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Effect of Testosterone Therapy on Penile Size in Two Children with 5-Alpha Reductase Type 2 Deficiency

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Abstract **Original Research Article**

5-alpha-reductase type 2 deficiency (5-ARD) is an autosomal recessive condition resulting in the inability to convert testosterone to the more physiologically active dihydrotestosterone (DHT). Genetic males with 5-ARD are born with genital ambiguity that varies in severity from small phallus to completely female looking genitalia. The hormonal replacement therapy is not very effective in improving the penile length and there is no agreement on optimal therapy. In this study, we report the effect of intramuscular testosterone injection on penile size in 2 children with 5-ARD. Both patients who reached the age of 14 had a penile length of 4.5 and 5.5cm. We conclude that testosterone therapy has an advantage in improving penile size in children with 5-ARD especially in countries where DHT cream is not available or not approved

Keywords: 5 alpha-reductase; Testosterone; Dihydrotestosterone; Micropenis; SRD5A2.

INTRODUCTION

5-alpha-reductase type 2 deficiency (5-ARD) is an autosomal recessive sex-limited condition resulting in the inability to convert testosterone (T) to the more physiologically active dihydrotestosterone (DHT). Because DHT is required for the normal masculinization of the external genitalia in utero, genetic males with 5-ARD are born with genital ambiguity that varies in severity from small phallus and hypospadias to completely female looking genitalia [1].

There are two isoforms of 5-alpha reductase, type 1 and type 2 [2]. 5-alpha reductase type 1 is encoded by the gene SRD5A1 [2]. The enzyme is transiently expressed in the neonatal skin and then repressed until puberty when it is permanently expressed [3]. The other isoenzyme is 5-alpha reductase type 2 which is encoded by the gene SRD5A2 and is expressed in genital skin and prostate [4]. Genetic alterations in SRD5A2 are the underlying genetic defects in 5-ARD [1, 5, 6], and the degree of atypical genital appearance varies depending on the residual SRD5A2 enzymatic activity [6].

The treatment of a child with 5-ARD depends on many factors, the most important being the phenotypic findings and gender of the child at the time of the diagnosis. If it is decided to raise the child as male, proper corrective surgery is needed and hormonal therapy is required to improve penile size. The hormonal therapy approach is still debatable and there is no agreement on optimal therapy. In this study, we report our experience with intramuscular testosterone injection on penile size in 2 children with 5-ARD until early adolescence.

METHODS

The effect of long term testosterone therapy was evaluated in two, 46 XY patients with 5-ARD. The diagnosis of 5-ARD was suspected clinically by the presence of varying degrees of non-salt wasting genital ambiguity, biochemically by elevated T to DHT ratio of more than 8.5, after stimulation with human chorionic gonadotropin (hCG) (3,000 U/m2 for 3 consecutive days and blood sampling on Day 4 [7], and confirmed genetically by SRD5A2 mutations. SRD5A2 gene was analyzed for these 2 patients by PCR-based sequencing as previously described [8].

The clinical diagnosis of microphallus was based on a stretched penile measurement of 2SD below the mean for age. Stretched penile lengths (SPL) were manually measured by the standardized method: 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 [9].The degree of virilization was assessed by Prader scale ranged from 0

to 6 and the external masculinization score (EMS) ranged from 0 to 12. [10]. Serum LH and FSH concentrations were examined by immunofluorometric assay, and T, DHT concentrations were determined by radioimmunoassay.

The 2 patients received 3 courses of 3-monthly 25-50 mg intramuscular testosterone injection throughout childhood (total of 9 injections). The first 3-monthly 25 mg course was given as early as possible and around the age of 2 months, when diagnosis was made, the second 3-monthly 50 mg course was given at the age of 5 years and the third and the last 3 monthly 50 mg course was given before puberty [11].

DHT gel is not officially or commercially available in Saudi Arabia, so it was not tried in these children.

Results (table 1)

Both children presented at birth with small phallus, penoscrotal hypospadias, bifid scrotum and bilateral undescended testes. Biochemically, HCG stimulated elevated T:DHT. The genetic studies revealed non-sense mutations.

