JCEM Case Reports, 2024, **2**, 1–3
https://doi.org/10.1210/jcemcr/luad159
Advance access publication 22 December 2023
Case Report

Gender Dysphoria in a Patient With Ovotesticular Disorder of Sex Development

Telma Moreno,[1,2] Sara Ribeiro,[1,2] and Pedro Rodrigues[1]

[1]Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário de São João, 4200-319 Porto, Portugal
[2]Faculty of Medicine, Universidade do Porto, 4200-319 Porto, Portugal

Correspondence: Telma Moreno, MD, Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário de São João, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. Email: u015840@chsj.min-saude.pt.

Abstract

Ovotesticular disorder of sex development (OT-DSD) is a rare condition characterized by the presence of both ovarian and testicular tissue in the gonads. Management and sex designation of these patients depend on several factors, and an underlying potential for gender dysphoria should be acknowledged. We present a case of a patient diagnosed with 46,XX OT-DSD at 12 months old who was attributed a female sex designation but started manifesting gender dysphoria during adolescence. Gender identity is an important factor to consider on long-term follow-up of OT-DSD patients.

Key Words: gender dysphoria, disorder of sex development, ovotestis, hormonal replacement therapy

Abbreviations: DSD, disorder of sex development; OT-DSD, ovotesticular disorder of sex development.

Introduction

Disorders of sex development are "congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical" [1]. Ovotesticular disorder of sex development (OT-DSD) is a rare condition characterized by the presence of both ovarian and testicular tissue in the same or the contralateral gonad and is more frequently associated with a 46,XX karyotype. Upregulation of genes involved in activation of testicular pathways or loss of function of genes responsible for repressing testicular development constitute the molecular basis for disorders of gonadal ovarian development. Clinical presentation may vary but atypical genitalia is a common feature in the majority of patients [2]. A normal puberty onset may occur if gonadal-sparing surgery is performed but hormonal replacement therapy may be required for full pubertal development and during adulthood [3].

Optimal management of patients with OT-DSD should involve multidisciplinary teams, including endocrinology, surgery, and mental health care. Being rare, data on long-term outcomes of patients presenting with OT-DSD is scarce and sex designation ruling depends on factors such as age at diagnosis, phenotype of the external genitalia, internal structures, and fertility potential. Gender identity should be an important factor to consider during follow-up, although the prevalence of gender dysphoria in this population remains unknown [2, 4].

We present a case of a patient with OT-DSD who was attributed a female sex designation at birth and later reported gender dysphoria and identified as male.

Case Presentation

A 12-month-old patient from Guinea-Bissau was referred to pediatric surgery for management of ambiguous genitalia. Parents were consanguineous (second cousins) and the gestational and perinatal periods were uneventful. Karyotype was 46,XX with a negative fluorescence in situ hybridization for sex-determining region Y (*SRY*). A pelvic magnetic resonance imaging scan showed penile hypoplasia, absence of an uterus, and suggested cryptorchidism at the right inguinal tract. Genitoscopy showed absence of a vagina and a cystoscopy revealed a male-phenotype urethra with a prostatic utricle. Serum 17-hydroxyprogesterone was 1.51 nmol/L (0.50 ng/mL) (<3.00 nmol/L; <1.00 ng/mL), ruling out congenital adrenal hyperplasia. A hormonal profile revealed a serum estradiol <18.4 pmol/L (<5.0 pg/mL) (<18.4-80.5 pmol/L; <5.0-21.9 pg/mL), elevated total testosterone for the female reference range (1.35 nmol/L, 0.39 ng/mL; <0.09-0.20 nmol/L, <0.03-0.06 ng/mL), FSH 0.93 IU/L (0.72-5.49 IU/L), and LH <0.10 IU/L (<0.10-0.10 IU/L). Anti-Müllerian hormone levels were not assessed at this point. Suspicion for the presence of testicular tissue in a 46,XX individual led to an exploratory laparotomy, and biopsy of the gonads was performed. Pathology report revealed ovarian tissue along with an associated fallopian tube in the left gonad and confirmed the presence of ovotestis in the right gonad, establishing the diagnosis of OT-DSD.

