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Research Article

Clinical Heterogenicity in Children with Ovotesticular Disorder of Sex Development: Experience at Children's Hospital of Mexico Federico Gomez

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ABSTRACT

Introduction: DSD are congenital alterations in which either sexual chromosomes, gonadal or anatomical development are atypical. It is estimated that about 1 in every 4500 live births has some type of DSD, ovotesticular DSD representing around 3-10% of the cases. Given the rarity of DSD, it is an underexplored area, and little is known of ovotesticular DSD.

Materials and Methods: A retrospective study on patients diagnosed with Ovotesticular DSD in a tertiary medical center from 2009 to 2018. The clinical presentation, phenotype, gonadal features, gender assignment and medical management were evaluated.

Results: A total of 184 cases matched the initial search criteria. Only 9 patients with confirmed histopathological diagnosis were selected. Eight out of the nine cases evaluated presented ambiguous genitalia at birth, and only one was detected until pubertal age with presence of bilateral gynecomastia. A female 46 XX karyotype was reported in six patients, whereas the remaining three patients had mosaicism. Four patients were at pubertal age at the time of the study, and three of them required induction of puberty due to lack of sexual steroid production due to loss of gonadal organs.

Discussion: Ovotesticular DSD is a rare finding with a heterogeneous spectrum concerning its genetic etiology, clinical presentation, and surgical findings. Most patients are diagnosed during infancy or childhood; few are diagnosed at pubertal age.

Conclusion: Actual management and decision on gender assigning and treatment is challenging and debatable; therefore, a scrupulous clinical examination, as well as hormonal, imaging, genetic and molecular investigation is needed for a correct diagnosis. Further investigation is required to fully understand the disease.

Introduction

Development sex disorders (DSD) are congenital alterations in which either sexual chromosomes, gonadal or anatomical development are atypical. To current date there have been innovation in the diagnosis, surgical management and the understanding of accompanying psychosocial alterations that patients with DSD develop [1].

It is estimated that about 1 in every 4500 live births has some type of DSD [1]. Ovotesticular DSD represent around 3-10% of the cases in newborns with ambiguous genitalia, with a broad spectrum of clinical manifestations ranging from ambiguous genitalia detectable at birth to undetectable alterations until pubertal age or even testicular torsion [2].

The diagnosis of ovotesticular DSD, previously known as true hermaphroditism, requires the identification of both ovary tissue (with presence of follicles) and testicular tissue in the same gonad or contralateral gonad. The development of the genital system in utero and the apparition of secondary sexual characteristics will have a broad spectrum depending on the functionality and presence of either ovary or

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testicular tissue. Most common clinical characteristics at birth include the presence of ambiguous genitalia characterized by hypospadias and cryptorchidism. Genital conducts derived structures usually follow the functionality of the ovary and testicular tissue, often with presence of rudimentary uterus or hemi uterus. Pubertal development occurs normally with mammary gland growth [3].

Treatment for ovotesticular DSD can vary broadly and mainly depends on age at diagnosis, phenotype and the reproductive capacity of the patient. Even though ovotesticular DSD is low in prevalence, it must be considered in the initial approach of the newborn with ambiguous genitalia; however, no epidemiological data exists in Mexico. Due to the lack of knowledge on the actual epidemiological status of this condition in the Mexican territory, it is necessary the identification of this DSD.

Materials and Methods

The study took place in a third-level medical institution in Mexico City at Children's Hospital of Mexico Federico Gomez. The medical archives of patients with diagnosis established as "ovotesticular DSD", "disorder of sex development", "hermaphroditism" and "genital ambiguity" in the time period of 2009-2018 was retrospectively reviewed. Only patients with karyotype result and biopsy confirmed diagnosis of ovotesticular syndrome were selected.

The clinical presentation, phenotype, gonadal features, gender assignment and medical management were evaluated. Confirmation of ovotesticular DSD was established by in-depth review of histological specimens of partial or complete gonadal tissue from the patients included in the present study. Positive histopathological specimens were reported with the presence of both testicular and ovarian tissue in one or both gonads.

Results

Over the study period, a total of 184 cases matched the initial search criteria. Clinical archives were reviewed and only patients with confirmed histopathological diagnosis were selected. A total of 9 cases were included. The characteristics of these nine patients are summarized in (Table 1). Cases 3, 4, 6 and 9 had pubertal age at the time of study, with cases 3 and 4 requiring induction of puberty with sexual steroids due to lack of spontaneous appearance of puberal characteristics.

