CASE REPORT

46,XY disorder of sex development due to 17-beta hydroxysteroid dehydrogenase type 3 deficiency: a plea for timely genetic testing

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Abstract
Background: 17β-hydroxysteroid dehydrogenase type 3 (17βHSD3) deficiency is a rare cause of disorder of sex development (DSD) due to impaired conversion of androstenedione to testosterone. Traditionally, the diagnosis was determined by βHCG-stimulated ratios of testosterone:androstenedione < 0.8.
Case presentation: An otherwise phenotypically female infant presented with bilateral inguinal masses and a 46,XY karyotype. βHCG stimulation (1500 IU IM for 2 days) suggested 17βHSD3 deficiency although androstenedione was only minimally stimulated (4.5 nmol/L to 5.4 nmol/L). Expedient genetic testing for the HSD17B3 gene provided the unequivocal diagnosis.
Conclusion: We advocate for urgent genetic testing in rare causes of DSD as indeterminate hormone results can delay diagnosis and prolong intervention.
Keywords: 17β-hydroxysteroid dehydrogenase type 3 deficiency, Disorders of sex development, 46,XY undervirilization

Background
Disorders of sex development (DSD) occur when there is discordance among chromosomal, hormonal, and phenotypic sex. They require prompt and timely diagnosis because certain etiologies can result in acute medical decompensation. Even in the absence of a medical emergency, ambiguous genitalia can present a social emergency to the parents when ascribing a sex to their newborn child. This can be further magnified if parents have already become accustomed to the child being a certain sex. The evaluation for the etiology of a DSD involves measurements of hormones with genetic testing historically reserved for confirmatory purposes. Hormonal assessments can direct genetic testing, but results may not be straightforward and can be influenced by a multitude of physiologic and practical factors. We present a case of a rare cause of 46,XY DSD where timely genetic testing resulted in a rapid diagnosis. The unequivocal result of genetic testing facilitated a more confident execution of a management and therapeutic plan.

Case presentation
A healthy 1-month-old female was referred to Pediatric Endocrinology for bilateral inguinal masses. She was the product of a non-consanguineous conception between parents of English and English/German descent. Physical examination revealed a healthy child with female external genitalia. She had prominence of the labial folds with palpable masses in the inguinal canals. There was a urogenital opening without clitoromegaly. Pelvic ultrasound demonstrated inguinal gonads and absence of uterus and ovaries.

Due to the presence of inguinal gonads but absence of Müllerian structures, investigations were pursued for causes of undervirilization. Cytogenetic analysis confirmed a normal 46,XY complement. Baseline Luteinizing Hormone,

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Follicle Stimulating Hormone, and cortisol concentrations measured at 6 weeks of age were 1.5 U/L, 1.6 U/L, and 621 nmol/L, respectively. Anti-Mullerian Hormone levels were appropriate for an infant male, implying the presence of functioning Sertoli cells. At 6 weeks of age, baseline androstenedione level was 4.5 nmol/L and testosterone 1.1 nmol/L. These levels in themselves were elevated, and the baseline testosterone:androstenedione (T:A) ratio of 0.2 hinted at the etiology of 17β-hydroxysteroid dehydrogenase type 3 (17ßHSD3) deficiency. However, even during the mini-puberty of infancy, hormonal values of various causes of 46,XY undervirilization can significantly overlap. The patient subsequently underwent a short βHCG stimulation test 1500 IU daily for 2 days (Table 1). The diagnosis of 17β-hydroxysteroid dehydrogenase type 3 (17ßHSD3) deficiency was further suspected based on the low stimulated T:A (testosterone 2.1 nmol/L, androstenedione 5.4 nmol/L, T:A 0.4). These results directed genetic testing for 17ßHSD3 deficiency. At the same time, the minimally increased value of the stimulated androstenedione level compared to the baseline (5.4 and 4.5 nmol/L, respectively) called into question the adequacy of the stimulation testing. Other causes of 46,XY undervirilization, such as 5-alpha reductase deficiency, remained possible. Additionally, approval for genetic testing was not a given. Taking into consideration the parents’ desire to cement a diagnosis, a prolonged βHCG stimulation test (1500 IU twice weekly for 2 weeks) was undertaken when the baby was 18 weeks old (Table 1).

