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Germ cell neoplasia in situ complicating 17 β -hydroxysteroid dehydrogenase type 3 deficiency

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Abstract

17 β -hydroxysteroid dehydrogenase type 3 (17 β HSD3) deficiency is an autosomal recessive disorder of male sex development that results in defective testosterone biosynthesis. Although mutations in the cognate *HSD17B3* gene cause a spectrum of phenotypic manifestations, the majority of affected patients are genetic males having female external genitalia. Many cases do not present until puberty, at which time peripheral conversion of androgen precursors causes progressive virilization. Measurement of the testosterone-to-androstenedione ratio is useful to screen for 17 β HSD3 deficiency, and genetic analysis can confirm the diagnosis. As some individuals with 17 β HSD3 deficiency transition from a female sex assignment to identifying as males, providers should ensure stable gender identity prior to recommending irreversible treatments. Gonadectomy is indicated to prevent further virilization if a female gender identity is established. The risk of testicular neoplasia is unknown, a point which should be discussed if patients elect to transition into a male gender role.

Keywords

17 β -hydroxysteroid dehydrogenase type 3 deficiency; testosterone; mutations; virilization; puberty; 46XY disorder of sex development

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1. Introduction

17 β -hydroxysteroid dehydrogenase type 3 (17 β HSD3) deficiency is a rare autosomal recessive sex-limited 46, XY disorder of sex development (DSD) that results in defective conversion of androstenedione to testosterone in the testis. Although 17 β HSD3 deficiency has been reported in patients residing in all six populated continents, the overall prevalence worldwide is unknown and varies widely by geographic location. The Netherlands reports an occurrence of 1 in 147,000 [1], while the highest prevalence is in the Arab population in the Gaza strip with an incidence of 1 in 100-150 [2]. Remarkably, fewer than twenty cases have been reported in the United States to date [3].

As the potent testosterone-derived metabolite dihydrotestosterone (DHT) is essential for the development of normal male genitalia, mutations in the testosterone biosynthetic pathway result in undervirilization of genetic males. Although 17 β HSD3 deficiency can rarely be associated with ambiguous genitalia, most patients have phenotypically female external genitalia and are sex-assigned female at birth. Thus, this disorder often does not become clinically apparent until the time of puberty, when affected patients present with either primary amenorrhea or sudden onset of virilization [4]. This abrupt virilization is thought to be secondary to increased testicular androstenedione synthesis as a result of increased pituitary gonadotropin secretion with subsequent conversion to testosterone and DHT in peripheral tissues via extragonadal 17 β HSD enzymatic activity [1 5 6]. Unless transition to a male gender is desired, gonadectomy is necessary to prevent further virilization [7]. Although histology commonly shows Leydig cell hyperplasia, true testicular neoplasia is exceptionally rare [8]. The purpose of this review is to summarize the pathophysiology, genetics, and clinical features of 17 β HSD3 deficiency, beginning with a previously unpublished case of this rare disorder.

2. Case

A 16-year-old Caucasian girl presented with primary amenorrhea. She had no significant past medical history. Her parents reported normal female external genitalia at birth. She noted the onset of both thelarche and adrenarche at age 12, with the development of hirsutism at age 15. There was no family history of consanguinity or DSD. On physical exam, she measured 179.8 cm in height (>97th percentile), and weighed 86.9 kg (>97th percentile), with a BMI of 26.9 (z-score +1.33). Physical exam was significant for mild facial acne and terminal hair growth on the upper lip and chin. Breasts were Tanner stage V, and genital exam revealed Tanner stage V pubic hair and an enlarged clitoris measuring 4 cm in length.

Laboratory evaluation revealed: estradiol 72 pg/mL (>30 pg/mL), LH 14.9 mU/mL (2-15 mU/mL), FSH 7.4 mU/mL (2.5-22 mU/mL), DHEAS 296 μ g/dL (35-430 μ g/dL), total testosterone 278 ng/dL (11-62 ng/dL), and androstenedione 1060 ng/dL (80-240 ng/dL), resulting in a T/A ratio of 0.2 (normal >0.8) [3]. Additional laboratory evaluation revealed undetectable Mullerian inhibiting substance and inhibin B. Karyotype was 46, XY. Pelvic ultrasound revealed a complete absence of Mullerian structures and bilateral inguinal gonads. Cystoscopy revealed a blind vaginal pouch measuring 3 cm in length. The

differential diagnosis for pubertal virilization in a phenotypic female includes 17 β HSD3 deficiency, androgen insensitivity, and 5- α reductase deficiency. Based on her physical exam and biochemical findings, she was given a clinical diagnosis of 17 β HSD3 deficiency. Molecular genetic testing revealed a heterozygous frameshift mutation in exon 1 of the *HSD17B3* gene (g.5109insC), which introduces a premature stop codon. A second mutation was presumed present but was not identified.

