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17 β -Hydroxysteroid Dehydrogenase Type 3 Deficiency: Diagnosis, Phenotypic Variability and Molecular Findings

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1. Introduction

The steroid hormones are lipophilic compounds with low molecular weight, derived from cholesterol, which play a crucial role in differentiation, development and physiological functions of many tissues. They are synthesized primarily by endocrine glands, such as the gonads, the adrenal glands and the feto-placental unit during pregnancy. In addition, the central nervous system (CNS) seems to be able to synthesize a number of biologically active steroids, termed “neurosteroids”, with autocrine or paracrine functions (Baulieu, 1991). The circulating steroid hormones act both on peripheral target tissues and on the CNS, coordinating physiological and behavioral responses with specific biological purposes, e.g. reproduction. Thus, they influence the sexual differentiation of the genitalia and their functional state in adulthood, the development of secondary sexual characteristics, and sexual behavior. Unlike the lower mammals in which the ovaries and testes are the exclusive source of androgens and estrogens, in humans the adrenals cortex secretes large amount of inactive steroid precursors. These adrenal steroid precursors exert their functions in target tissues after conversion into active estrogens and/or androgens. This phenomenon which describes the conversion and action of steroid hormones within peripheral target tissues has been called “intracrinology” (Labrie, 1991, 2000).

The rate of formation of each sex steroid hormone depends on the level of expression of the specific enzymes that synthesize androgens and estrogens in each cell of each tissue (Labrie et al., 1998; Stewart & Sheppard, 1992).

The final step in the biosynthesis of active steroid hormones is catalyzed by members of the family of 17 β -hydroxysteroid dehydrogenase (17 β -HSD), which comprises different enzymes involved in steroidogenesis.

2. 17 β -hydroxysteroid dehydrogenases

The 17 β -hydroxysteroid dehydrogenases (17 β -HSDs) belong to the short-chain dehydrogenase reductase (SDR) protein superfamily, which also includes the 3 β -hydroxysteroid dehydrogenase (3 β -HSD). These enzymes regulate the levels of bioactive steroid hormones in many tissues and they are expressed not only in genital tissues, which are the primary target, but also in peripheral blood. The 17 β -HSDs, along with other steroid

metabolizing enzymes such as aromatase, steroid sulfatase, 3β -HSD and 5α -reductase are able to produce their own hormones at the peripheral cells (intracrine activity). In steroidogenic tissues (the gonads and adrenal cortex) they catalyze the final step in androgens, estrogens and progesterone biosynthesis; in peripheral tissues, they convert active steroid hormones into their metabolites, and regulate hormone binding to their nuclear receptor. So far, 14 17β -HSDs have been characterized in mammals, which show little amino acid homology but that are all members of the SDR family, with the exception of 17β -HSD type 5 (17β -HSD5) which is an aldo-keto reductase (Lukacik et al., 2006; Luu The, 2001; Prehn et al., 2009). These isoenzymes differ as regards tissue-specific expression, catalytic activity, substrate and cofactors specificity (NAD/NADH *vs* NADP/NADPH), and subcellular localization (Payne & Hales, 2004). Although *in vitro* they act both as reductase or as oxidase enzymes, *in vivo* they work in a predominant one-way, or reductive or oxidative, converting inactive 17-ketosteroids in their active 17β -hydroxy forms (Khan et al., 2004). Thus, they can be grouped into *in vivo* oxidative enzymes (17β -HSD types 2, 4, 6, 8, 9, 10, 11 and 14) and *in vivo* reductive enzymes (17β -HSD types 1, 3, 5 and 7).

2.1 Family members of 17β -HSDs

The main function of 17β -HSD type 1 (17β -HSD1), which has its highest concentration in the ovaries and placenta, is the catalytic reduction of estrone to estradiol (Luu The et al., 1989). 17β -HSD type 2 (17β -HSD2) plays a major role in the inactivation of the sex steroid hormones by oxidizing estradiol and testosterone (T) to estrone and $\Delta 4$ -Androstenedione ($\Delta 4$ -A), respectively (Wu et al., 1993), and has a broad tissue distribution (Casey et al., 1994). 17β -HSD type 3 (17β -HSD3) plays a predominant role in male T production from $\Delta 4$ -A (Geissler et al., 1994). Although this enzyme is found primarily in the testes, it is also present in adipose tissue, brain, sebaceous glands and bone. 17β -HSD type 4 (17β -HSD4) is expressed in the liver (Adamski et al., 1996) and in the peroxisomes (Markus et al., 1995); this isoenzyme plays a major function in the metabolism of fatty acids, as has been described in murine models, while it has a minor role in the metabolism of steroids. In humans, mutations of the gene encoding for 17β -HSD4 isoenzyme lead to serious illness and death within the first year of life (Moller et al., 2001). 17β -HSD type 5 (17β -HSD5), which is highly expressed in the testes, prostate, adrenals and liver, is believed to play a major role in the conversion of $\Delta 4$ -A to T and therefore could explain the virilization obtained in patients affected with alterations of 17β -HSD3. 17β -HSD type 7 (17β -HSD7) has been shown to play a role in metabolism of cholesterol (Marijanovic Z et al., 2003). 17β -HSD type 8 (17β -HSD8) has been linked to a recessive form of polycystic kidney disease (Fomitcheva et al., 1998). Several of the 17β -HSD enzymes show overlap with enzymes involved in lipid metabolism (Tab.1).

Since most of the 17β -HSD enzymes are steroid metabolizing enzymes, they are possible drug targets in many cancers, such as breast and prostate cancer, as well as common diseases, such as obesity and metabolic syndrome.

2.2 The role of 17β -HSDs

In a study conducted to observe the tissue-specificity of the transcriptional profiles of the 17β -HSDs, the expression of 17β -HSDs type 1, 2, 3, 4, 5, 7 and 10 was observed both in the genital skin fibroblasts (both scrotal and foreskin) and in the peripheral blood, with the