The evaluation and management of an infant born with a DSD should be conducted in interdisciplinary teams with experience in caring for these very rare conditions, including endocrinology, genetics, urology, social work, and clinical chemistry. At the same time, the particulars of the local socio-political and geographic environment dictate the distribution of medical resources and, in our case, the availability of genetic testing. While the prolonged βHCG stimulation test was transpiring, our multidisciplinary clinical team pursued genetic testing for 17ßHSD3 deficiency as the most likely diagnosis on the basis of the clinical evaluation and initial low T:A. This effort involved actively petitioning for government funding to cover genetic testing as per routine in our medical jurisdiction when genetic testing is performed in a lab outside the province. We could not be assured funding for genetic testing and pursued prolonged βHCG testing during the limited time frame of neonatal puberty. The prolonged βHCG stimulation testing proved overwhelming for the family due to the multiple injections, cost of βHCG, and the practicalities of their having to travel back and forth from their remotely located home to the laboratory. In addition, the parents were committed to raising the baby as a girl and experienced considerable anxiety over the presence of testes and the delays in diagnosis.

DNA sequencing analysis for the HSDB173 gene was conducted in a commercially available, FDA accredited laboratory (Prevention Genetics, Marshfield, WI, USA) by Sanger sequencing of the full coding regions of exons 1-11, as well as ~20 basepairs of flanking non-coding DNA on either side of each exon. This revealed a homozygous mutation, previously reported as pathogenic with complete loss of enzymatic activity (c.389 A > G) [1]. Genetic analysis of the parents revealed that both were heterozygous for the same mutation in the HSD17B3 gene. Array CGH analysis was completed using the CytoSure TM ISCA 8x60K V2.0 Oligonucleotide array (Oxford Gene Technology) and showed normal dosage across the genome.

The genetic analysis was reported before the prolonged βHCG protocol was completed. Once funding was approved, the prolonged testing was discontinued. The cost of genetic testing was comparable to prolonged βHCG stimulation testing. With the genetic diagnosis, our team was able to provide focused, anticipatory guidance and allay many of the parents’ anxieties.

**Discussion**

46,XY disorders of sex development (DSD) are uncommon and may stem from disorders of androgen synthesis in the adrenal glands or testes or disturbances in androgen action [2]. Making a timely diagnosis is important to prevent medical crises due to associated hormonal

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### Table 1 Hormone Levels and Ratios with βHCG Stimulation (SI units)

|                  | Short βHCG protocol<sup>a</sup> | Prolonged βHCG Protocol<sup>b</sup> |                  |                  |                  | Reference Ranges |
|------------------|---------------------------------|-----------------------------------|------------------|------------------|------------------|------------------|
|                  | Baseline | Stimulated | Baseline | Stimulated |                  |                  |
| Androstenedione (A) | 4.5 5.4 | 1.7 20.5 | < 3.0 nmol/L |
| Testosterone (T)   | 1.1 2.1 | < 0.2 | 10.9 | < 14 nmol/L |
| Dihydrotestosterone (DHT) | 227.7 559 | N/A | N/A | 414–2933 pmol/L |
| T:A               | 0.2 0.4 | 0.5 | > 0.8 |
| T:DHT             | 4.8 3.7 | N/A | N/A | > 10 |

<sup>a</sup>1500 Units βHCG daily for two consecutive days at age 6 weeks. Stimulated levels were measured 24 h following the second injection.

<sup>b</sup>1500 Units βHCG every other day (2 times per week) for 2 weeks at age 18 weeks. Stimulated levels were measured 24 h following the 3rd injection.

The Prolonged βHCG Protocol was discontinued when the genetic result became available. The protocols were adapted from [12].
Deficiencies. Identifying the etiology is also helpful in assigning a sex of rearing, predicting response to hormonal therapy in infancy, counselling about expected challenges at puberty, and guiding decisions regarding gonadectomy. However, a lack of diagnosis can occur in up to 50 % of cases with sexual ambiguity and a male karyotype [3].