As the patient's gender identity was female, she requested and underwent gonadectomy. Pathology of the left gonad revealed testicular tissue with germ cell neoplasia in situ (GCNIS), with positive OCT4 immunostaining, as seen in Figure 1. Expression of OCT4 is both sensitive and specific for GCNIS. This is the first reported case of GCNIS in an individual with 17 β HSD3 deficiency.

3.1. Pathophysiology

In order to understand the physiologic basis for the undervirilization in patients with 17 β HSD3 deficiency, it is imperative to review the pathways for normal male genital development. Male virilization is dependent on DHT, the potent metabolite of testosterone. DHT is produced via the conventional pathway and the alternate, or backdoor pathway [9 10]. The conventional pathway occurs in the testicular Leydig cell, with the rate-limiting step being the conversion of cholesterol to pregnenolone by the cholesterol side-chain cleavage enzyme (CYP11A1) [9]. Pregnenolone proceeds predominantly through the ⁵ steroid biosynthetic pathway, where 17 α -hydroxylase/17,20 lyase (CYP17A1) first transforms it into 17-hydroxypregnenolone, then to dehydroepiandrosterone (DHEA). DHEA becomes androstenediol via the action of 17 β HSD3, and is then converted into testosterone by 3 β -hydroxysteroid dehydrogenase type II (3 β HSDII). Testosterone is then converted in the target tissues by 5 α -reductase type 2 to DHT, the potent androgen responsible for male virilization. A small proportion of pregnenolone progresses through the ⁴ steroid biosynthetic pathway, where 3 β HSDII transforms it into progesterone, which is then converted by CYP17A1 into 17-hydroxyprogesterone, then androstenedione, where 17 β HSD3 performs the conversion from androstenedione to testosterone. For completeness, the conversion of DHEA to DHT can also occur via the order DHEA to 5-androstenediol to testosterone (via 17 β HSD3) to DHT or DHEA to androstenedione to 5 α -androstenedione to DHT (via 17 β HSD3). Regardless of order, 17 β HSD3 catalyzes one of the key steps to DHT (Figure 2).

The backdoor pathway of androgen synthesis allows for production of DHT without a testosterone intermediary. This pathway was first described in the tammar wallaby, a small marsupial found in Australia [10]. Newly born pouch tammar wallaby males produce DHT from androstenediol, rather than androstenedione or 5 α -androstenedione, alleviating the need for testosterone as a precursor [11]. In humans, it is known that both 5 α -dihydroprogesterone and 17-hydroxy-5 α -dihydroprogesterone undergo 3 α -reduction to alloprenanolone and Pdiol, respectively. Pdiol is then converted into androsterone via CYP17A1, which both 17 β HSD3 and aldo-keto reductase 1C2 (AKR1C2) reduce to androstenediol. Androstenediol is 3 α -oxidized in target tissues to DHT [12]. This pathway

might be responsible for the partial virilization seen in humans with deficiency of 5 α -reductase type 2.

As seen in both the conventional and backdoor pathways, 17 β HSD3 is required for efficient formation of DHT, the androgen responsible for male virilization. In disorders where 17 β HSD3 is deficient or absent, the production of both testosterone and DHT is impaired, which results in insufficient virilization in 46, XY individuals.

