Chapter 3
46,XY DSD due to 17β-HSD3 Deficiency and 5α-Reductase Type 2 Deficiency

Marlene Inacio, Maria Helena P. Sircili, Vinicius N. Brito, Sorahia Domenice, Ari Alves Oliveira-Junior, Ivo J.P. Arnhold, Francisco D. Tibor, Elaine M.F. Costa, and Berenice B. Mendonca

Introduction

The 46,XY disorders of sex development (46,XY DSD) are characterized by ambiguous or female external genitalia, caused by incomplete intrauterine masculinization. Complete absence of virilization results in normal female external genitalia and these patients generally seek medical attention at pubertal age, due to the absence of breast development and/or primary amenorrhea. 46,XY DSD can result either from decreased synthesis of testosterone or from the impairment of androgen metabolism or action [1, 2].

46,XY DSD due to 17β-HSD3 Deficiency

This disorder consists in a defect in the last phase of steroidogenesis, when androstenedione is converted into testosterone and estrone into estradiol [3].

There are five steroid 17β-HSD enzymes which catalyze this reaction [4] and 46,XY DSD results from mutations in the gene encoding the 17β-HSD3 isoenzyme [4, 5]. The *HSD17B3* gene contains 11 exons and is located on chromosome 9q22.

Phenotype: Patients present female-like or ambiguous genitalia at birth, with the presence of a blind vaginal pouch, intra-abdominal or inguinal testes and epididymides, vasa deferentia, seminal vesicles, and ejaculatory ducts. Most affected males are raised as females [6, 7], but some have less severe defects in virilization and are raised as males [4]. Virilization in subjects with 17β-HSD3 deficiency occurs at puberty. This late virilization is usually a consequence of the presence of testosterone in the circulation as a result of the conversion of androstenedione

Author disclosure summary: The authors declare that they have no competing financial interests.

B.B. Mendonca (✉)
Unidade de Endocrinologia do Desenvolvimento, Laboratorio de Hormonios e Genetica Molecular, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil
e-mail: beremen@usp.br

M.I. New, J.L. Simpson (eds.), *Hormonal and Genetic Basis of Sexual Differentiation Disorders and Hot Topics in Endocrinology*, Advances in Experimental Medicine and Biology 707, DOI 10.1007/978-1-4419-8002-1_3,

to testosterone by some other 17β-HSD isoenzyme (presumably 17β-HSD5) in extra-gonadal tissue and, occasionally, of the secretion of testosterone by the testes when LH levels are elevated in subjects with some residual 17β-HSD3 function [4]. Bilateral orchiectomy resulted in a clear reduction of androstenedione levels indicating that the principal origin of this androgen is the testis [4, 7]. 46,XY DSD phenotype is sufficiently variable in 17β-HSD3 deficiency to cause problems in accurate diagnosis, particularly in distinguishing it from partial androgen insensitivity syndrome [6, 8].

Most 46,XY patients are raised as girls during childhood and change to male gender role behavior at puberty has been described in subjects who were reared as females [7, 9–11] including members of a large consanguineous family in the Gaza strip [12]. 46,XX subjects homozygous for *HSD17B3* mutations presented normal phenotype [13].

We report here clinical, psychological, and therapeutic studies of eleven 46,XY DSD subjects from eight Brazilian families with 17β-HSD3 deficiency. The 11 subjects were evaluated and followed at the Hospital das Clinicas, University of Sao Paulo, and were assessed by the same psychologist. Sexual ambiguity was noted at birth in nine subjects, but all were registered and raised as females because of incomplete virilization of the external genitalia. Two were diagnosed prepubertally, and the diagnosis was made in the others between 12.5 and 34 years. At the time of diagnosis, the external genitalia were characterized by proximal hypospadias, a small phallus (<2 SDS below the age-matched normal range), a bifid scrotum, and a blind-ending vaginal pouch. Nine subjects had separate urethral and vaginal openings and two had a single perineal opening with a short urogenital sinus.

All subjects had bilateral inguinal testes except one whose right testis was intra-abdominal. The testes in the postpubertal subjects were normal or near normal in size. All subjects of postpubertal age had male *habitus* and phallic enlargement but penile length remains below <2 SDS in the three male patients. All subjects had normal heights for age, and bone age was compatible with the chronologic age. In three subjects gender identity changed from female to male at puberty; in these subjects, penile length ranged from 5.0 to 6.8 cm. The remaining eight affected subjects (including two who were castrated prepubertally) have maintained a female social sex; in these subjects penile length ranged from 4.5 to 7.0 cm. In one family, the two siblings carrying the same mutation had a different gender role [14]. Gynecomastia was present in only one case (Tanner III stage) in contrast to the report of frequent gynecomastia in earlier studies [3].