Type of 17 β -HSD (Gene Name)	Locations	Functions	Cofactor/ reactions	Gene location
17 β -HSD type 1 (HSD17B1)	liver, ovary, mammary glands and placenta	catalyzes the interconversion of E1 to E2	NADPH/ reduction	17q21.2
17 β -HSD type 2 (HSD17B2)	placenta, liver, intestine, endometrium, kidney, prostate, pancreas	inactivates both E2 into E1 and T into Δ 4-A	NAD+/ oxidation	16q23.3
17 β -HSD type 3 (HSD17B3)	mainly testes, adipose tissue, brain, sebaceous glands and bone	converts Δ 4-A to T	NADPH/ reduction	9q22.32
17 β -HSD type 4 (HSD17B4)	liver, heart, prostate, testes, lung, skeletal muscle, kidney, pancreas, thymus, ovary, intestine, placenta and breast cancer lines	inactivates both E2 into E1, and 5-diol into DHEA- β ; oxidation of FA	NAD+/ oxidation	5q23.1
17 β -HSD type 5 (AKR1C3)	placenta, testes, prostate, adrenals and liver	converts Δ 4-A to T in peripheral tissues; bile acid production and detoxification; eicosanoid synthesis	NADPH/ reduction	10p15.1
17 β -HSD type 6 (HSD17B6/RODH)	not determined	only retinoid metabolism identified in humans	NAD+/ oxidation	12q13.3
17 β -HSD type 7 (HSD17B7)	not determined	cholesterol synthesis; catalyzes the interconversion of E1 to E2	NADPH/ reduction	10p11.2 1q23
17 β -HSD type 8 (HSD17B8)	widespread, liver, kidney, ovary, testes	possible role in fatty acid metabolism; inactivates both E2 into E1 and androgens	NAD+/ oxidation	6p21.32
17 β -HSD type 9 (HSD17B8/RDH5)	not determined	only retinoid metabolism identified in humans	not determine d	12q13.2
17 β -HSD type 10 (HSD17B10)	widespread, liver, CNS, kidney, testes	oxidation of fatty acids; catalyzes the synthesis of DHT from 5 α - androstane-3 α , 17 β diol; oxidation of the 21OH groups on C21 steroids	NAD+/ oxidation	Xp11.22

Type of 17β-HSD (Gene Name)	Locations	Functions	Cofactor/ reactions	Gene location
17β-HSD type 11 (HSD17B11)	steroidogenic tissues, pancreas, liver, kidney, lung and heart	converts 5α-androstane-3α, 17βdiol to androsterone; lipid metabolism	NAD+/ oxidation	4q22.1
17β-HSD type 12 (HSD17B12)	not determined	fatty acid synthesis; 3-ketoacyl-CoA reductase	NADPH/ reduction	11p11.2
17β-HSD type 13 (HSD17B13)	not determined	enzymatically not characterized	not determined	4q22.1
17β-HSD type 14 (HSD17B14)	CNS, kidney	inactivates both E2 into E1 and T into Δ4A; β oxidation of FA	NAD+/ oxidation	19q13.33

E 1 = Estrone; E2 = 17β-estradiol; 5-diol = androst-5-ene 3α; DHEA = dihydroepiandrosterone; NADPH/NADP+ = nicotinamide adenine di nucleotide phosphate; Δ4-A = androstenedione; T = testosterone; FA = fatty acids

Table 1. The different types of identified 17β-HSD with corresponding locations and function

exception of the 17β-HSD-2 which was not seen in peripheral blood (Hoppe et al., 2006). All 17β-HSDs except 17β–HSD1 showed a significantly higher mRNA concentration in the foreskin compared to the scrotal tissue, demonstrating a tissue-specific local control of steroid hormone synthesis and action in addition to systemic effects (Hoppe et al., 2006). It has been demonstrated that the expression of 17β-HSD5 increases with aging in scrotal skin fibroblasts and in peripheral blood mononuclear cells, while the 17β-HSD3 mRNA expression is higher in the younger age subjects (Hammer et al., 2005; Hoppe et al., 2006). This implicates that 17β-HSD3 has a more important role in childhood, which later is taken over by the 17β-HSD5 after puberty.

It was also demonstrated the existence of a large inter individual variability of the enzymatic transcription patterns (Hoppe et al., 2006). Microarray investigation of multiple blood samples taken on different days from the same individual showed time-dependent differences in gene clustering. The nature and extent of inter individual and temporal variation in gene expression patterns in specific cells and tissues is an important and relatively unexplored issue in human biology (Whitney et al., 2003). In light of such intra- and inter individual variability, basal and after stimulation levels of the steroid hormones can vary a within wide range in normal subjects.

2.3 17β-hydroxysteroid dehydrogenase type 3

17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) isoenzyme catalyzes the reductive conversion of the inactive C-19 steroid, Δ4-A, into the biologically active androgen, T, in the Leydig cells of the testes (Payne § Hales, 2004). This protein shows a 23% sequence homology with the other 17β-HSD isoenzymes, utilizes NAPDH as cofactor and it seems to be prevalently expressed in the fetal and adult testes. Extragonadal tissues such as bone, adipose tissue, sebaceous glands and brain have also been shown to express this enzyme

(Lukacik et al., 2006). It is encoded by *HSD17B3* gene which maps to chromosome 9q22; it is 60 kb in length and contains 11 exons. The cDNA encodes a protein of 310 amino-acids with a molecular mass of 34.5 kDa and no apparent membrane-spanning domain (Andersson et al., 1996).

It has been demonstrated that *HSD17B3* gene is constitutively suppressed and its transcription begins only upon removal of suppressors that act on the Alu repeat region located upstream of the translation site start of the gene promoter region (Xiaofei et al., 2006).

HSD17B3 gene alterations affecting the enzyme function have been associated with a rare form of 46,XY disorder of sexual development (DSD), termed 17 β -hydroxysteroid dehydrogenase deficiency (Geissler et al., 1994).

3. Development of the male genitalia

The development of the male internal and external genitalia in an XY fetus requires a complex interplay of many critical genes, enzymes and cofactors (Hannema & Hughes, 2007). Wolffian ducts (mesonephric ducts) and mullerian ducts (paramesonephric ducts) are both present in early fetal life in the bipotential embryo. The wolffian ducts are the embryological structures that form the epididymis, vas deferens and seminal vesicles. T is produced by Leydig cells as early as 8 weeks of gestation and acts on the androgen receptor to stabilize the wolffian ducts (Tong et al., 1996). T and its 5 α -reduced end product, dihydrotestosterone (DHT), induce the formation of male external genitalia, including the urethra, prostate, penis and scrotum (Wilson, 1978). The mullerian ducts should regress in a male with the presence of the mullerian inhibiting substance produced by Sertoli cells in the testes. In addition, multiple other factors are necessary for the male phenotype to be congruent with a 46,XY genotype. The enzyme 17 β -HSD3 is present almost exclusively in the testes and converts Δ^4 -A to T. The 5 α -reductase type 2 enzyme is needed to convert T to DHT. In order for T and DHT to exert their androgenic role, there must be an intact androgen receptor. The lack of any one of these critical factors, including 17 β -HSD3, can lead to a child with a DSD.