Treatment

Because of the absence of a clear male external genitalia appearance, the patient had been raised as female from birth. According to karyotype and in agreement with parental preference, a decision was made to perform bilateral gonadectomy and clitoroplasty at age 12 months. The child went back to Guinea-Bissau and returned to Portugal at the age of

Received: 17 July 2023. **Editorial Decision:** 27 November 2023. **Corrected and Typeset:** 22 December 2023

8 years old, initiating an endocrinology follow-up. Physical examination revealed weight of 48.6 kg (>P97), height 135.5 cm (P90-97), Tanner stage I, and a blind vagina with normal clitoris size. Blood tests showed elevated FSH 12.53 mUI/mL (0.39-6.59 mUI/mL), within reference range LH 1.07 mUI/mL (<0.10-1.19 mUI/mL) and low levels of estradiol 21.3 pmol/L (5.8 pg/mL) (<18.4-167.0 pmol/L; <5.0-45.5 pg/mL), and total testosterone 0.14 nmol/L (0.04 ng/mL) (<0.09-0.88 nmol/L; <0.03-0.25 ng/mL). Anti-Müllerian hormone levels were undetectable (0.07 pmol/L, 0.01 ng/mL; 4.43-55.71 pmol/L, 0.62-7.8 ng/mL).

Outcome and Follow-up

Given the history of bilateral gonadectomy, spontaneous puberty onset was not expected. Transdermal estradiol was initiated at age 15 years, somewhat later than the recommended age of 11 to 12 years for initiation of sex steroid replacement. Regarding surgical procedures, the patient was submitted to a vaginoplasty at age 13 years.

Seven months after estradiol initiation, the patient chose to interrupt treatment and was referred for psychiatric evaluation, where a diagnosis of gender dysphoria was established. Intramuscular testosterone enanthate 250 mg at 4-week intervals was initiated at age 18 years but was stopped after a 6-month trial because the patient identifies as male but is not interested in seeking gender-affirming hormone therapy at the present time. A bone density scan revealed a normal hip and lumbar spine Z-score for the female reference range.

Discussion

OT-DSD is an uncommon condition, more prevalent in children from the sub-Saharan Africa, with the majority of cases presenting as 46,XX OT-DSD [5], as was the case of our patient. Being a rare condition, relevant data to guide clinical management, including how to best decide gender of rearing, is lacking. A multidisciplinary team evaluation, along with parental counseling and consent, is advisable in a scenario in which either male or female sex designation may be suitable. Most studies report a predominant male sex assignment, which could be in part explained by sociocultural factors [3, 6]. Furthermore, the presence of significant external virilization and poorly formed internal Müllerian structures may argue in favor of a male sex designation. In this particular case, the decision of sex designation was mostly made in regard to genotype in a way that, being a 46,XX individual, a female sex was attributed. That the patient later reported gender dysphoria highlights the importance of keeping several factors in mind that might influence the decision of sex designation and should not be guided solely by karyotype.

Karyotype is essential for initial classification of disorders of sex development (DSD) in 3 main groups: sex chromosome DSD, 46,XY DSD, and 46,XX DSD. Further genetic testing may be undertaken as knowledge of the underlying genes involved in DSD expands. Expression of "pro-testis" genes such as *SOX9* and *NR5A1* or down-regulation of pro-ovarian genes (*RSPO1*, *WNT4*, and *NR2F2*) have been implicated in 46,XX OT-DSD. Translocations involving *SRY*, the main trigger for testicular differentiation, may also be found; in our patient, this was excluded through fluorescence in situ hybridization. Sequencing of gene panels relevant to DSD can be applied to help identify the causative gene [2, 3]. Interpretation of positive findings can be challenging and a clinical geneticist may be valuable, once again underlining the importance of multidisciplinary teams.