Biochemical diagnosis: Laboratory diagnosis is based on elevated serum levels of androstenedione and estrone and low levels of testosterone and estradiol in basal conditions and after hCG stimulation resulting in elevated androstenedione/testosterone and estrone/estradiol ratios indicating impairment in the conversion of 17-keto into 17-hydroxysteroids. At puberty, serum LH and testosterone levels rise in all affected 46,XY subjects and testosterone levels may be in the normal adult male range [7].

Molecular defect: The disorder is due to homozygous or compound heterozygous mutations in the *HSD17B3* gene which encodes the 17β-HSD3 isoenzyme and several mutations have been reported [4, 15].

The diagnosis of 17β-HSD3 deficiency was confirmed in all eight families by analysis of the mutations, demonstrating compound heterozygous mutations in one family and homozygous defects in seven. Identical mutations recurred in apparently unrelated families, namely, R80Q in two families, 326-1, G→C in three families, and A203V in two families. The R80Q mutation was originally described in a Palestinian family from the Gaza strip but we were unable to document Palestinian ancestry in the Brazilian families. The A203V, S209P, E215D, and 326-1, G→C mutations appear to be unique to Brazil. Whether the existence of the same mutation in different families is due to recurring new mutations or to a common ancestor is not known. Family 2 is Black, while 17β-HSD3 deficiency has rarely been described in Blacks (13).

Treatment: Gonadectomy and estrogen replacement at puberty are indicated for patients reared in the female social sex. In male patients, androgen replacement is necessary when they present low levels of testosterone. In patients with mild defects testosterone replacement is not usually necessary.

5α-Reductase Type 2 Deficiency

This disorder is the only DSD condition in which the brain of affected subjects is prenatally exposed to normal testosterone levels. There are two steroid 5α-reductase enzymes that catalyze 5α-reductase reaction [16–18]. 46,XY DSD results from mutations in *SRD5A2* gene which encodes the steroid 5α-RD2 isoenzyme [19–21]. The *5α-RD2* gene contains five exons and four introns and is located at chromosome 2 p23. The 5α-RD2 isoenzyme promotes the conversion of testosterone to its 5α-reduced metabolite dihydrotestosterone (DHT).

Phenotype: Affected patients present with ambiguous external genitalia, micropenis, normal internal male genitalia, prostate hypoplasia, and testes with normal differentiation with normal or reduced spermatogenesis. The testes are usually located in the inguinal region, suggesting that DHT influences testis migration to the scrotum [21]. Virilization and deep voice appear at puberty, along with penile enlargement and muscle mass development without gynecomastia. These patients present scarce facial and body hair and absence of temporal male baldness, acne, and prostate enlargement, since these features depend on DHT action. Most of the patients are reared in the female social sex due to female-like external genitalia at birth but many patients who have not been submitted to orchiectomy in childhood undergo male social sex change at puberty [14, 21–25]. In our experience with 30 cases of 46,XY DSD due to 5α-RD2 deficiency from 18 families, all subjects were registered in the female social sex except for 2 cases – one who has an affected uncle and the other who was diagnosed before being registered [14, 26]. Fourteen patients changed to male gender role. No correlation was observed between *SRD5A2*

mutation, T/DHT ratio, and gender role change in these patients. In one family, the two siblings carry the same mutation but presented a different gender role [14]. Ten cases are adults now and nine of them are married. Three cases adopted children and in two cases in vitro fertilization using the patient's sperm cells resulted in twin siblings in one family and in a singleton pregnancy in the other 14, 26]. Fourteen patients maintained the female sexual identification. Three of them were castrated in childhood and the others, despite the virilization signs developed at puberty, kept the female social sex and sought medical treatment to correct the absence of breast development and primary amenorrhea. None of the 10 adult female patients, now aged 24–52 years are married but 8 of them have satisfactory sexual activity.

Inheritance: The mode of inheritance for 5α-RD2 deficiency is autosomal recessive. A different mode of transmission of 5α-RD2 deficiency due to uniparental disomy was described in two unrelated patients [27].