3.1 Disorders of sexual development

Disorders of sexual development (DSDs) are congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical (Houk et al., 2006; Hughes et al., 2006). These disorders are classified into three major categories: sex chromosome DSD, 46,XX DSD and 46,XY DSD. This designation was proposed to replace the former term of pseudohermaphroditism, according to the consensus statement on management of intersex disorders (Hughes et al., 2006). 46,XY DSD are a heterogeneous group of clinical conditions characterized by 46,XY karyotype, either normal or dysgenetic testes and female or ambiguous phenotype of external (and possibly internal) genitalia (Hughes et al., 2006). This disorder can have several etiologies, but more frequently is due to a disruption in androgen production and/or action. Defects in androgen action and metabolism include mutations in the androgen receptor gene (complete, partial or mild androgen insensitivity syndrome-AIS and Kennedy syndrome), or in the steroid 5 α -reductase type 2 gene, encoding the enzyme which convert T into DHT in the uro-genital tract (Quigley et al., 1995; Wilson et al., 1993). Instead, disorders of androgens biosynthesis are rare and usually due to alteration of enzyme involved in the conversion of cholesterol to T, such as the steroidogenic acute

regulatory (stAR) protein, the steroidogenic enzyme P450_{scc}, 3 β -HSD type 2, 17 α -hydroxylase/17-20 lyase and 17 β -hydroxysteroid dehydrogenase type 3 (17 β -HSD3) (Gobinet et al., 2002; Miller et al., 2005), (Fig.1)

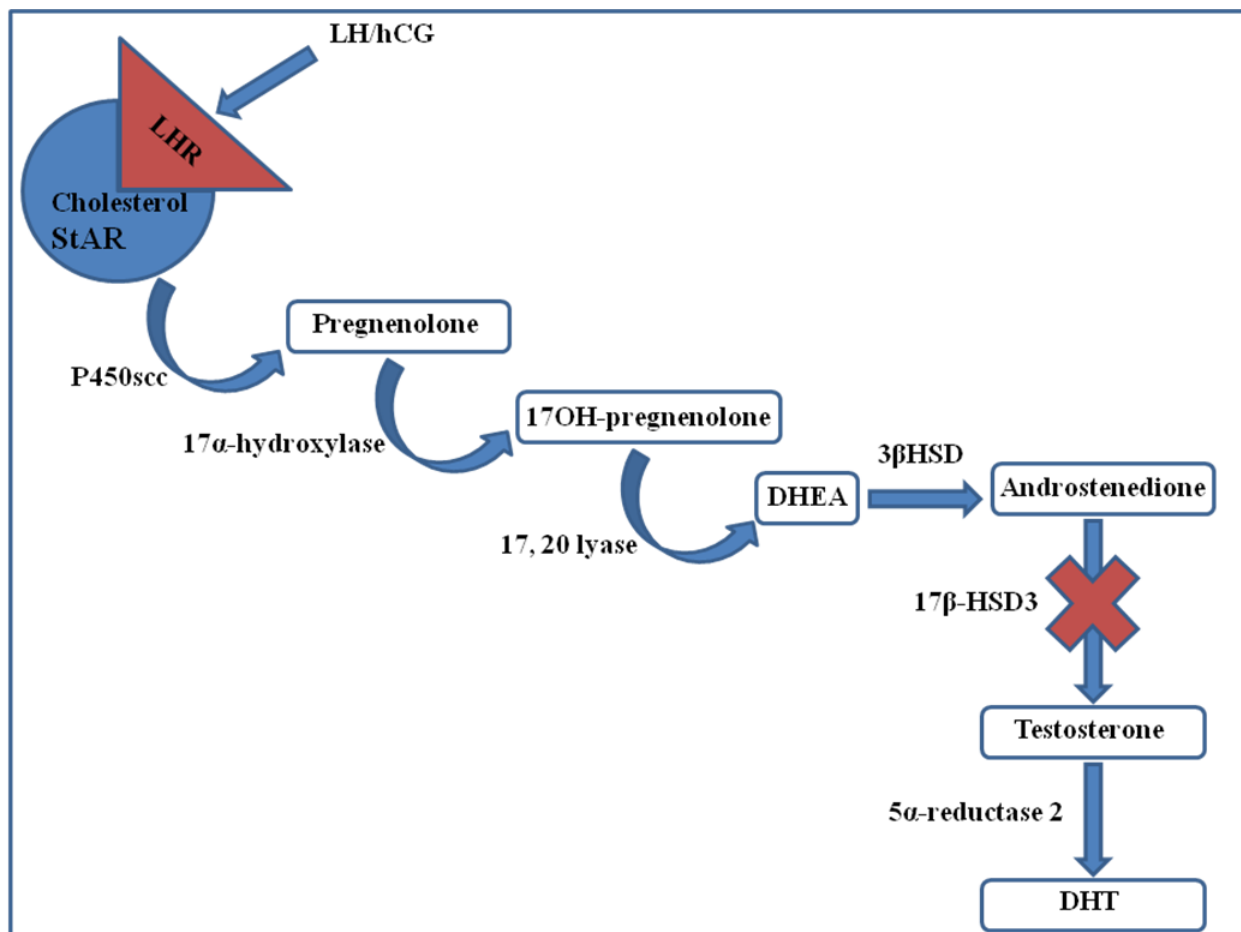


Fig. 1. Steroidogenic pathway and role of 17 β -HSD3

4. 17 β -hydroxysteroid dehydrogenase type 3 deficiency

17 β -hydroxysteroid dehydrogenase type 3 (17 β -HSD3) deficiency (OMIM #264300), originally described as 17-ketosteroid reductase deficiency (Saez et al., 1971), is an autosomal recessive disorder which represents the most common defect of the biosynthesis of T in 46,XY DSD (Bertelloni et al., 2004; Mendonca et al., 2000). This disorder is due to an impaired conversion of Δ^4 -A into T in the testes (Bertelloni et al., 2009; Faienza et al., 2008). Deficiency in the 17 β -HSD3 enzyme can be caused by either homozygous or compound heterozygous mutations in the *HSD17B3* gene (Geissler et al., 1994). Mutations in the *HSD17B3* gene confer a spectrum of 46,XY disorders of sexual organ development ranging from completely undervirilized external female genitalia (Sinnecker type 5), predominantly female (Sinnecker type 4), ambiguous (Sinnecker type 3), to predominantly male with micropenis and hypospadias (Sinnecker type 2) (Boehmer et al., 1999; Sinnecker et al., 1996). The most frequent presentation of 17 β -HSD3 deficiency is a 46,XY individual with female external genitalia, labial fusion and a blind ending vagina, with or without clitoromegaly (Sinnecker types 5 and 4).

