

Effects of pre- and post-pubertal dihydrotestosterone treatment on penile length in 5 α -reductase type 2 deficiency

Goro Sasaki¹⁾, Tomohiro Ishii²⁾, Naoaki Hori²⁾, Naoko Amano²⁾, Keiko Homma³⁾, Seiji Sato²⁾ and Tomonobu Hasegawa²⁾

¹⁾ Department of Pediatrics, Tokyo Dental College Ichikawa General Hospital, Chiba 272-8513, Japan

²⁾ Department of Pediatrics, Keio University School of Medicine, Tokyo 160-8582, Japan

³⁾ Clinical Laboratory, Keio University Hospital, Tokyo 160-8582, Japan

Abstract. Steroid 5 α -reductase type 2 deficiency (5 α RD2) is a congenital disorder of sex development caused by impairment of conversion from testosterone (T) to 5 α -dihydrotestosterone (DHT). DHT deficiency leads to various degrees of undervirilized external genitalia including micropenis, primarily correlated with mutations of the *SRD5A2* gene that encodes 5 α -reductase type 2. Four Japanese boys with isolated micropenis were diagnosed as 5 α RD2 by elevated ratios of serum T/DHT, and decreased ratios of urinary 5 α /5 β -reduced steroid metabolites. Genetic analyses for *SRD5A2* identified that the four patients shared a hypomorphic mutation R227Q that has a residual activity related to the mild-form of 5 α RD2. For prepubertal micropenis, DHT was transdermally applied to the four patients at the ages of 4–11 year, increasing a median of stretched penile lengths (SPLs) from 2.6 cm (–2.5 SD) to 4.4 cm (–0.2 SD). Nevertheless, the post-pubertal penile growth was apparently retarded, despite normal levels of T secreted from well-developed testes. The second course of DHT treatment underwent at ages of 12–18 year, but unable to normalize SPLs at a range of 6.0 to 7.0 cm (–3.4 to –2.4 SD). The prostate volumes of two patients were variable at 8.1 and 21 cm³, and a sperm cell count of one patient was normal as young adult. DHT treatment contributes to development of the penis and prostate, which are favorable for the potential fertility of 5 α RD2 adults. Meanwhile, the retarded penile growth and a risk of prostate overgrowth may complicate the post-pubertal management with DHT for 5 α RD2 males.

Key words: Micropenis, Dihydrotestosterone, 5 α -reductase, *SRD5A2*, Prostate

STEROID 5 α -reductase type 2 deficiency (5 α RD2) is an autosomal recessive disorder of sex development, caused by impaired conversion of testosterone (T) to 5 α -dihydrotestosterone (DHT) [1]. DHT deficiency leads to undervirilized external genitalia but normally differentiated testes and Wolffian ducts and normally regressed Mullerian ducts, consistent with an essential role for development of male external genitalia where the enzyme expressed. The external genitalia of affected 46, XY patients are in a broad range from predominantly female to male with isolated micropenis [2], primarily correlated with genotype of the *SRD5A2* gene that encodes 5 α -reductase type 2 enzyme.

Micropenis is a heterogeneous condition defined as

significantly small penis without genital ambiguity such as hypospadias [3]. Although generally accepted as a rare cause of micropenis, 5 α RD2 were found in 3.7% of Japanese prepubertal boys with isolated micropenis [4]. The affected males were clinically distinguished by poor response to testosterone enanthate (TE) [5], then applied for DHT to enlarge penile lengths [2, 4]. However, long-term outcome of the DHT treatment for 5 α RD2 males have rarely documented.

In this report, we describe a longitudinal data for four 5 α RD2 patients with isolate micropenis that were treated with transdermal DHT at pre- and post-pubertal stages.