3.2. Genetics of 17 β HSD3 deficiency

The *HSD17B3* gene is 60 kb in length, contains 11 exons, and is located on the long arm of chromosome 9, at 9q22, as shown in Figure 3 [4]. Although multiple human 17 β HSD isoforms exist, each encoded from a separate gene, pathologic mutations have thus far only been discovered in the *HSD17B3* gene that encodes for 17 β HSD3 and is expressed exclusively in the testes [13]. To date, over 40 distinct mutations have been described including missense, premature stop codon, polymorphic, and splice junction mutations, as shown in Figure 4 [14–16]. The majority involve exon 9 of the *HSD17B3* gene, and most result in complete eradication of enzymatic activity [4, 17]. One exception is the R80Q mutation found in exon 3, which has been described in kindred from Brazil and Palestine. Rather than disrupting enzyme folding or steroid binding, this mutation significantly decreases the enzyme's affinity for NADPH, which is the necessary cofactor for 17 β HSD3 reduction of 17-ketosteroids to 17 β -hydroxysteroids [18, 19]. The molecular genetic heterogeneity of 17 β HSD3 deficiency was demonstrated in a study of 14 affected individuals from seven families, in whom seven different mutations were found, all but one of which were homozygous [17]. The patient with a presumed heterozygous mutation had only one pathologic allele identified as was the case in our patient. A similar situation has been reported in a clinically affected individual from the Netherlands in whom only one affected allele was found [1]. As 17 β HSD3 deficiency is an autosomal recessive disease, mutations on both alleles are required in order for the condition to be expressed. Because most molecular studies examine only the 1 kb of exons and flanking intronic DNA, the most likely reason for the discrepancy in these patients is that the second mutation resulting in their phenotypic disease expression is a deletion or intronic mutation. In addition to traditional methodologies for the analysis of genomic DNA, the use of newer techniques has also led to the discovery of mutations in *HSD17B3*. A recent study used targeted next-generation sequencing (TNGS) to analyze patients with 46, XY DSD in whom the etiology was unknown and, 30% were found to have mutations in *HSD17B3* [20]. Thus, 17 β HSD3 deficiency might be more common than previously recognized, as is true for 5 α -reductase type 2 deficiency. Broader application of comprehensive genetic testing will likely reveal more cases of 17 β HSD3 deficiency previously dismissed as a mild and nonspecific form of hypospadias or 46, XY DSD.

3.3. Clinical features

As 17 β HSD3 primarily catalyzes the transformation of androstenedione to testosterone or other 17-ketosteroids to androgens in the testis, this disorder is only phenotypically evident in those with 46, XY karyotypes. Although most affected patients have characteristic female external genitalia at birth with a blind vaginal opening, rare cases of ambiguous genitalia

have been reported [1 4 6 18]. Patients typically have hypoplastic Wolffian duct derivatives and absent Mullerian structures, with gonads often found in the inguinal canal or a bifid scrotum if present. A case series of 14 patients with 17 β HSD3 deficiency illustrates the clinical spectrum of genital development. While most subjects had typical female external genitalia, others had ambiguous genitalia with specific findings of clitoromegaly, absent labia minora, a single urogenital opening, and perineoscrotal hypospadias [17].

The most useful initial screening test when considering the diagnosis of 17 β HSD3 deficiency is the testosterone-to-androstenedione ratio (T/A) [4]. An abnormally low T/A <0.8 has 100% sensitivity and 91% specificity for 17 β HSD3 deficiency [21]. This biochemical abnormality is often readily apparent both during the minipuberty of infancy as well as during actual puberty, and baseline measurements of androstenedione and testosterone are likely sufficient. However, in pre-pubertal children suspected to harbor the condition, hCG stimulation testing may be needed to establish the diagnosis due to the quiescence of the HPG axis and normally low testicular testosterone production during this developmental stage [22]. Note that the T/A ratio should only be applied in the clinical context of a 46, XY child with virilization at puberty, because a low T/A also occurs in the virilizing forms of congenital adrenal hyperplasia and other forms of adrenal androgen excess.

Many patients do not present until the onset of puberty, at which time increased gonadotropin stimulation of the testes results in amplified androstenedione production. Androgen precursors are likely converted to testosterone in the peripheral tissues, resulting in progressive virilization [6], which manifests as deepening of the voice, enlargement of the phallic structure, increased musculature, male pattern hair growth, and increased muscle mass [21]. Because aromatase can also convert the increased androstenedione into estrogens, female appearing breast development is also common [17].

The differential diagnosis for a phenotypically female girl with clinical evidence of significant hyperandrogenism includes a virilizing adrenal or ovarian tumor, partial androgen insensitivity syndrome (PAIS), 5 α -reductase type 2 deficiency, and 17 β HSD3 deficiency (Table 1). The virilizing tumors can occur in 46, XX females, whereas the other three diagnoses are limited to 46, XY individuals. A key distinguishing feature is breast development, which occurs in PAIS and 17 β HSD3 deficiency but not in 5 α -reductase type 2 deficiency. In PAIS, the T/A is normal, whereas T/A is low in 17 β HSD3 deficiency. Without proper biochemical and genetic testing, however, these disorders are very difficult to distinguish clinically at first presentation.