Deficiency of 17βHSD3 is a rare cause of XY undervirilization affecting 1 in 147 000 live births [4]. This may be an underestimate as patients with 17βHSD3 deficiency can be incorrectly diagnosed with androgen insensitivity syndrome (AIS) [5]. The 17βHSD3 enzyme is present mainly in testicular tissue and converts the relatively weak androgen, androstenedione, to its potent metabolite, testosterone. There are at least 12 isoforms of 17βHSD present in organs including the liver, brain, and skin [6, 7]. Impairment of testosterone synthesis during fetal development results in undervirilization of male external genitalia. Although testosterone synthesis is insufficient, Anti-Müllerian Hormone production remains intact, leading to absence of internal Müllerian structures. The phenotypic spectrum ranges from normal-appearing female external genitalia to microphallus with hypospadias and variable degrees of genital ambiguity in between [7].

Assessment of basal hormone levels is typically the first step in diagnosis. Baseline androstenedione, testosterone, and dihydrotestosterone (DHT) levels and their ratios may help discriminate between 17βHSD3 deficiency and other causes of 46,XY DSD [4, 8]. However, considerable overlap in hormone levels has been shown [4, 5, 8, 9]. A T:A less than 0.8 was originally thought to be diagnostic of 17βHSD3 deficiency [4, 5]. This ratio only applies if there is an observed stimulation of androstenedione because low T:A can be seen in other defects in testosterone synthesis, including Leydig cell hypoplasia and testicular dysgenesis. In our case, while the baseline and stimulated levels and ratios suggested the possibility of 17βHSD3 deficiency, the baseline and stimulated levels did not differ significantly from one another; the T:A ratio of less than 0.8 could not by itself be used to diagnose 17βHSD3 deficiency. Unfortunately, there is no consensus as to the minimum threshold of androstenedione that reflects adequate βHCG stimulation. Variations in assays may, in part, underlie the overlap observed among hormone results.

Beta-HCG stimulation testing does not definitively diagnose 17βHSD3 deficiency nor distinguish it from other causes of 46,XY DSD. In patients with genetically-proven HSD17B3 mutations, βHCG stimulation does not consistently stimulate androstenedione levels, making it challenging to interpret a T:A ratio [9, 10]. Other studies have demonstrated that the T:A ratio can be > 0.8 before and after βHCG stimulation in proven cases of 17βHSD3 deficiency; solely relying on T:A < 0.8 as a diagnostic criterion would have ruled out the diagnosis [4, 9, 10]. One report describes three related patients with stimulated T:A ratios of 0.5, 1.5 and 3.4, even though they shared the same HSD17B3 mutation (homozygous S232L) [10]. In another study, a stimulated T:A ratio of < 0.8 falsely suggested 17βHSD3 deficiency in 4–6 % of patients with a confirmed diagnosis of complete or partial androgen insensitivity based on androgen binding studies and mutational analysis, and over half of the cases of testicular dysgenesis had a low T:A ratio [5, 11]. These studies provide evidence that the stimulated T:A ratio is not reliably diagnostic of 17βHSD3 deficiency. With our case, we pursued genetic testing for 17βHSD3 deficiency to reach an unequivocal diagnosis, given that neither baseline nor stimulated T:A ratios are absolutely reliable.

Failure of hormone testing to elucidate clearly the cause of XY undervirilization may relate to the variability and lack of consensus among βHCG stimulation protocols. The protocols differ in dose and duration, ranging from 500 to 1500 units per day and as long as 2 days to one month [4, 8, 12–15]. Evidently there is no clear consensus on duration or dose of βHCG, with most studies recommending an initial short course of βHCG followed by prolonged βHCG stimulation if there is an inadequate rise in precursors such as androstenedione or testosterone [12]. Our patient’s baseline precursors did not increase much following the short βHCG stimulation protocol. As a result, our patient underwent a prolonged stimulation protocol, and the androstenedione demonstrated a more convincing rise from 1.7 to 20.5 nmol/L with the T:A ratio remaining < 0.8.