Subjects and Methods

The study involved four Japanese boys with 5 α RD2 (Table 1), who showed definite micropenis [6, 7] with minor anomalies of the external genitalia, such mild bifid scrotum (Pt. 1), thickened mid-band of scrotum (Pts. 2 and 4), or bilateral cryptorchidism (Pt. 3). The micrope-

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Correspondence to: Goro Sasaki, Department of Pediatrics, Tokyo Dental College Ichikawa General Hospital, 5-11-13 Sugano, Ichikawa, Chiba 272-8513, Japan.
E-mail: sasakigoro@1993.jukuin.keio.ac.jp

Table 1 Clinical features at the diagnosis of 5 α -reductase deficiency

Pt	Clinical findings					Laboratory data			
	Age (yr)	TV (mL)	SPL		Remarks	T ¹⁾ (ng/mL)	DHT ¹⁾ (ng/mL)	T/DHT ¹⁾²⁾	SRD5A2 mutation
(cm)	(SDS)								
1	11	3	2.8	-2.6	bifid scrotum	3.8	0.06	63	p.Y26X/p.R227Q
2	9	2	2.0	-3.6	thickened band of scrotum	2.2	0.08	28	p.G34R/p.R227Q
3	3	1	2.2	-2.6	bilateral cryptorchidism	0.64	0.02	32	p.R227Q/p.R227Q
4	2	1	2.0	-2.8	thickened band of scrotum	4.8	0.17	28	p.R227Q/p.R227Q

Pt: Patient, TV: testicular volume, SPL: stretched penile length, T: testosterone, DHT: dihydrotestosterone.

¹⁾ Evaluated after human CG stimulation (3,000 U/m² for three consecutive days and blood sampling on Day 4)

²⁾ Standard values of our laboratories are 9–15.

nis with 5 α RD2 has been featured in our previous report [4]: Cases 1–3 corresponded to Pts. 1–3 in this study, respectively. Prepubertal diagnoses for 5 α RD2 were established by serum ratios of T/DHT after human CG stimulation (3,000 U/m² for three consecutive days and blood sampling on Day 4), and urinary ratios of 5 α /5 β -reduced steroid metabolites using a gas chromatograph-mass spectrometry. *SRD5A2* gene was analyzed for the patients by PCR-based sequencing as previously described [4].

Transdermal DHT treatment was provided for Pts. 1–4 (Table 2): Daily 12.5 mg (<10 years of age) or 25 mg (\geq 10 years of age) of 2.5% DHT gel (Andractim[®], Besins Healthcare, Monaco) was applied to skin of the external genitalia for 4–16 weeks [8]. Stretched penile lengths (SPLs) were manually measured by the standardized method as follows: the distance from the pubic ramus to the tip of the glans penis with the end of the measuring tape against the pubic ramus with traction along the penile shaft to the point of increased resistance [7]. Serum LH and FSH concentrations were examined by immunofluorometric assay, and T, DHT and estradiol (E₂) concentrations were determined by radioimmunoassay. Prostate volumes were measured with transabdominal ultrasonography, calculated by using prolate ellipse volume (cm³) = (length \times width \times height) \times $\pi/6$. One young adult (Pt. 2) agreed with semen analysis.

Since the DHT gel is not officially or commercially available in Japan, the administration for the patients has been approved by Institutional Review Board at Keio University Hospital (#12-08). Informed consent to this study was obtained from all participants and their parents.

Results

The four patients with isolated micropenis were diagnosed as 5 α RD2 (Table 1) by elevated ratios of serum T/DHT after human CG stimulation, decreased ratios of

urine 5 α /5 β -reduced C19 and C21 steroid metabolites (data not shown), and *SRD5A2* mutations identified as compound heterozygotes (Pts. 1 and 2) or homozygotes (Pts. 3 and 4). As previously described, the standard TE therapy for Pts. 1–3 had little effect by 0.2–0.6 cm in SPL [4].

DHT was transdermally applied for the four 5 α RD2 patients at ages of 4–11 year (Table 2). Daily application of 25 mg (Pts. 1 and 2) or 12.5 mg (Pts. 3 and 4) of DHT for 8–16 weeks increased SPL by 1.2–2.8 cm (Fig. 1). Although Pt. 1 complained rash and itch in the skin where the DHT gel applied, other adverse effects were not observed concerning bone maturation or lipid metabolism (data not shown). While serum DHT concentrations arose to 0.20–1.1 ng/mL during the treatment, serum LH and FSH levels were apparently suppressed in Pts. 1–4 (Table 2), then recovered to normal ranges at 1–2 months after the treatment is completed (data not shown).

