed in Dunedin Public Hospital, New Zealand by BJW, VS, and YHC. Clinical assessment at each visit included stretched penile length (SPL), Tanner staging of puberty, and testicular volume assessment by orchidometry. Their pre-surgical PAIS severity was graded by the Quigley Scale (14).

Blood was sampled in the morning, non-fasting, and tested by the local clinical laboratory using commercial ELISA methods (Canterbury Health Laboratories, New Zealand) for the following hormones: total testosterone, free testosterone, sex hormone binding globulin, DHT, 17B oestradiol, luteinising hormone (LH), and follicle stimulating hormone (FSH).

All three patients applied topical DHT gel (2.5% Andractim™, Besins, France), once daily at 0.3 mg/kg for 4 months, having been given careful instructions about its use and the need to prevent exposure of others.

Written informed consents were obtained for all three patients, for the purpose of journal publication. These patients were primarily managed for their medical condition and, therefore, did not necessitate review by the Local Ethics Committee. This case series complies with the World Medical Association Declaration of Helsinki regarding the ethical conduct of research involving human subjects.

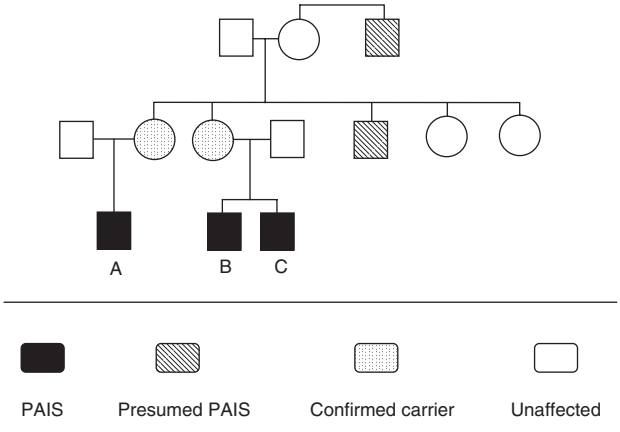

Figure 1: Family tree.

Patients

Patient A

Patient A was born with micropenis, peno-scrotal hypospadias, and bifid scrotum (Quigley Scale Grade 3). He underwent a two-stage hypospadias repair and bilateral orchidopexy. At age 14 years, he presented to the endocrine service for investigation for moderate bilateral gynaecomastia with a two-year progression. His pubertal status was Tanner Stage 3 with 12 mL testicles. Endocrine investigations revealed the following plasma testosterone of 52 nmol/L (Reference range RR 8–38), LH of 14.4 IU/L (RR 2–12), FSH 2.6 IU/L (RR 1–8), TSH 2.8 mIU/L (RR 0.25–4), and estradiol 112 pmol/L (RR <75).

A diagnosis of PAIS was made, supported by recent similar neonatal presentations in two maternal cousins (Figure 1, Patients B and C). Anecdotally, an uncle and a great-uncle were similarly affected. Molecular genetic analysis revealed a previously described mutation in the AR gene, with substitution of phenylalanine in place of leucine at codon 712 (p.L712F).

At 16 years of age, he commenced intramuscular testosterone enanthate 250 mg weekly, for a total of 9 months. He reported more confidence, but no difference in penis size, frequency of erections, amount of body and facial hair, or the presence of acne. Tamoxifen 20 mg daily was commenced for his gynecomastia with uncertain efficacy, and he consequently underwent bilateral mastectomy at 17 years. At age 24 years, he trialled topical androstanolone/DHT gel to his penis [stretched penile length (SPL) 6.1 cm, 2.5th centile (15)]. Baseline, follow up biochemistry, and outcomes are reported in Tables 1 and 2 respectively.

Table 1: Baseline patient characteristics.