Gonadal function varies, partly depending on gonadal surgery decision. In patients submitted to gonadal-sparing surgery, endocrine function and a normal onset of puberty may be possible, although some will require hormonal replacement therapy to complete pubertal development and during adulthood [7]. Progressive gonadal failure is common, particularly affecting the testicular component, which becomes dysgenetic/fibrotic over time with the need for testosterone replacement therapy. On the other hand, ovarian tissue can remain functional, leading to spontaneous ovulatory cycles during puberty in a significant proportion of cases [2–4]. Our patient underwent bilateral gonadectomy at age 12 months and required hormonal replacement therapy for pubertal development. The patient reported distress at the physical changes caused by estrogen, and gender dysphoria was diagnosed. Regarding the genital surgeries performed, the patient does not currently express dissatisfaction with genitalia appearance and is not considering undergoing additional surgical procedures. Nevertheless, current guidelines recommend that surgeries that are "cosmetic rather than vital for health" should be deferred until adolescence/early adulthood, when patients' preferences can inform decision-making and they are psychologically motivated in the procedure [1]. We believe this could have been the best course of action for our patient vs the decision to perform clitoroplasty and vaginoplasty at such young ages. We assume that psychosocial and/or cultural factors may have played a part on the anticipation of these surgeries.

Another important matter in patients with DSD is the risk of germ cell tumors that depends on underlying diagnosis, localization of the gonads, and patient age; presence of Y chromosome material, dysgenetic gonads, and intra-abdominal location increase the risk of such tumors. In 46,XX OT-DSD, the risk was reported to be very low with rates of 2% to 4% as the Y chromosome, which contains the gonadoblastoma locus, is lacking and the testicular tissue is usually well differentiated [2, 3]. However, a recent study including 15 46,XX OT-DSD *SRY*-negative patients raises concern whether such patients should be considered at low risk for germ cell tumors [8]. Histological evaluation of the gonads at the time of diagnosis could be informative on the presence of precursor lesions of malignancy, but no specific surveillance recommendations exist. At best, screening could be adapted from other DSD conditions in which regular self-examination and annual ultrasonography from puberty onward is advised [2, 3]. Accordingly, in our patient, it is not clear if gonadectomy could have been safely deferred. On 1 hand, the patient returned to Guinea-Bissau during childhood and surveillance for gonadal tumor risk would have been difficult. On the other hand, even if gonadectomy was performed, removing only the ovotestis while keeping the left gonad intact might have been a more appropriate choice. A third option would be to perform (partial) gonadectomy before onset of puberty at a time when the patient could participate in the decision or, if gender identity was uncertain, temporary use of GnRH analogues could have been considered [2].

Gender dysphoria relates to the "distress and unease experienced if gender identity and designated gender are not completely congruent" [9]. Gender identity is likely dependent on the interaction of several biological, environmental, and sociocultural factors. Studies in patients with DSD suggest a higher prevalence of gender dysphoria, pointing to a possible

effect of pre- and neonatal androgen brain exposure in gender development and behavior [3, 4, 9]. In line with these observations, we can hypothesize that the presence of testicular tissue led to prenatal exposure to high testosterone levels, as seen by the degree of internal and external genitalia androgenization, which may have contributed to brain masculinization that played a role in the patient's psychosexual development.

Gender dysphoria rates in patients with OT-DSD are unknown. Small sample studies show that patients with gender dysphoria more often are those who were assigned a female sex at infancy [3, 7, 10]. A South African study analyzing 64 patients with OT-DSD, with two-thirds assigned as males, reported gender dysphoria in 8 patients who were all first assigned female; 5 of these underwent gender reassignment [10]. In a small Brazilian cohort of 20 patients, similarly with two-thirds of the patients assigned male at birth, 3 of the 7 females were reassigned to the male gender [7]. Another study investigating pubertal outcomes of 23 patients with OT-DSD in South Korea, in which the majority of patients were initially assigned as male, reported 1 case of gender dysphoria [4]. Our case report is in accordance with these results. Nevertheless, such small cohorts are prohibitive from drawing clear conclusions regarding gender dysphoria in this population but are a reminder that it should be an important factor to consider on long-term follow up of OT-DSD.