After pubertal development was initiated in Pts. 1–3 at 11–12 years of age, skeletal growth, testicular enlargement, and pubic hair appearance were recognized within normal maturation among Japanese boys [9]. While serum T and DHT concentrations increased, the penile growth was retarded staying at 5.0–5.8 cm in SPL, required for the second course of DHT treatment at ages of 18, 16, or 12 year, respectively (Table 2). Pt. 4 remained prepubertal at the latest follow-up, excluded from further studies.

In adulthood, Pts. 1–3 exhibited 6.0 (–3.4), 6.4 (–3.0) and 7.0 (–2.4) cm in SPL (SDS) [10], respectively, with well-developed testis and pubic hair (Table 3). While serum T and E₂ levels were sustained as healthy adults, T/DHT ratios remained higher (16–21) than normal (9–15), reflecting impaired 5 α -reductase type 2 activity. Ultrasonography for prostate displayed small (Pt. 2) or somewhat large volumes (Pt. 3) for age-matched reference ranges [11], whereas serum levels of prostate-specific antigen (PSA) remained low (Table 3). Semen

Table 2 Pre and post-pubertal DHT treatment

Pt	Pre-pubertal					Post-pubertal				
	Age (yr)	DHT dose (mg/day)	Duration (weeks)	LH ¹⁾ (IU/L)	FSH ¹⁾ (IU/L)	Increment in SPL (cm) [SDS]	Age (yr)	DHT dose (mg/day)	Duration (weeks)	Increment in SPL (cm) [SDS]
1	11	25	8	1.4 → <0.2	3.8 → 1.7	3.3 [-1.9] → 4.5 [-0.4]	18	25	4	5.0 [-5.0] → 6.0 [-3.7]
2	10–11	25	16	<0.2 → <0.2	0.6 → <0.2	2.2 [-3.1] → 5.0 [+0.3]	16–17	25	16	5.8 [-3.5] → 6.4 [-2.9]
3	8	12.5	8	<0.2 → <0.2	1.2 → <0.2	2.8 [-2.3] → 4.2 [0.0]	12	25	12	5.5 [0.0] → 6.0 [+0.6]
4	4	12.5	16	<0.2 → <0.2	0.5 → 0.4	2.0 [-2.7] → 3.5 [-0.5]	NA	NA	NA	NA

Pt: Patient, DHT: dihydrotestosterone, SPL: stretched penile length, NA: not available.

¹⁾ Changing serum levels of pituitary gonadotropins before → during the DHT application, respectively

analysis in Pt. 2 revealed normal sperm count and sub-normal semen volume at the age of 20 year (Table 3). No physical concerns such as libido, masturbation, or ejaculate of semen have been documented, but a couple of patients mentioned some anxieties about their micropenis. While all patients preserve gender identity for male, they have not yet experienced sexual intercourse until the latest evaluation.

Discussion

The four patients with 5 α RD2 presented notable features (Pts. 1–4, Table 1) as previously described [4]. Briefly, R227Q-SRD5A2 that the four patients shared retains the residual activity of 3.2% [12], associated with the mild phenotype that has rarely seen in classical 5 α RD2 [1]. The partial DHT synthesis in fetus permits the small but well-differentiated penis with little ambiguity to be easily assigned as male. Additionally, systemic administration of TE failed to exert penile enlargement in the 5 α RD2 patients [4], implying that the TE therapy is based on conversion to DHT in the penile tissue where 5 α -reductase type 2 expressed, rather than rising blood T concentrations. The findings also suggest that the postnatal penile growth could be retarded, especially after puberty when increased T secretion from developing testes. Considering therapeutic strategy, 5 α RD2 should be initially ruled out from other etiologies of micropenis by hormonal and genetic analyses that are practicable even for early ages [1, 4].