In some cultures, the onset of masculinization at puberty results in a transition from female to male gender identity in a subset of affected individuals [23 24]. Although data are limited, one retrospective study reported the percentage of patients who change from a female to male gender role at puberty to be between 39-64% [25]. Gender identity change is unpredictable even within kindreds, with some individuals maintaining a female gender identity and others converting to male gender identity at puberty [8]. Geographical location and cultural influences also affect gender identity and expression. Among the Arab population in the Gaza Strip, the diagnosis is frequently made at birth resulting in early

orchiopexy, genitoplasty and testosterone treatment in anticipation of a male gender identity in these patients [26]. The female-to-male gender reversal at puberty is also a common feature of 5 α -reductase type 2 deficiency, which like 17 β HSD3 deficiency involves one of the last two steps in DHT synthesis.

Gonadectomy is necessary in individuals who maintain female gender identity in order to prevent further virilization [7]. Today, gonadectomy is typically an outpatient procedure performed under local or regional anesthesia, with a recovery time of 2-3 weeks. Several case reports describe the immediate use of a gonadotropin-releasing hormone agonist to arrest puberty at the onset of male-typical secondary sexual development. This maneuver prevents further virilization and allow the patient and family some time for counseling and careful consideration about gender identity and trajectory, to assist in optimal decision-making before irreversible procedures are employed. Testicular histology from patients with 17 β HSD3 deficiency who have undergone orchiectomy commonly shows Leydig cell hyperplasia, which progresses with age, thought to be secondary to LH stimulation [8 27]. Sertoli cell histology is more variable as the cells can be either mature or immature, and either abundant or reduced in number. In pubertal patients, spermatogonia count is typically low or absent, reflecting poor intratesticular testosterone synthesis. There has been one previously reported case of 17 β HSD3 deficiency with suspected germ cell neoplasia in situ, where histological evaluation of the seminiferous tubules revealed atypical spermatogonia with likely calcifications; however, OCT3/4 immunohistochemical confirmation was not performed [28]. There are no cases of fertility yet described in patients with 17 β HSD3 deficiency; however, the potential for viable sperm in patients with mild forms of the disease cannot be excluded.

Although Leydig cell hyperplasia is common and expected, to our knowledge the patient reported here is the first known case of GCNIS with positive OCT4 immunostaining in a patient with 17 β HSD3 deficiency, expanding the pathologic spectrum in this rare disorder. Intratesticular neoplasia results from abnormal gonadocyte precursor cells that fail to differentiate completely into mature gonadal tissue. These cells remain dormant until the onset of puberty but continue to express proteins consistent with primitive germ cells, including c-KIT and OCT4 [29]. Collectively, these immature gonadocytes develop into malignant germ cells in the seminiferous tubules and over time may develop the capability to differentiate into a mature germ cell tumor and invade through the gonadal stroma. Risk factors for developing testicular germ cell tumors include a positive family history, DSD, cryptorchidism, and abnormally high maternal estrogen during fetal development [29].

There is only one report in the literature of a testicular interstitial (Leydig) cell tumor in a patient with 17 β HSD3 deficiency. This patient was 61 years old at presentation, and pathology of the testicular lesions revealed a malignant interstitial cell carcinoma with widespread metastasis. The patient was treated with surgery and chemotherapy, but due to the extent of disease burden, died one year after presentation [30]. The consensus statement for management of DSD estimates the risk of any germ cell malignancy in 17 β HSD3 deficiency at 28% and places it in the intermediate risk category. However, this recommendation is limited by the paucity of patients reported with this diagnosis [31]. As there are only seven reported cases of germ cell malignancies associated with 17 β HSD3

deficiency, the optimal approach to surveillance in patients who have not undergone gonadectomy has not yet been established.

4. Conclusion

17 β HSD3 deficiency is one of a few DSDs that manifest only in 46, XY individuals. As the testis is the exclusive site for both enzyme production and function, a deficiency of 17 β HSD3 results in undervirilization of genetic males. Genomic DNA extraction and amplification through PCR techniques, as well as TNGS are available for confirmative diagnostic testing, and the T/A, measured either at baseline during infancy and puberty, or after hCG stimulation in pre-pubertal patients, is a conventional diagnostic test with limitations. Interestingly, phenotypic expression of the disease varies even in individuals within the same pedigree with identical mutations, which results in some patients being more severely undervirilized than others [17]. One possible reason for this discrepancy is that some individuals may have higher levels of enzymatic conversion of androstenedione to testosterone in peripheral tissues, possibly secondary to the backdoor pathway and/or alternative 17 β HSD isoenzymes. However, this hypothesis requires further studies to be confirmed.