4.1 Epidemiology and demographic

The DSD affect 1 in 5,000 to 5,500 people (0.018%) (Parisi et al., 2007; Thyen et al., 2006). Although the precise incidence of 17 β -HSD3 deficiency is unknown, a nation-wide survey in the Netherlands showed a minimal incidence of 17 β -HSD3 deficiency of about 1:147,000 newborns, with a frequency of heterozygotes of 1 in 135 (Boehmer et al., 1999). The frequency of complete androgen insensitivity syndrome (CAIS) from the same population was 1 in 99,000, which indicates that the frequency of 17 β -HSD3 deficiency is 0.65 times that of CAIS (Boehmer et al., 1999). 17 β -HSD3 deficiency is rare in Western countries, whereas in areas of high consanguinity, such as among the Gaza Strip Arab population, the incidence of 17 β -HSD3 deficiency has been reported to be 1 in 100–300 people (Rosler et al., 1996, 2006). Of the known cases of 17 β -HSD3 deficiency, most of the patients have been reported in Europe, Asia, Australia and South America, whereas only 11 cases have been reported in the United States (Mains et al., 2008; Moeller & Adamski, 2009). In a recent study from a gender assessment team in the United States that looked at DSD over a 25-year period, no patient with 17 β -HSD3 deficiency was diagnosed (Paris et al., 2007). Moreover, in the United Kingdom DSD database, patients with 17 β -HSD3 represent about the 4% of the total 46,XY DSD subjects (13/322) (Hughes, 2008). Probably the rate of 17 β -HSD3 deficiency in the United States is not so low, but many cases are misdiagnosed. In one study, patients who were later confirmed to have 17 β -HSD3 deficiency were initially misdiagnosed with AIS, and the rate of misdiagnosis was calculated to be 67% (Faisal et al., 2000). The risk of misdiagnosis is especially problematic because the clinical findings in 17 β -HSD3 deficiency may mimic AIS in childhood and 5 α -reductase deficiency in puberty (Lee et al., 2007). Thus, correct diagnosis should be made early so that treatment, management and genetic counseling can be specifically directed toward 17 β -HSD3 deficiency (Hiort et al., 2003; Johannsen et al., 2006).

4.2 Clinical features

The characteristic phenotype of 17 β -HSD3 deficiency is a 46,XY individual with testes and male wolffian-duct derived urogenital structure (e.g. epididymus, vas deferens and seminal vesicles), but with undervirilization of the external genitalia. Patients show a phenotypic variability ranging from undervirilization of the external genitalia with or without clitoromegaly and/or labial fusion, to complete female external genitalia and a blind-ending vagina; testes may be situated in the abdomen or in the inguinal channels or in the labia majora (Grumbach et al., 1998). Gynecomastia, likely as consequence of high Δ 4-A levels and its conversion to estrogens in peripheral tissues, is not usually present (Andersson et al., 1996; Balducci et al., 1985; Mendonca et al., 2000). Two late-onset variants of uncertain pathophysiology, one of which is characterized by gynecomastia in boys (Rogers et al., 1985; Castro-Magana et al., 1993) and the other by polycystic disease in woman have been described (Pang et al., 1987).

4.2.1 Birth

Patients with mutations in the *HSD17B3* gene may go unnoticed at birth as they commonly have female external genitalia (Balducci et al., 1985; Lee et al., 2007; Rosler et al., 1996). These children are usually assigned the female gender and grow up as such, and the diagnosis may be missed until adolescence (Andersson et al., 1996; Balducci et al., 1985; Boehmer et al., 1999; Faienza et al., 2007; Lee et al., 2007; Mendonca et al., 2000; Rosler et al., 2006).

Those subjects who come to medical attention in childhood have some degree of virilization or inguinal hernia with testes present along the inguinal canals or labioscrotal folds (Andersson et al., 1996; Bohmer et al., 1999; Lee et al., 2007). Less often patients have ambiguous external genitalia (Can et al., 1998; Eckstein et al., 1989), male genitalia with a micropenis (Ulloa-Aguirre et al., 1985) or hypospadias (Andersson et al., 1996). In these patients, the male sex is assigned at birth and they are raised accordingly (Rosler et al., 1996).

The degree of virilization can vary from Sinnecker stage 5 to stage 2 as mentioned above. This is speculated to be due to the partial activity of 17 β -HSD3 in the testes and extratesticular T conversion by other members of the family, such as 17 β -HSD5 (Lee et al., 2007; Qiu et al., 2004).

On examination, a separate urethral and vaginal opening is noted in many subjects, although a short urogenital sinus is reported in some (Bertelloni et al., 2006; Lee et al., 2007). Blind ending vagina that have length ranging from 1 to 7 cm has been reported in this condition (Faenza et al., 2007; Mendonca et al., 2000).

Although these findings are not specific for 17 β -HSD-3 deficiency and can be seen in other 46,XY DSD, they should raise suspicion for 17 β -HSD3 deficiency.

4.2.2 Pubertal

At the time of puberty, patients initially reared as females who have not undergone gonadectomy may have primary amenorrhea and varying degrees of virilization, including development of male body habitus, increased body hair and deepening of the voice (Faenza et al., 2007; Lee et al., 2007; Mains et al., 2008; Mendonca et al., 2000; Rosler et al., 1992; Rosler et al., 1996;). The clitoris can enlarge to as much as 5–8 cm in length due to peripheral conversion of T (Balducci et al., 1985; Mendonca et al., 2000;), but still remains smaller than a normal-sized penis and may be affected by chordee (Farkas & Rosler, 1993).

The paradox of the failure of intrauterine virilization but virilization in puberty remains an enigma not fully explained. A limited capacity of the extragonadal tissues to convert Δ 4-A to T in embryonic life might explain the lack of virilization at birth (Ulloa-Aguirre et al., 1985). This might then be overcome at puberty, when the levels of Δ 4-A are more elevated and thus activate the peripheral conversion into T. It has been demonstrated that in these subjects more than 90% of circulating T derives from peripheral conversion of Δ 4-A into T by other isoenzymes (Andersson et al., 1996; Goebelsmann et al., 1973). There is abundant evidence of the presence of 17 β -HSDs and other enzymes involved in androgen formation in a large series of human tissues, particularly liver, skin and adipose tissue (Martel et al., 1992).

This extragonadal activity is presumable under different genetic control (17 β -HSD type 1, 2 or 5 encoding gene) which is apparently unimpaired in these patients (Andersson et al., 1996; Luu-The et al., 1989).

Moreover, there seems to be a correlation between the type of mutation and the percentage of enzyme inactivation. There are several reports showing a residual enzymatic activity (15–20%) in cultured mammalian cells carrying the R80Q mutation, after several hours of incubation with the substrate (androstenedione). On the contrary, most missense mutations seems to severely impair the enzyme activity (Andersson et al., 1996; Geissler et al., 1994;).