Finally, psychosocial support must be an integral part of management of OT-DSD. Mental health staff with expertise in DSD is essential to ease decisions on gender assignment, timing of surgery, discussing gender identity concerns, and supporting decisions on sex hormone replacement [1]. Since coming back to Portugal, our patient has regular follow-up appointments with a mental health team.

In conclusion, OT-DSD is a rare condition characterized by the presence of both ovarian and testicular tissue in the same individual. Sex assignment should acknowledge factors such as age at diagnosis, phenotype, internal structures, fertility potential, and sociocultural factors. Even though gender identity will be consistent with the assigned gender in most cases, a potential for gender dysphoria should be recognized. This case report underlines the importance of discussion of such a rare complex disorder, for which clear management guidelines are lacking, in multidisciplinary teams, and also the need to reflect on previous practices to improve care for DSD patients, as our knowledge in this field evolves.

Learning Points

- Ovotesticular disorder of sex development is a rare condition characterized by the presence of both ovarian and testicular tissue in the same individual
- Sex rearing of these patients should be discussed by a multidisciplinary team and depends on several factors such as age at diagnosis, phenotype, internal structures, and fertility potential, even though clear management guidelines are lacking
- A potential for gender dysphoria in patients with ovotesticular disorder of sex development should be acknowledged even though in most cases gender identity will be consistent with the assigned gender

Contributors

All authors made individual contributions to authorship. T.M. and P.R. were involved in management of this patient and manuscript submission. S.R. was involved in manuscript submission. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

References

1. Hughes IA, Houk C, Ahmed SF, Lee PA, Group LC, Group EC. Consensus statement on management of intersex disorders. *Arch Dis Child*. 2006;91(7):554-563.
2. Shlomo M, Richard AJ, Allison GB, Ronald KJ, Clifford RJ. *Williams Textbook of Endocrinology*. 14th ed. Elsevier; 2020.
3. Kilberg MJ, McLoughlin M, Pyle LC, Vogiatzi MG. Endocrine management of ovotesticular DSD, an index case and review of the literature. *Pediatr Endocrinol Rev*. 2019;17(2):110-116.
4. Kim YM, Oh A, Kim KS, Yoo HW, Choi JH. Pubertal outcomes and sex of rearing of patients with ovotesticular disorder of sex development and mixed gonadal dysgenesis. *Ann Pediatr Endocrinol Metab*. 2019;24(4):231-236.
5. Krob G, Braun A, Kuhnle U. True hermaphroditism: geographical distribution, clinical findings, chromosomes and gonadal histology. *Eur J Pediatr*. 1994;153(1):2-10.
6. Khadilkar KS, Budyal SR, Kasaliwal R, *et al*. OVOTESTICULAR DISORDER OF SEX DEVELOPMENT: A SINGLE-CENTER EXPERIENCE. *Endocr Pract*. 2015;21(7):770-776.
7. Sircili MH, Denes FT, Costa EM, *et al*. Long-term followup of a large cohort of patients with ovotesticular disorder of sex development. *J Urol*. 2014;191(5S):1532-1536.
8. Costanzo M, Touzon MS, Marino R, *et al*. Gonadal tumor development in 46, XX disorders of gonadal development. *Eur J Endocrinol*. 2022;187(3):451-462.
9. Hembree WC, Cohen-Kettenis PT, Gooren L, *et al*. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903.
10. Ganie Y, Aldous C, Balakrishna Y, Wiersma R. The spectrum of ovotesticular disorders of sex development in South Africa: a single-centre experience. *Horm Res Paediatr*. 2017;87(5):307-314.