Table 1: Summary of the clinical and gonadal features of nine patients with ovotesticular DSD.

	Sex of rearing	Karyotype	Clinical presentation	Phenotype	Right gonad	Left gonad	Age at gonadectomy or gonadal biopsy	Spontaneous puberty
Case 1	Male	48 XXYY[33]/ 46 XX[86]	Ambiguos genitalia at birth.	Unilateral right cryptorchidism, bifid scrotum, hypospadias.	UPB and LPB: Mature testicular tissue.	LPB: well differentiated ovary tissue.	2 months	-
Case 2	Female	46 XX[100]	Ambiguos genitalia at birth.	Bilateral cryptorchidism , hypospadias.	Ovotestes.	UPB: no gonadal tissue detected. LPB: testicular parenchyma.	1 month	-
Case 3	Female	46 XX[100]	Ambiguos genitalia at birth.	Unilateral right cryptorchidism, left gonad not palpable, hypospadias.	Immature testicular tissue.	Ovary tissue.	1 year 5 months	No, induced puberty at 10 years.
Case 4	Male	46 XY[70]/ 46 XX[30]	Ambiguos genitalia at birth.	Non palpable gonads, hypospadias.	Ovotestes.	Ovary tissue.	1 year 8 months	No, induced puberty at 11 years.
Case 5	Male	46 XX	Ambiguos genitalia at birth.	Non palpable gonads, hypospadias.	Ovotestes.	Immature testicular tissue.	5 years	-
Case 6	Male	46 XX[51]/ 46 XY[49]	Gynecomastia	Unilateral left cryptorchidism, hypospadias.	Mature ovaric tissue.	Mature testicular tissue.	10 years	Yes
Case 7	Male	46 XX[100]	Ambiguos genitalia at birth.	Gonads in scrotal pouch, hypospadias.	UPB: mature testicular tissue. LPB: Ovary tissue.	UPB: mature testicular tissue. LPB: Ovary tissue.	4 years	-
Case 8	Female	46 XX[30]	Ambiguos genitalia at birth.	Non palpable gonads, hypospadias.	Ovotestes.	Ovotestes.	7 months	-
Case 9	Male	46 XX	Ambiguos genitalia at birth.	Retractile left gonad, hypospadias.	Ovotestes.	Mature testicular tissue.	7 years 8 months	No, induced puberty at 14 years.

UPB: Upper Pole Biopsy; LPB: Lower Pole Biopsy.

Case 1 was born with ambiguous genitalia. He had the presence of bifid scrotum, right cryptorchidism and a normal phallus of 2.8cm. Image studies showed no presence of Mullerian remnant structures. Initial approach for DSD was made with the realization of a karyotype which revealed mosaicism 48 XXYY (33)/46 XX (86) and gonadal biopsy was performed.

Case 2 was born with ambiguous genitalia. She had the presence of bilateral intraabdominal gonads, as well as non-fused labia with hyperpigmentation, and normal phallus of 2.8cm. Image studies revealed Mullerian remnant structures. Laparoscopic approach for gonadal search revealed both intraabdominal gonads with ovotestes appearance.

Case 3 was born with ambiguous genitalia. She had a phenotype with right cryptorchidism with palpable gonad in mid groin canal and left gonad not palpable, as well as hypospadias and a short phallus of 1.5cm. Image studies revealed the presence of uterine cavity. Gonadectomy was performed with histopathological result for ovotesticular DSD. Pubertal induction was performed at 10 years 6 months due to lack of gonadal tissue.

Case 4 was born with ambiguous genitalia. He had non-palpable gonads, scrotum like structure and small phallus of 1.2cm. Image studies revealed the presence of uterine cavity. Laparoscopic approach revealed an aberrant looking left gonad, later found to be compatible with gonadoblastoma, and a streak-looking right gonad. Patient continued surveillance for germline tumor. Pubertal induction was performed at 11 years due to previous resection of gonadal tissue.

Case 5 was born with ambiguous genitalia. He had non-palpable gonads scrotum-like structure and normal phallus of 3cm with hypospadias. No alterations were found on abdominal ultrasonography.