A late onset form of 17 β -HSD3 deficiency causing breast development was reported in up to 6% of the patients with idiopathic pubertal gynecomastia (Castro-Magana et al., 1993).

It appeared to be related to the functional inactivity of 17 β -HSD3 during puberty and increased aromatization of Δ 4-A to produce excessive estrogens; however, the *HSD17B3* gene was not studied for defects in this study (Balducci et al., 1985; Bertelloni et al., 2009b).

4.2.3 Prenatal

Recently, the first case of prenatally identified 17 β -HSD3 deficiency was reported in a child with discordance between 46,XY karyotype and female external genitalia with phallic structure (Bertelloni et al., 2009b).

4.3 Endocrine findings

The phenotype of 17 β -HSD3 deficiency is clinically indistinguishable from that of AIS or 5 α -reductase 2 deficiency. In fact, the majority of the subjects had a misdiagnosis of AIS or 5 α -reductase deficiency before adequate assessment, and these two latter DSD represent the principal differential diagnoses in infancy and adolescence, respectively (Balducci et al., 1985; Bertelloni et al., 2009a; Lee et al., 2007) (Fig. 2). 17 β -HSD3 however, can be reliably diagnosed by systematic endocrine evaluation (Fig. 2) and the diagnosis confirmed by molecular genetics study.

The characteristic hormonal profile of 17 β -HSD3 deficiency is of increased concentrations of Δ 4-A and reduced levels of T (Faisal et al., 2000). In particular, a diagnostic hallmark of 17 β -HSD3 deficiency is a decreased serum T/ Δ 4-A ratio (<0.8-0.9) after human chorionic gonadotropin (hCG) stimulation in prepubertal subjects, while baseline values seems to be informative in early infancy and adolescence (Rosler et al., 1996). A normal ratio above 0.8 after hCG stimulation raises the suspicion of other diagnoses such as androgen receptor mutation. An elevated T/DHT raises the suspicion of a 5 α -reductase type 2 deficiency. However, low basal T/ Δ 4-A ratio is not specific for 17 β -HSD3 deficiency, being sometimes also found in patients with other defects in T synthesis or with Leydig cell hypoplasia. The clinical phenotype of Leydig cell hypoplasia may also resemble that of 17 β -HSD3 deficiency before puberty, but the absence of all testicular androgens (baseline and after hCG stimulation) and the lack of pubertal development or isosexual pubertal arrest should allow to differentiate between them (Bertelloni et al., 2009a).

A diagnostic tool could be represented by the urinary ketosteroid analysis performed by means gas chromatography tandem mass spectrometry, a high sensitive technique for the detection of anabolic steroid residues in urine (Van Poucke et al., 2005).

The DHT levels in 17 β -HSD-3 deficiency can be decreased, normal or high, while the dehydroepiandrosterone (DHEA) levels are typically high (Mendonca et al., 2000).

Elevated serum LH and FSH levels at baseline and after GnRH test administration, indicating the impairment of the pituitary regulatory control by gonadal hormones, have been found in these subjects (Mendonca et al., 2000). Increased serum LH causes elevated Δ 4-A levels, allowing the formation of some T either in extra glandular tissues or in the testes, when some residual enzyme activity is present (Andersson et al., 1996). Elevation of FSH may also be due to a damage to the spermatogenic tubules as a result of long term cryptorchidism as documented in histological specimens from adult subjects. However, FSH levels have been reported to be normal in some subjects (Van Poucke et al., 2005; Rosler et al., 1992).