Clinical	Patient A	Patient B	Patient C
Age, years	24	13	11
Tanner stage	G5P? (shaved)	G3P2	G1P1
Pre-surgical PAIS Grade Quigley Scale (15)	3	3	3
Testicular volume	20 mL	6 mL	2 mL
Serum Hormones			
T (RR 9–38 nmol/L)	50 nmol/L	19 nmol/L	2.1 nmol/L
FT (RR 250–800 pmol/L)	1087 pmol/L	561 pmol/L	38 pmol/L
DHT (RR 1000–6000 pmol/L)	3233 pmol/L	1743 pmol/L	Not taken
SHBG (RR 9–60 nmol/L)	48 nmol/L	17 nmol/L	34 nmol/L
17B Oestradiol (RR <141 pmol/L)	187 pmol/L	119 pmol/L	<44 pmol/L
LH (adult RR 2–9 IU/L)	14.2 IU/L	14.2 IU/L	0.2 IU/L
FSH (adult RR 1–8 IU/L)	8 IU/L	7.9 IU/L	2.5 IU/L

PAIS, partial androgen insensitivity syndrome; RR, reference range; T, testosterone; FT, Free Testosterone; DHT, dihydrotestosterone; SHBG, sex hormone binding globulin; LH, Luteinising hormone; FSH, follicle stimulating hormone.

Table 2: Clinical outcomes following topical DHT.

	Patient A	Patient B	Patient C
SPL (baseline)	6.1 cm (<10th centile)	3.5 cm (<5th centile)	2.5 cm (<5th centile)
SPL (2 months)	6.1 cm	5.5 cm	3.5 cm
At completion-4 months			
SPL	6.1 cm (No increase)	5.7 cm (63% increase)	3.5 cm (40% increase)
Tanner stage	G5P4	G3P3	G1P1
Testicular volume	20 mL	6 mL	3 mL
DHT (RR 1000–6000)	1155 pmol/L	4346 pmol/L	245 pmol/L
Testosterone (RR 9–38 nmol/L)		29 nmol/L	1.7 nmol/L
LH (RR 2–9 IU/L)		15.7 IU/L	2.4 IU/L

DHT, dihydrotestosterone; SPL, stretched penile length; RR, reference range; LH, luteinising hormone.

Patient B

Patient B similarly had micropenis, peno-scrotal-hypospadias, and a bifid scrotum at birth. He had additional high-riding right testicle and a non-palpable left testicle. His karyotype was confirmed as 46XY, and no further investigations were undertaken. At one year of age, he had the first of a two-stage hypospadias repair, with the second stage a year later. In between the two operations, his (SPL) was recorded as 2.5 cm [<5th centile (16)] and 2 months later following two doses of monthly IM testosterone enanthate at 25 mg, his SPL measured 3.5 cm. At 5 years of age, he was diagnosed with PAIS following the diagnosis of his cousin (Patient A), with a confirmed identical mutation of his AR. At age 9 years, he underwent surgical correction for bilateral undescended testicles.

At age 12.8 years, his pubertal status was Tanner Stage 2 with 6 mL testicles, and an unchanged SPL measuring 3.5 cm [<5th centile (16)]. He also had moderate gynecomastia, which was subsequently managed with 20 mg Tamoxifen. At age 13 years, with his SPL or Tanner staging remaining unchanged, he was commenced on topical DHT gel to his penis. His biochemistry and clinical profile at baseline and follow-up are reported in Tables 1 and 2, respectively.

Patient C

Patient C is the younger brother of Patient B, and presented at birth with similar genital features of PAIS. He underwent a single stage correction of the hypospadias at age 3 years, without complications. Unlike the other cases, he never received early androgen therapy. At age 11 years, he was Tanner stage 1 with 2 mL testicles, and SPL measuring 2.5 cm [<5th centile (16)]. No gynecomastia was present due to his pre-pubertal status. He underwent clinical trial of topical DHT gel at age 11 years, with profiles similarly reported in Tables 1 and 2.

Topical DHT gel

Patients C and B commenced DHT at the same time, aged 11 and 13 years (Tanner Stages 1 and 2), respectively, while Patient A started the trial at age 24 years, 2 months later. No adverse effects were detected on history or clinical examination for all three patients, over the 4-month period. Beneficial effects were observed in Patients B and C, but not in Patient A (Table 2).