Patients who do not present until puberty present a unique clinical and therapeutic challenge, as a sizeable proportion of individuals with 17 β HSD3 deficiency have been reported to transition from female to male gender identity. After confirming the diagnosis, it is the provider's responsibility to ensure that gender identity is firmly established prior to initiating irreversible hormonal or surgical interventions. In those with a confirmed female gender identity, it is important to ensure that gonadectomy is performed in a timely manner to prevent further virilization. Ours is the first reported case of GCNIS in a patient with 17 β HSD3 deficiency, which highlights the fact that the overall risk of gonadal neoplasia in patients with 17 β HSD3 deficiency is currently unknown, and that germ cell abnormalities can be present as early as the second decade of life. This risk of malignancy is paramount to consider, particularly in patients who elect to retain their testicular tissue and transition into a male gender role. Large-scale studies are needed to develop specific screening recommendations aimed at the identification and treatment of potential testicular malignancies in this specialized group of patients. Although rare, 17 β HSD3 deficiency remains an important diagnosis to consider in patients with 46, XY DSD, and one that affords unique and fascinating insights into reproductive physiology and the socialization of gender. Taken together, clinical findings and genetic analysis can provide a diagnosis in the majority of those affected, and both individual patient characteristics and gender identity should guide short and long-term treatment goals.

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Abbreviations

3βHSDII	3 β -hydroxysteroid dehydrogenase type II
AKR1C2	aldo-keto reductase1C2
BMI	body mass index
CYP11A1	cholesterol side-chain cleavage enzyme
CYP17A1	17 α -hydroxylase/17,20 lyase
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
DSD	disorder of sex development
FSH	follicle stimulating hormone
GCNIS	germ cell neoplasia in situ
H&E	hemotoxylin and eosin
hCG	human chorionic gonadotropin
HPG axis	hypothalamic-pituitary-gonadal axis
17βHSD3	17-beta hydroxysteroid dehydrogenase 3
IHC	immunohistochemical
LH	luteinizing hormone
OCT4	octamer-binding transcription factor 4
StAR	steroidogenic acute regulatory protein
T/A	testosterone-to-androstenedione ratio
TNGS	targeted next-generation sequencing

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Highlights

- * The etiologies of 46,XY DSD with masculinization at puberty is limited
- * A T/A ratio <0.8 is a sensitive screening test for 17 β HSD3 deficiency
- * Gender reversal at puberty occurs commonly in 17 β HSD3 deficiency
- * We present the first case of 17 β HSD3 deficiency with germ cell neoplasia in situ

Figure 1.
GCNIS in a patient with 17 β HSD3 deficiency.
Panel A shows GCNIS via H&E staining of left testicular tissue.
Panel B shows IHC staining with positive C-kit/CD117 (OCT4) of left testicular tissue.

Figure 2. Pathways to DHT and activities of 17 β HSD3. Conventional pathways are to the left, and backdoor pathway to the right. Dotted arrow indicating poor activity for the formation of androstenedione, and “ $\pm$ ” indicates that effect of cofactor is modest. The 5α , 4α , 5α , and 5α , 3α -pathways are indicated with boxed symbols. Abbreviations are as in text, plus 17OH-, 17-hydroxy; 5α R1, 5α -reductase type 1, 5α R2, 5α -reductase type 2; Cyt b_5 , cytochrome b_5 ; 17 β HSD6, 17 β -hydroxysteroid dehydrogenase type 6. AKR1Cs indicates that the AKR1C isoenzymes that perform this reaction are not known with certainty.

Figure 3.
Location of the *HSD17B3* gene on chromosome 9, and sites of known mutations.

Figure 4.

Documented mutations in HSD17B3 gene in patients with 17 β HSD3 deficiency. Recurrent mutations are represented in framed boxes. Adapted from Castro et al [32].

Table 1.

Differential diagnosis of female-to-male contrasexual pubertal development

Diagnosis	Karyotype	Gynecomastia	T/A
Virilizing tumor	46, XX	Variable	Normal
Partial Androgen Insensitivity	46, XY	Present	Normal
5 α -Reductase Type 2 Deficiency	46, XY	Absent	Normal
17 β HSD3 Deficiency	46, XY	Present	Low