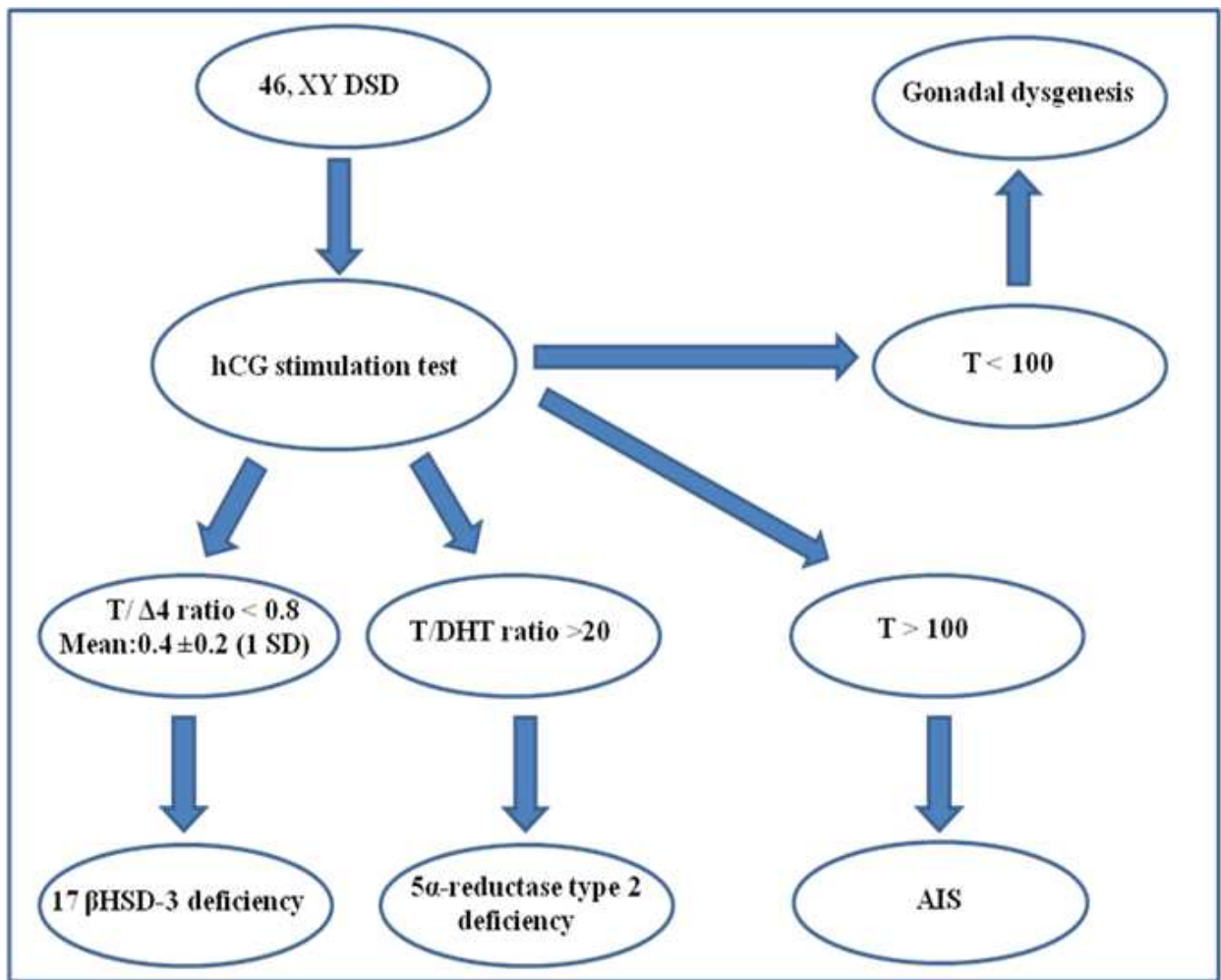


Fig. 2. A diagnostic algorithm to elucidate the various etiologies of 46,XY DSD. The diagram shows the importance of hCG stimulation in the diagnosis of 46,XY DSD. Upon hCG stimulation, if the T/ Δ 4-A ratio is >0.8 , the diagnosis of 17 β -HSD3 can be suspected; if the T/DHT ratio is >20 , a diagnosis of 5 α -reductase deficiency can be suspected. If the response of T is >100 ng/dl, androgen insensitivity syndrome (AIS) is possible. However, if the response is <100 ng/dl, causes of gonadal dysgenesis should be sought. Once a diagnosis is suspected, molecular genetic studies can be used for definitive diagnosis.

4.4 Molecular diagnosis

HSD17B3 gene alterations have been identified in patients showing clinical and biochemical characteristics of 17 β -HSD3 deficiency. The disease is genetically heterogeneous and genotype-phenotype correlations have not been found. To date, 27 mutations in the *HSD17B3* gene have been reported. These include intronic splice junction abnormalities, exonic deletions and missense mutations (Table 2) (Mains et al., 2008). The majority are missense mutations inherited as homozygous or compound heterozygous mutations, occurring most frequent in exons 3,9,10 of the gene; 4 are splice junction abnormalities (Andersson et al., 1996; Boehmer et al., 1999), 1 is a small deletion (Δ 777-783), and 1 is a thymidine deletion resulting in a frame shift mutation which alters the amino acid sequence from codon position 187 onward with a premature termination in codon 226 (Boehmer et al., 1999; Twesten et al., 2000).

Age of diagnosis	Phenotype Clinical presentation	Ethnicity	Mutation	Mutation type Effect	Reference
16 years	46,XY DSD; hirsutism, clitoromegaly, failure to menstruate	Iranian	p.Ser65Leu	missense/ inactivates enzyme	Andersson et al., 1996
6 months, 11 years	46,XY DSD; female prepubertal external genitalia, pubertal virilization, severe hair growth, voice changes and clitoral enlargement (6 months, child diagnosed because of family history)	South Asian	p.Ala56Thr	missense/ severe impairment of enzyme	Lee et al., 2007 Moghrabi et al., 1998
4–16 years	46,XY DSD; ambiguous genitalia, pubertal virilization	Dutch	p.Asn74Thr	missense	Boehmer et al., 1999
4–43 years	46,XY DSD; ambiguous genitalia at birth to mild clitoromegaly, pubertal virilization, male gender role, and many reassigned as males if raised as girls	Arab, Dutch, Brazilian, Portuguese	p.Arg80Gln	missense/ impaired enzyme activity (NADPH binding site)	Mendonca et al., 2000 Geissler et al., 1994 Boehmer et al., 1999 Roesler et al., 1996 Roesler et al., 1992 Mendonca et al., 1999
Newborn– 12 years	46,XY DSD; female external genitalia, palpable gonads, clitoral enlargement and virilization at puberty	Spanish, Italian, Lebanese	p.Arg80Trp	missense/ complete loss of enzyme activity (NADPH binding site)	McKeever et al., 2002 Faienza et al., 2007 Bilbao et al., 1998
4 months– 15 years	46,XY DSD; pubertal virilization, mild clitoromegaly, voice changes	English, German	c.325+4,A-T	splice junction/ disrupts splice acceptor site	Mendonca et al., 2000 Boehmer et al., 1999 Andersson et al., 1996
8, 23, 34 years 15 years	46,XY DSD; inguinal hernia, failure of breast development, facial and body hair growth, voice changes, clitoral enlargement	Dutch, Brazilian	c.326–1,G-C	splice junction	Mendonca et al., 2000 Geissler et al., 1994 Boehmer et al., 1999 Andersson et al., 1996 Mendonca et al., 1999 Moghrabi et al., 1998
14,15 years	46,XY DSD; pubertal virilization, mild clitoromegaly, voice changes	English, German	p.Asn130Ser	missense/ severe impairment of enzyme activity	Lee et al., 2007 Bertelloni et al., 2009 Moghrabi et al., 1998

Unknown	46,XY DSD	unknown	c.538-1,G-A	splice junction	Mueller § Coovadia, 2009
13 years	46,XY DSD; clitoromegaly and coarsening of voice, scrotalization of labia majora and inguinal masses	American (Italian, German, Irish)	p.Gln176Pro	missense	Andersson et al., 1996 Moghrabi et al., 1998
12 years	46,XY DSD; female prepubertal development, clitoral enlargement at 12 years of age, testes in inguinal canal	German	c.608delT	downstream premature stop codon	Twosten et al., 2000
10 years	46,XY DSD; prepubertal female external genitalia, inguinal mass	Turkish	p.Ala188Val	missense/ inactivates enzyme	Boehmer et al., 1999
12 years	46,XY DSD; pubertal virilization, facial hair, 4-8 cm phallus and labioscrotal folds	Afghan	p.Met197Lys	missense/ alters secondary protein structure	Lee et al., 2007
10,16,17 years	46,XY DSD; prepubertal female external genitalia, pubertal virilization, male gender rol	Syrian, Turkish, Dutch, Greek-American	c.655-1,G-A	splice junction/ disrupts splice acceptance site	Geissler et al., 1994 Boehmer et al., 1999 Andersson et al., 1996 Moghrabi et al., 1998 Ademola Akesode et al., 1977
13, 18, 21, 26 years	46,XY DSD; absence of menses, failure of breast development, facial and chest hair and clitoral enlargement, male and female gender identity in siblings	African-Brazilian, Italian	p.Ala203Val	missense/ inactivates enzyme	Mendonca et al., 2000 Geissler et al., 1994 Mendonca et al., 1999 Moghrabi et al., 1998
Unknown	46,XY DSD; pubertal virilization	Southern Italian	p.Ala203Glu	missense	Mendonca et al., 2000 Bertelloni et al., 2009
Newborn, 20 years	46,XY DSD; prepubertal female external genitalia to perineoscrotal hypospadias, primary amenorrhea, mild clitoromegaly	White American, English	p.Val205Glu	missense/ inactivates enzyme	Lee et al., 2007 Andersson et al., 1996