The prepubertal micropenis of Pts. 1–4 responded to transdermal DHT with increments from –2.5 to –0.2 SDS in a median of SPLs (Table 2), comparable with those from –2.6 to –0.7 SDS by the TE therapy for idiopathic micropenis [13]. For 5 α RD2, the resistance to the TE therapy is difficult to be compensated by a higher dose or longer term of TE or other androgens than DHT, or consecutive administration of human CG that stimulates testicular secretion of T, because such excessive androgen has a considerable risk of adverse effects on skeletal growth by conversion to estrogens that predominantly accelerate bone maturation [14]. In contrast, DHT has biochemical characteristics including the potent binding affinity to androgen receptor (AR) and the inability to be converted to estrogens by aromatase [15], accounting for the efficacy and safety for young patients [8]. Meanwhile, super-physiological doses of DHT markedly suppress the hypothalamus-pituitary-testicular axis by a negative feedback as seen in our patients (Table 2) or adult volunteers [16], suggesting that prolonged administration of DHT could be unfavorable for testicular development and function. Hence, the intermittent administration of DHT would be reasonable to attain normalized penile

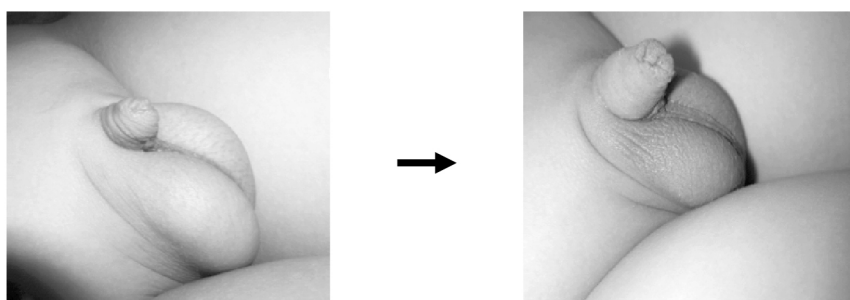


Fig. 1 Effect of dihydrotestosterone on stretched penile length in a prepubertal 5 α RD2 patient

Patient 2 (Table 1) was treated with 25 mg per day of dihydrotestosterone (DHT) for 8 weeks at the age of 10–11 years. The stretched penile length (SPL) was enlarged from 2.2 cm (-3.1 SD, left) to 3.2 cm (-1.9 SD, right). Then additional 8-week application of DHT extended to 5.0 cm ($+0.3$ SD) in SPL as summarized in Table 2. Thickened band of scrotum is also presented.

lengths with minimized side effects for prepubertal micropenis, in a similar manner to the original TE therapy [5].

In Pts. 1–3, post-pubertal penile growth was subtle or arrested during adolescence. The lack of growth spurt implicates again that *in situ* DHT production predominantly regulates penile growth, rather than circulating T or DHT supplied from others. Consistent with this speculation, the second course of DHT treatment can not produce sufficient catch-up on penile growth in Pts. 1–3 (Table 2), resulting in apparent small penis for young adults (-2.4 to -3.4 SD in Table 3) [10]. The unexpected outcomes are difficult to be explained by serum DHT concentrations, which are markedly lower than those in the target tissues where DHT *de novo* synthesized by 5 α -reductase type 2 [17]. Since DHT also up-regulates AR expression by both promoting synthesis and repressing degradation [18], intracellular DHT deficiency could diminish androgen sensitivity in the DHT-dependent tissues [19], consistent with the limited effects of endogenous and exogenous DHT in 5 α RD2 (Tables 2 and 3). Furthermore, several clinical studies showed that DHT supplement for middle-aged volunteers does not make remarkable changes in the external genitalia [16, 17], compatible with the age-limiting effects. These findings support that further treatment with DHT would be unable to resume penile growth, albeit the micropenis makes their anxiety deepened. This study can not elucidate benefits of early intervention with DHT, whereas the previous research concerning effects of the TE therapy revealed an inverse correlation between ages and increments of penile SDS [13]. Further studies could clarify whether more intensive treatment can produce a better consequence for micropenis including Pt. 4 (Table 2).

Since prostate is another DHT dependent tissue, congenital DHT deficiency generally causes hypoplastic prostate [20]. After the DHT treatment, prostate volumes are apparently small in Pt. 2, by contrast modestly over-

growth in Pt. 3 without elevated serum PSA (Table 3) [11], demonstrating various degrees of DHT effects on prostate growth with a possible risk of prostate hypertrophy [21]. While the subnormal semen volume could reflect the small size of prostate in Pt. 2 (Table 3), normal sperm cell counts were consistent with the observation that 5 α RD2 males are potentially fertile [22]. Thus, DHT treatment is favorable for 5 α RD2 males to preserve their fertility by increased prostate volumes, as long as prostate overgrowth does not occur during or after DHT administration.