Biochemical diagnosis: After hCG stimulation, affected children show lower DHT levels and elevated T/DHT ratio [5, 28]. Postpubertal affected patients present normal or elevated testosterone levels, low DHT levels, and elevated T/DHT ratio in basal conditions. Low DHT production after exogenous testosterone administration is also capable of identifying 5α-RD2 deficiency [14]. Elevated 5β/5α urinary metabolites ratio is also an accurate method to diagnose 5α-reductase 2 even at prepubertal age and in orchiectomized adult patients [14, 29].

Molecular defects: There are more than 50 families with this disorder described in several parts of the world [21–24]. In a few cases of 46,XY DSD due to 5α-RD2 deficiency diagnosed by clinical and hormonal findings, no mutations were identified in *SRD5A2* gene [19, 21–24].

Treatment: In male patients with 5α-RD2 deficiency, higher doses of testosterone esters (250–500 mg twice a week) are used to increase DHT levels and consequently penis size and male secondary characteristics. Maximum penis enlargement is obtained after 6 months of high doses and after that the normal dosage is reinstituted [14, 21]. The use of topic DHT gel is also useful to increase penis size with the advantage of not causing gynaecomastia and promoting a faster increase of penis size as it is 50 times more active than testosterone. DHT is not aromatized, allowing the use of higher doses than testosterone during prepubertal age.

At diagnosis, the comparison of mean penile length among 46,XY groups showed that 5α-RD2 deficiency group had the smallest penile length. At final evaluation, after surgical and hormonal treatment, mean penile length was also smaller in the 5α-RD2 deficiency group (–5.4 ± 1 SDS) compared to the groups with testosterone production deficiency ($p < 0.05$). There was no statistical difference of the mean penile length before and after treatment in each of the two etiological groups ($p > 0.05$) indicating that current treatment do not result in penis size enlargement. Two variables were significantly associated with the change of male social sex in patients 46,XY female which were registered and non-castrated in childhood: male kids games and self-perceived physical appearance as male or ambiguous in childhood.

Overall, most of our patients reported satisfaction with the treatment, although specific complaints about small penile length, sexual activity, and urinary symptoms

were frequent. A recent review analyzing articles which reported on mental or physical health outcomes of DSD patients concludes that it is still not clear how sexual function contributes to quality of life of these patients [30].

References

1. Griffin, J. E., McPhaul, M. J., Russell, D. W., Wilson, J. D. et al.: The androgen resistance syndromes: steroid 5-reductase 2 deficiency, testicular feminization, and related disorders. In: Scriver CR, Beaudet AL, Valle D, Sly WS, eds. The metabolic and molecular bases of inherited diseases, New York: McGraw-Hill, **3**(8)**:** 4117–4146, 2001
2. Hughes, I. A., Houk, C., Ahmed, S. F. et al.: Consensus statement on management of intersex disorders. Arch Dis Child, **91:** 554, 2006
3. Saez, J. M., De Peretti, E., Morera, A. M. et al.: Familial male pseudohermaphroditism with gynecomastia due to a testicular 17-ketosteroid reductase defect. I. Studies in vivo. J Clin Endocrinol Metab, **32:** 604, 1971
4. Andersson, S., Moghrabi, N.: Physiology and molecular genetics of 17 beta-hydroxysteroid dehydrogenases. Steroids, **62:** 143, 1997
5. Andersson, S., Geissler, W. M., Wu, L. et al.: Molecular genetics and pathophysiology of 17 beta-hydroxysteroid dehydrogenase 3 deficiency. J Clin Endocrinol Metab, **81:** 130, 1996
6. Lee, Y. S., Kirk, J. M., Stanhope, R. G. et al.: Phenotypic variability in 17beta-hydroxysteroid dehydrogenase-3 deficiency and diagnostic pitfalls. Clin Endocrinol (Oxf), **67:** 20, 2007
7. Mendonca, B. B., Inacio, M., Arnhold, I. J. et al.: Male pseudohermaphroditism due to 17 beta-hydroxysteroid dehydrogenase 3 deficiency. Diagnosis, psychological evaluation, and management. Medicine (Baltimore), **79:** 299, 2000
8. Bertelloni, S., Maggio, M. C., Federico, G. et al.: 17Beta-hydroxysteroid dehydrogenase-3 deficiency: a rare endocrine cause of male-to-female sex reversal. Gynecol Endocrinol, **22:** 488, 2006
9. Wilson, J. D.: Androgens, androgen receptors, and male gender role behavior. Horm Behav, **40:** 358, 2001
10. Imperato-McGinley, J., Peterson, R. E., Gautier, T. et al.: Androgens and the evolution of male-gender identity among male pseudohermaphrodites with 5alpha-reductase deficiency. N Engl J Med, **300:** 1233, 1979
11. Imperato-McGinley, J., Peterson, R. E., Stoller, R. et al.: Male pseudohermaphroditism secondary to 17 beta-hydroxysteroid dehydrogenase deficiency: gender role change with puberty. J Clin Endocrinol Metab, **49:** 391, 1979
12. Rosler, A., Kohn, G.: Male pseudohermaphroditism due to 17 beta-hydroxysteroid dehydrogenase deficiency: studies on the natural history of the defect and effect of androgens on gender role. J Steroid Biochem, **19:** 663, 1983
13. Mendonca, B. B., Arnhold, I. J., Bloise, W. et al.: 17Beta-hydroxysteroid dehydrogenase 3 deficiency in women. J Clin Endocrinol Metab, **84:** 802, 1999
14. Mendonca, B. B.: Male pseudohermaphroditism due to 5 alpha reductase 2 deficiency: outcome of a Brazilian cohort. Endocrinologist, **13:** 201, 2003
15. Rosler, A., Silverstein, S., Abeliovich, D.: A (R80Q) mutation in 17 beta-hydroxysteroid dehydrogenase type 3 gene among Arabs of Israel is associated with pseudohermaphroditism in males and normal asymptomatic females. J Clin Endocrinol Metab, **81:** 1827, 1996
16. Russell, D. W., Wilson, J. D.: Steroid 5 alpha-reductase: two genes/two enzymes. Annu Rev Biochem, **63:** 25, 1994
17. Thigpen, A. E., Silver, R. I., Guileyardo, J. M. et al.: Tissue distribution and ontogeny of steroid 5 alpha-reductase isozyme expression. J Clin Invest, **92:** 903, 1993
18. Wigley, W. C., Prihoda, J. S., Mowszowicz, I. et al.: Natural mutagenesis study of the human steroid 5 alpha-reductase 2 isozyme. Biochemistry, **33:** 1265, 1994