Newborn	46,XY DSD; ambiguous genitalia, clitoromegaly (1.5 cm) and posterior fusion and scrotalization of the labia majora which contained palpable masses	German	p.Phe208Ile	missense/ inactivates enzyme	Andersson et al., 1996
2 years, 3 months	46,XY DSD; inguinal mass, mild clitoromegaly	Italian	p.Leu212Gln	missense/ inactivates enzyme	Geissler et al., 1994 Bertelloni et al., 2006
14, 15, 21 years	46,XY DSD; female or ambiguous genitalia at birth, male behaviors in childhood, pubertal virilization, absence of menses, male gender role	White Brazilian, English	p.Glu215Asp	missense/ inactivates enzyme	Mendonca et al., 2000 Lee et al., 2007 Andersson et al.,1996
2 months, 2, 6, 17 years	46,XY DSD; clitoromegaly, primary amenorrhea, absent labia minora, severe hypospadias with undermasculinization- raised as males and females	African- American, South Asian	p.Ser232Leu	missense/ inactivates enzyme	Geissler et al.,1994 Lee et al., 2007 Moghrabi et al., 1998
17 years	46,XY DSD; clitoromegaly, primary amenorrhea, inguinal masses	African- American, Italian	p.Met235Val	missense/ inactivates enzyme	Geissler et al.,1994 Bertelloni et al., 2006 Moghrabi et al., 1998
15 years	46,XY DSD; testes in herniorrhaphy sac, failure to menstruate	Polish	c.777- 783delGAT AACC	deletion/ frame shift truncates protein	Andersson et al.,1996
5, 18 months, 2-4 years	46,XY DSD; prominent clitoris, palpable inguinal gonads	Pakistani	p.Cys268YT yr	missense/ inactivates enzyme	Lee et al., 2007 Lindqvist et al., 2001
Unknown	46,XY DSD	French	p.His271Arg	missense/ inactivates enzyme	Bachelot et al., 2006
12, 14 years	46,XY DSD; clitoromegaly, failure of breast development and deepening of voice	White American, Dutch	p.Pro282Leu	missense/ inactivates enzyme	Boehmer et al., 1999 Andersson et al.,1996
6 months	46,XY DSD; normal female prepubertal genitalia, bilateral inguinal hernia at sonography	Italian, West Indian	p.Gly289Ser	polymorphism / unknown	Boehmer et al., 1999 Bertelloni et al., 2009

Table 2. Mutations reported to date in patients with 17 β -HSD3 deficiency phenotype

Two missense mutations, the 239 G to A resulting in an Arg to Gln (R80Q) substitution, which is the most frequent alteration described in the Arab population living in the Gaza Strip (Boehmer et al., 1999; Mains et al., 2008; Rosler et al., 1996), and the 238 C to T resulting in an Arg to Trp (R80W) substitution (Bilbao et al., 1998; Faienza et al., 2007) involve the same arginine residue in exon 3 at position 80. This site has been extensively studied by systematic replacement of the wild-type arginine at position 80 and has been shown to be extremely important for both forming the salt bridge with the terminal phosphate moiety of the NADPH, as well as providing for a hydrophobic pocket for the purine ring of the adenosine portion of the NADPH (McKeever et al., 2002). Thus, this arginine is critical for cofactor binding and the substitution by different amino acids results in alteration of cofactor preference, switching from NADPH to NADH (Payne & Hales, 2004).

One polymorphic substitution (G289S) has been described in a heterozygous form in apparently normal individuals. This polymorphism does not impair the kinetic properties of the normal enzyme (Moghrabi et al., 1998). A possible role of the G289S variation has been demonstrated in prostate cancer (Margiotti et al., 2002).

Most gene alterations severely compromise the enzyme activity, but the R80Q mutation results in a 17 β -HSD3 residual enzyme activity (20%), showing a significantly lower reaction velocity as compared to the normal enzyme (Geissler et al., 1994).

4.5 Worldwide distribution of ancient and *de novo* mutations

Haplotype analysis of genetic markers flanking the *HSD17B3* gene has been performed to establish the ancient or *de novo* occurrence of mutations described in European, North American, Latin American, Australian and Arab populations (Boehmer et al., 1999). Dutch, German, white Australian and white American patients carrying the 325+4,A -T mutation share the same genetic markers and seem to have a common European ancestor. A founder effect was also demonstrated for the R80Q mutation that is common in Dutch, Arab (in Gaza), white Brazilian, and white Portuguese patients. As this mutation is associated with a specific haplotype, a common ancestor introduced during the Phoenician migration has been hypothesized (Rosler et al., 2006). An additional founder effect has been suggested for 655-1,G-T mutation found in Greeks, Turks and Syrians patients that may have spread to the Mediterranean area during Ottoman Empire (Boehmer et al., 1999). On the contrary, patients harboring the 326-1,G-C and the c.Pro282Leu mutations have a different marker genotype suggesting that these are the *de novo* mutations (Boehmer et al., 1999).

4.6 Genotype-phenotype correlation

No phenotype-genotype correlation has been noted in 17 β -HSD3 deficiency, as exemplified by members of the same family who have different phenotypes despite the same genotype (Lee et al., 2007). A variable T/ Δ 4-A ratio after human chorionic gonadotropin (hCG) stimulation was also seen despite the same homozygous mutation in different subjects of the same pedigree. This can be attributed to the extratesticular ability of some subjects to convert Δ 4-A to T by other enzymes such as 17 β -HSD5 (Qiu et al., 2004).

4.7 Imaging studies

Imaging studies that reveal the absence of müllerian structures and persistent wolffian structures also point to the diagnosis of 17 β -HSD3 deficiency, but this is not pathognomonic as 5 α -reductase type 2 deficiency will also have similar findings. Histological evidence from

gonadal tissue may show normal testicular structures, which can help to exclude any structural abnormalities (testicular dysgenesis) as the cause for the 46,XY DSD. Despite an early orchidopexy, an absent spermatogenesis has been seen in patients affected with 17β-HSD3 deficiency raised as males (Dumic et al., 1985). So far, no patient with 17β-HSD3 deficiency was fertile although raised as male, thus infertility appears to be the rule in adulthood (Tab. 3) (Bertelloni et al., 2009a; Rosler et al., 1996).

Patients	Epididimus	Testes ml ^a SDS	Spematogonia cells	Sertoli cells	Leydig	Micro- calcifications
1	Yes	1.4 -1.0	Scarce	Normal	Normal	No
2	Yes	1.0 -0.5	Present (sub-normal)	Normal	Normal	Yes
3	Yes	2.0 2.0	Present	Normal	Normal	No
4	Yes	9.0 1.3	Absent/ very scarce	Normal	Hypertrophic	No

^a mean of the two gonads; SDS: SD score.
Normal values from Cassorla et al., 1981 for patients 1-3 and from Taranger et al., 1976 for patient 4.