Despite well-developed testes, scrotum, and pubic hair appearance with almost normal levels of T, E₂, and pituitary gonadotropins (Table 3), our 5 α RD2 patients addressed some concerns relevant to adult micropenis or DHT deficiency. First, since SPL closely correlates with erect penile length (EPL), the small penis could raise a problem of sexual intercourse in future. According to guidelines for penile augmentation, penis elongation surgery should be considered when SPL or EPL is less than 7.5 cm [23], although involving the risk of complications associated with the procedure [24]. Paternity has been archived in 5 α RD2 males even in the presence of more severely undervirilized genitalia than micropenis, using intrauterine insemination [25] or *in vitro* fertilization-intracytoplasmic sperm injection [26]. Second, relatively low levels of DHT still remain in the adult patients (Table 3), implicating that circulating DHT partially depends on 5 α -reductase type 2 activities [1], although DHT is independently produced by an isoenzyme 5 α -reductase type 1 that is expressed in the liver and non-genital skin [27]. Endocrine DHT deficiency unlikely causes a clinical concern [1, 15], whereas lessened semen parameters including sperm count and semen volume are seen in men under medication of a 5 α -reductase inhibitor [28]. Finally, long-term efficacy and safety of DHT administration have not been established for 5 α RD2. DHT supplement for healthy or hypogonadal

Table 3 Clinical features during adolescence and young adulthood

Pt	Age (yrs)	Ht (cm)	SPL (cm) [SDS]	TV (mL)	Pubic Hair ¹⁾	LH (IU/L)	FSH (IU/L)	T (ng/mL)	DHT (ng/mL)	T/DHT ²⁾	E ₂ (pg/mL)	PSA (ng/mL)	Prostate Volume ³⁾ (cm ³)	Sperm Counts ⁴⁾ [(mL)] ($\times 10^6$)
1	18	167	6.0 [-3.4]	25	5	3.6	2.8	5.5	0.26	21	NA	NA	NA	NA
2	21	175	6.4 [-3.0]	25	4	3.3	1	6.9	0.42	16	30	0.12	8.1	82 [2.2]
3	20	177	7.0 [-2.4]	20	5	8.1	4.1	4.4	0.23	19	43	0.15	21	NA

Pt: Patient, Ht: height, SPL: stretched penile length, TV: Testicular volume, T: testosterone, DHT: dihydrotestosterone, E₂: estradiol, PSA: prostate-specific antigen, NA: not available.

¹⁾ Scales of Tanner stage

²⁾ Standard values of our laboratories are 9–15.

³⁾ Calculated by using prolate ellipse volume (cm³) = (length \times width \times height) \times $\pi/6$. The age-matched reference ranges 16.0 \pm 3.9 cm³ [11].

⁴⁾ The lower reference limits in sperm counts and semen volume are 15 \times 10⁶ and 1.5 mL, respectively.

men is considered safe [15], but does not seem to evidence a certain advantage over T supplement as a hormone replacement therapy, speculating that the potent androgen action of DHT could be offset by suppressing endogenous T and E₂ [15, 17]. In particular, the diminished estrogen action may introduce some disadvantages in the estrogen-related roles including bone mineralization, spermatogenesis, libido, or erectile function [14, 29]. Moreover, persistent gynecomastia, which is another indication of DHT [30], is an uncommon condition in 5 α RD2 by contrast to androgen insensitivity syndrome [1], involved in normally developed testes and well-balanced T and E₂ levels (Table 3). These findings collectively support a notion that transdermal DHT does not become a true substitution therapy for 5 α RD2 males.

The intermittent administration of DHT contributes to development of the penis and prostate for 5 α RD2 males. However, the post-pubertal management is complicated by the reason that DHT supplement is unable to mimic the physiological production. We hope that the longitudinal data would be helpful for better management of 5 α RD2 patients.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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