The current age of children is 14 years. The 2 subjects underwent corrective surgeries which included orchidopexy and perineal hypospadias/chordee repair. The 2 children received 3 courses of intramuscular testosterone injections. No side effects were observed apart from early pubic hair in one of the patients and mild gynecomastia in both.

Heights of patients ranged from -1.5SD and -1.6SD. Bone age was normal for chronological age.

Table-1: The clinical, biochemical and the genetic characters of the 2 children

PATIENT	1	2
AGE OF DIAGNOSIS	birth	birth
ASSIGNED SEX AT PRESENTATION	female	male
CURRENT AGE	14 year	14 years
CURRENT SEX ASSIGNMENT	male	male
CLINICAL PICTURE	microphallus hypospadias undescended testes	microphallus hypospadias bifid scrotum undescended testes
EMS	2	2.5
PRADER SCORE	4	4
T/DHT RATIO	23/0.35=66	13/0.5=26
MUTATION	c.542C>T, p.P181L	c.682G>A, p.A228T
NUMBER OF TESTOSTERONE COURSES	3	3
STRETCHED PENILE LENGTH PRE-TESTOSTERONE THERAPY	1 cm (-4.8SD)	1 cm (-4.8SD)
STRETCHED PENILE LENGTH POST-TESTOSTERONE THERAPY	4.5 cm (-3SD)	5.5 cm (-2.5SD)

DISCUSSION

Sex assignment remains one of the most clinically challenging and controversial topics in 5-ARD given external genitalia are typically undervirilized at birth. Historically, most individuals with 5-ARD were raised females. However, reports that over half of patients who underwent a virilizing puberty adopted an adult male gender identity have challenged this practice. Consensus guidelines on assignment of sex of rearing at birth are equivocal or favor male assignment in the most virilized cases [12].

The management plan includes psychological, surgical and hormonal therapy [13]. The psychological evaluation must be performed prior to 27 months of age before hormonal or surgical treatment is undertaken to avoid identity conflicts. The surgical treatment of male-raised children consists of orthophaloplasty, scrotumplasty, urethroplasty, and orchidopexy when necessary. The hormonal therapeutic options include testosterone injections and/or DHT cream [13].

There are few reports on the use of DHT cream and testosterone injections in these children and long-term outcome are rarely documented [14]. One of the first trials by Carpenter et al. showed increase in SPL in a child with 5-ARD from 1.8 to 3.8 cm with DHT cream [15]. Similarly Odame *et al.* reported successful usage of DHT gel in 2 affected siblings with very small phalluses and bifid scrotum with significant enlargement up to 2.6 to 4.5 cm in 6 months (16). Bertelloni *et al.* demonstrated that the DHT cream achieved an increase of at least 120% in penile length in 3 Italian newborns with 5-ARD [17]. One of the recently published long term studies by a Sasaki *et al.* on 4 Japanese children looked at the effect of transdermal DHT on penile size. DHT was applied at the ages of 4-11 year, which increased the median SPL from 2.6 cm (-2.5 SD) to 4.4 cm (-0.2 SD). Nevertheless, the post-pubertal penile growth was retarded. The second course of DHT treatment underwent at ages of 12-18 year, but was unable to normalize SPLs, however the maximum range was 6.0

to 7.0 cm (-3.4 to -2.4 SD) [18]. Kats *et al.* was successful to treat a patient with DHT cream until age of 35 years resulted in a final penile length of 7.5cm and a circumference of 6.5cm [19].

The affected males with 5-ARD are clinically distinguished by poor response to testosterone therapy [14]. In this study, we showed that testosterone therapy in therapeutic dosages is able to improve penile size, although the acceptable final penile length was not achieved. However it was comparable to DHT cream. We did not measure the 5 alpha reductase activity in our patients, but we believe it is low at least in children with missense mutations. There was no genotype phenotype correlation in our 2 children and also there was no difference in penile size response to testosterone. There was a concern that testosterone may cause bone age advancement and gynecomastia since it is aromatized to estrogen, however our 2 children had mild gynecomastia and a height within the family acceptable range.

We conclude that testosterone therapy has an advantage in improving penile size in children with 5-ARD especially in countries where DHT cream is not available or not approved. Our future plan is to use injectable testosterone in conjunction with DHT gel to determine if this combined therapy has a better result on final adult penile size than DHT cream alone.

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