Table 3. Gonadal findings in 4 subjects with 17β-HSD3 deficiency

4.8 Gender behavior

In the absence of a correct diagnosis before puberty, most patients with 17β-HSD deficiency are raised as females and undergo virilization during adolescence due to extratesticular conversion of Δ4-A to T, secondary to some residual function of the enzyme and increased substrate availability in Δ4-A at puberty (Andersson et al., 1996). In cases with partial virilization, early post-natal diagnosis and consequence successful androgen treatment may result in a male sex assignment and in a nearly normal male phenotype in adulthood. Gonadectomy is recommended before puberty for those individuals who have been raised as females and wish to remain so. In these subjects, female sex characteristics should be induced or maintained with appropriate hormone replacement therapy (Hiort et al., 2003). Vaginal dilation using the modified Frank’s procedure or vaginal reconstruction surgery may be necessary to create a vaginal cavity with adequate capacity for sexual relations (Castro-Magana et al., 1993). The patient and family will need appropriate psychological counseling to accept the diagnosis and the infertility that accompanies it (Gooren, 2002). In patients with a male attitude, it is possible to achieve adequate male development without medical intervention, when corrective surgery has been judged to be warranted (Boehmer et al., 1999; Farkas § Rosler, 1993; Rosler et al., 1996). Exogenous T treatment does not seem to yield additional benefits in adulthood (Mendonca et al., 2000; Farkas § Rosler, 1993), while pre-operative T administration may result in a better cosmetic appearance of the external genitalia (Farkas § Rosler., 1993). Gender role changes have been reported in 39-60% of cases of 17β-HSD3 deficiency who have been raised as girls (Wilson, 1999). Genetic and endocrine evidence indicates that androgens play an important role in male gender behavior and identity. However the fact that many individuals with mutations of the 5α-reductase and 17β-HSD3 encoding genes do not change their gender role behavior implies that other

factors (social, psychological or biological) contribute to modulating human sexual behavior. Because gender-appropriate rearing, and not the chromosomal, gonadal or genital factors plays a crucial role in gender identity development, early diagnosis and treatment of patients with the 17 β -HSD3 deficiency is very important.

4.9 Psychological aspects

Sex assignment of children with DSD is a subject of intense debate. The early pioneers in this field coined the term 'optimal gender policy', which advocated for early corrective surgery to help the affected children and their parents to facilitate stable gender identity and appropriate gender role behavior (Money et al., 1955). Opponents of early surgery argue for a 'full consent policy', in which surgery is not performed in non-emergency situations before full consent may be obtained from the child (Kipnis & Diamond, 1998). In 17 β -HSD3 deficiency, as in all situations characterized by severe undervirilization (Sinnecker stage 5 or 4), is not always feasible to wait the start of the virilization and/or the age for a reliable full consent for major intervention, because in this waiting period the patient could assume a female gender role and identity. According to the recent guidelines regarding ethical principles and recommendations for the medical management of DSD in children and adolescents, the parents take the first-line responsibility in defining what might be best for the child, and this might vary according to their individual experience and lifestyle, cultural expectations and religious beliefs (Wiesemann et al., 2010). The child, according to his or her developmental level, can express own preference. Each case must be weighed on its own merits. When there is a doubt, the psychological and social support of the child and the parent is to be ranked higher than the creation of biological normalcy.

4.10 Malignancy risk

The external genitalia are mostly female in 17 β -HSD3 deficiency, but the internal structures are derivatives of wolffian structures. The testes are usually positioned in the inguinal canal, sometimes at the labia majora and rarely in the abdominal cavity (Mendonca et al., 2000). The consensus statement for management of DSD puts the risk of germ cell malignancy at 28% in 17 β -HSD3 deficiency (Houk et al., 2006; Hughes et al., 2006). This puts it in the intermediate risk group for malignancies and close monitoring is recommended for someone who is raised as a male rather than having gonadectomy at the time of diagnosis.

5. Conclusions

Diagnosis and consequently early treatment of the 17 β -HSD3 deficiency is frequently difficult because clinical signs are often mild or absent from birth until puberty. Moreover, the 17 β -HSD3 deficiency is clinically indistinguishable from other forms of 46,XY DSD such as AIS or 5 α -reductase 2 gene deficiency. The correct diagnosis can be arrived at by systematic endocrine evaluation and, most importantly, by the calculation of the T/ Δ 4-A ratio. The diagnostic power of biochemical parameters is not always specific, because no normal reference range has yet been established in strictly age-matched controls and because of overlapping with other causes of 46,XY DSD due to impaired T biosynthesis. Molecular genetic testing confirms the diagnosis and provides the orientation for genetic counseling. A high index of suspicion should be present for any female who presents with inguinal hernias or mild clitoromegaly in infancy or early childhood. The virilization in the

adolescent girl should also arouse suspicion. Since there are unique clinical implications based on the diagnosis of this condition, it is important to be as prompt and accurate as possible. In conclusion, endocrine evaluation is an important tool for the selection of patients with a suspected 17 β -HSD3 deficiency. In these patients, mutational analysis of the *HSD17B3* gene, supported by a knowledge of the ethnic distribution of mutations, is irreplaceable in confirming the diagnosis.

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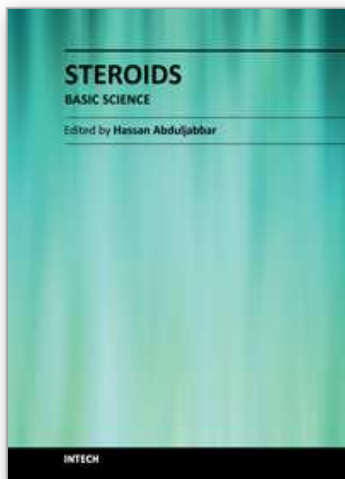
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This book explains the basic science of steroids and is targeted towards professionals engaged in health services. It should be noted that medical science evolves rapidly and some information like the understanding of steroids and their therapeutic use may change with new concepts quickly. Steroids are either naturally occurring or synthetic fat-soluble organic compounds. They are found in plants, animals, and fungi. They mediate a very diverse set of biological responses. The most widespread steroid in the body is cholesterol, an essential component of cell membranes, and the starting point for the synthesis of other steroids. Since the science of steroids has an enormous scope, we decided to put the clinical aspects of steroids in a different book titled "Steroids-Clinical Aspects". The two books complete each other. We hope that the reader will gain valuable information from both books and enrich their knowledge about this fascinating topic.

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