19. Thigpen, A. E., Davis, D. L., Milatovich, A. et al.: Molecular genetics of steroid 5 alpha-reductase 2 deficiency. J Clin Invest, **90:** 799, 1992
20. Andersson, S., Berman, D. M., Jenkins, E. P. et al.: Deletion of steroid 5 alpha-reductase 2 gene in male pseudohermaphroditism. Nature, **354:** 159, 1991
21. Mendonca, B. B., Inacio, M., Costa, E. M. et al.: Male pseudohermaphroditism due to steroid 5alpha-reductase 2 deficiency. Diagnosis, psychological evaluation, and management. Medicine (Baltimore), **75:** 64, 1996
22. Imperato-McGinley, J., Guerrero, L., Gautier, T. et al.: Steroid 5alpha-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science, **186:** 1213, 1974
23. Imperato-McGinley, J., Miller, M., Wilson, J. D. et al.: A cluster of male pseudohermaphrodites with 5 alpha-reductase deficiency in Papua New Guinea. Clin Endocrinol (Oxf), **34:** 293, 1991
24. Wilson, J. D., Griffin, J. E., Russell, D. W.: Steroid 5 alpha-reductase 2 deficiency. Endocr Rev, **14:** 577, 1993
25. Cohen-Kettenis, P. T.: Gender change in 46,XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. Arch Sex Behav, **34:** 399, 2005
26. Mendonca, B. B., Domenice, S., Arnhold, I. J. et al.: 46,XY disorders of sex development. Clin Endocrinol (Oxf), **70**(2)**:** 173–187. Review, 2009
27. Chavez, B., Valdez, E., Vilchis, F.: Uniparental disomy in steroid 5alpha-reductase 2 deficiency. J Clin Endocrinol Metab, **85:** 3147, 2000
28. Imperato-McGinley, J.: 5 Alpha-reductase-2 deficiency. Curr Ther Endocrinol Metab, **6:** 384, 1997
29. Imperato-McGinley, J., Peterson, R. E., Gautier, T. et al.: Decreased urinary C19 and C21 steroid 5 alpha-metabolites in parents of male pseudohermaphrodites with 5 alpha-reductase deficiency: detection of carriers. J Clin Endocrinol Metab, **60:** 553, 1985
30. Wisniewski, A. B., Mazur, T.: 46,XY DSD with female or ambiguous external genitalia at birth due to androgen insensitivity syndrome, 5alpha-reductase-2 deficiency, or 17beta-hydroxysteroid dehydrogenase deficiency: a review of quality of life outcomes. Int J Pediatr Endocrinol, **2009:** 567430, 2009