Discussion

Our findings suggest that in children, DHT administered topically appeared to be safe and efficacious for penile growth in micropenis secondary to PAIS. Regardless of neonatal testosterone exposure, DHT led to increased penile length, comparable to results seen for similar doses and duration in micropenis from non-PAIS causes (10–13). At this dose, we saw increases in SPL of 40% and 63%, or 1 and 2.2 cm, respectively, in pre- and peri-pubertal males. However, no benefits were seen in our adult PAIS patient.

Therefore, in this case series of PAIS with L712F mutations, final penile length was modifiable up to and including the pubertal transition, but not in adulthood. This is consistent with known animal models (17–19), and would be the first demonstrable evidence of this in human literature. An alternative explanation is the exposure to previous high-dose weekly testosterone. In the only other case report using topical DHT in PAIS, beneficial response to DHT gel was seen in a 30-year-old male, having a Y571H (tyrosine to histidine substitution at codon 571) AR mutation, after 6 months of treatment (13). In contrast to our case, this patient had had no response to 1 year of prior high-dose weekly testosterone therapy. We speculate that in Patient A, the potential positive virilizing response to 1 year of weekly testosterone reached the maximum potential for penile growth; or possibly, a 4-month treatment period was too short, albeit that in most reports (and in our Patients B and C), the maximal response occurred within the first 2 months of therapy (10, 11). Alternatively, responses may vary according to the specific AR mutation, and the differing degrees of androgen resistance imposed (13).

DHT has several potential advantages over high-dose intramuscular testosterone therapy. First, it avoids contributing to increased systemic oestrogen levels via aromatization, a known side effect of testosterone treatment. This is attractive for the management of PAIS, in light of the already high incidence of gynecomastia, due to elevations of estrogen (6, 9). Second, topical DHT avoids inducing central precocious puberty, a known side effect of high-dose testosterone (8). A disadvantage of topical DHT therapy is cost, which in the New Zealand context, is not routinely funded by the public health system (although in the present cases, special approval has been obtained for publically funded access).

In the available literature, topical DHT appears to be safe when used for periods of 3–4 months at the doses noted above (11). Our data support this assumption, with no side effects of treatment reported, or noted on clinical examination, for the duration of therapy. At higher doses, subtle and reversible (on cessation) adverse effects have been reported, including local itch/irritation for the first 2 weeks of therapy, suppression of the hypothalmamic-pituitary-gonadal axis, decreases in HDL cholesterol, and increases in alkaline phosphatase (10). Additionally, as with other topical androgen preparations, patient education must include warnings about the risk topical DHT poses to close contacts, in particular children and women, following direct contact with contaminated skin (20).

The strengths of this case series are that all three subjects share the same androgen receptor mutation, and that all clinical care and measurements are conducted/supervised by a single clinician (BW). Weaknesses include the case series design and the possibility of introducing bias regarding measurements and/or reporting even though all efforts have been made to avoid these. Additionally, a limitation in assessing treatment of patients with PAIS and micropenis is the lack of normative longitudinal data for expected penile growth in this condition, especially during puberty. This makes comparison between treatments difficult, and we cannot exclude that the increases in penile size observed in the two boys of pubertal age might simply have reflected the natural history of PAIS. Nevertheless, the positive growth described in these two cases exceeds that available for comparison in the non-hormone exposed literature (21, 22).

Conclusion

Topical DHT treatment appears to be a safe and well-tolerated alternative to high-dose IM testosterone for micropenis associated with PAIS. Our case series suggests that for pre- and peri-pubertal boys, this may be a very effective therapy, even when there has been prior neonatal exposure to intramuscular testosterone. Questions remain regarding efficacy in adults, particularly in the context of prior prolonged testosterone therapy. This may be attributed to the

fact that prior positive response to high-dose testosterone attenuates any additional effect of topical DHT.

Consent

Written informed consents were obtained from the patients for publication of this case series. A copy of the written consent form is available for review by the Editor-in-Chief of this journal.

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