The parental perspective and experience during investigations are essential considerations. In our case, the parents were committed to raising their 1-month-old infant as a girl, and they experienced significant emotional distress over the uncertainty of a diagnosis of 17βHSD3 deficiency. We debated the timing of gonadectomy as a previous literature review demonstrated that early orchiectomy resulted in 100 % retention of the female gender role while 54 % of patients changed to the male gender role if orchiectomy was delayed [16]. Delaying gonadectomy until puberty would provide the opportunity to observe whether the child was predisposed to a male gender identity but may also theoretically contribute to gender dysphoria [16]. However, these outcome data are limited and based on a small sample of patients. A review of published studies found that 39–64 % of female-assigned patients with 17βHSD3 deficiency underwent gender role changes [16, 17]. It is also important to decide on gonadectomy before puberty to prevent unintended virilization. This is highlighted in case reports where phenotypic females were diagnosed with 17βHSD3 deficiency at puberty after developing significant virilization. It is hypothesized that androstenedione is converted to testosterone by extra-testicular 17βHSD isoforms at puberty, and removal of the testes reduces the main source of
androstenedione [18, 19]. Furthermore, there is a risk of
gonadoblastoma, quoted as high as 28 % in some studies,
and this risk should be factored into decisions on gonad-
ectomy [7, 20]. The decision about sex of rearing should
be made in light of the best possible prediction of future
sexual function, virilization, and satisfaction with gender
identity. These predictions are often only a best guess,
further blurred if the etiology is in question.

Historically, genetic testing for rare causes of DSDs has
been reserved for confirmatory purposes, guided by the
results of hormonal testing. In our case, we had enough
suspicion following the short-course βHCG stimulation
testing to rationalize the request for genetic testing for
17βHSD3 deficiency as the most likely diagnosis. In the
mean time, prolonged βHCG stimulation was initiated
with the hopes of clarifying the diagnosis and in case gen-
etic testing was denied, βHCG was not covered by insurance
for the baby’s specific indication, and the parents
were required to pay out-of-pocket for two vials. It re-
quired 3 extra medical appointments to receive the injec-
tions and 2 laboratory visits to draw the blood work.
The cost of genetic testing was $780 USD (Prevention Genet-
ics, Marshfield WI, USA). We advocate that this cost is
acceptable and that earlier genetic testing could mitigate
against the financial and human costs associated with sole
reliance on equivocal, hormone-based investigations.

Genetic and molecular knowledge, research, and
innovation are rapidly changing the way we investigate,
diagnose, and treat medical conditions. Recent advance-
ments in genetic testing have allowed for more cost-
effective methods using gene panels to test for genetically
heterogeneous Mendelian conditions [21]. Single-gene test-
ing is preferred if, following clinical and laboratory evalua-
tions, a specific diagnosis is likely, as demonstrated by our
case. However, in many centres, including ours, genetic
testing and confirmation are not readily accessible due to
lack of testing facilities and/or prohibitive costs. These
issues can also cause undue delay. Therefore, although the
utility of genetic testing is well-appreciated, clinical use of
these tests in an expedient manner is not yet optimally
implemented. The intended ears for our plea belong not
only to we who care for patients with DSD, but also to
policy-makers, researchers, governments, and funding
agencies, so that we may work together to improve access
to these technologies.

Conclusion
Sex assignment in an infant with a 46,XY disorder of sex
development can be a social emergency because it
requires urgent decision-making about the sex of rearing
and considerations of potential fertility, the role of
gonadectomy, and future gender identity. We contend
that such decisions should not be made without a con-
certed effort to confirm the diagnosis. Many publications
recommend βHCG stimulation to aid in the diagnosis,
but βHCG-stimulated hormone results can be unreliable
with overlap across diagnoses. The appropriate protocol
for βHCG stimulation remains uncertain. It seems rea-
tonable to try a short βHCG stimulation test to direct
confirmatory genetic testing. With recent advancements
in the field of clinical and molecular genetics, we advo-
cate for a more prominent role for, and more expedient
access to, urgent genetic testing to enable early and
accurate diagnosis of rare DSDs.

Consent
Written informed consent was obtained from the pat-
tient’s parents for publication of this case report. A copy
of the written consent is available for review by the
Editor-in-Chief of this journal.

Abbreviations
17βHSD3: 17β-hydroxysteroid dehydrogenase type 3; A: androstenedione;
DHT: dihydrotestosterone; DSD: disorders of sex development;
T: testosterone; βHCG: beta human chorionic gonadotropin.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
Authors CG, MJ, and ER conceived of the case report design and outlined
the manuscript’s content. CG conducted much of the background research,
while all reviewed the references for relevance and accuracy. CG drafted
the initial manuscript. OC and PM wrote sections particular to their areas of
expertise, i.e. genetics and urology, respectively. All authors read and
approved the final manuscript.

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