Case 6 was born with normal-looking male genitalia. At the time of evaluation, he was 10 years old and seeked medical attention for the presence of bilateral gynecomastia. On closer examination unilateral left cryptorchidism and hypospadias was detected with a normal 8cm phallus. Initial approach revealed a karyotype with mosaicism 46 XX [51]/ 46 XY [49] and plasmatic levels of both sexual steroids; testosterone 501ng/ml, estradiol 128mg/dl, as well as the presence of uterine cavity in ultrasonographic imaging. Laparoscopic search of left gonad was performed with identification of ovotesticular tissue. Uterus, mammary gland and left gonad were resected, and no sex reassignment was performed. Male pubertal activity appeared spontaneously and is being kept under surveillance.

Case 7 was born with ambiguous genitalia. Patient was known at the institution until 4 years of age, referred from primary care facility after detection of hypospadias. At initial consult, normal scrotum with palpable bilateral gonads of 2cc, normal phallus of 3.5cm and hypospadias were observed. Normal image studies were obtained. Karyotype was performed with the presence of 46 XX [100] results. No testosterone production was detected after gonadotropin stimulation; however, estradiol production was detected. Gonadal biopsy was performed, and testicular and ovarian tissue were encountered.

Case 8 was born with ambiguous genitalia. She had non-palpable gonads, scrotum-like structure, small phallus of 2.3cm and a clinical presentation of inguinal hernia. Image studies reported the presence of uterine cavity and karyotype was compatible con 46 XX [30]. Laparoscopic approach for correction of inguinal hernia was performed with detection of intrabdominal streak gonads, therefore realizing bilateral gonadectomy with posterior histological finding for ovotesticular DSD.

Case 9 was born with ambiguous genitalia. He had normal scrotum, palpable bilateral gonads, however, left gonad was retractile, as well as 3.5cm long phallus with hypospadias. Initial DSD approach revealed a 46 XX karyotype and absence of Mullerian remnant structures on ultrasonography. Neither female nor male sexual steroids were identified after gonadotropin stimulation test. Laparoscopic approach for locating gonads was performed with biopsy taken from both gonads with histological report for ovotesticular DSD.

Discussion

Ovotesticular DSD is a rare finding with a heterogeneous spectrum concerning its genetic etiology, clinical presentation, and surgical findings [4]. In this retrospective review we have shown that the most common karyotype in our cohort was 46 XX, as it was reported previously in Africa and China [5, 7]. Most of the patients were reared as males with no gender reassignment during the follow-up. This gender of rearing is in line with the reported literature [8].

The majority of patients are diagnosed during infancy or childhood due to ambiguous genitalia, being this the most common first complaint in our cohort. Given the heterogenous clinical presentation, it can be presented during adolescence, because of a normal phenotypic development or because of the lack of an accurate physical examination during infancy. As in the patient described in case 6 who looked for medical attention until the age of 10, with presence of bilateral gynecomastia, but during complete physical examination cryptorchidism and hypospadias were also detected. Other forms of late presentation are cyclic hematuria, phenotypic female with masculinization at puberty and there are reported cases of testicular torsion related to ovotesticular DSD. Cyclic and intermittent scrotal pain, and hematuria can be attributed to the cyclic action of the estrogens in the ovarian part of the ovotesticles [4, 8].

Regarding gonadal tissue preservation, the decision has to be made taking into account the reared gender and, if possible, in association with a multidisciplinary team that should evaluate all the possible outcomes. This consensus of the team in order to decrease the need of hormonal replacement therapy and to maximize reproduction capability of the patient.

The study had a number of limitations. Amongst the present limitation, the study is a retrospective descriptive approach, and it included a small number of cases. As well, not all the patients had been investigated for the presence of the *SRY* gene or other genetic alterations associated with ovotesticular DSD. Some other limitations were the long-term outcomes, such as onset of puberty due to lack of prospective follow-up, or loss of continuity by the patient.

Conclusion

Ovotesticular DSD is an uncommon disease. Actual management and decision on gender assigning and treatment is challenging and debatable; therefore, a scrupulous clinical examination, as well as hormonal, imaging, genetic and molecular investigation are needed for a correct diagnosis [9].

Taking care of children with ovotesticular DSD should also take into account the quality of life as the primary goal. As it has been reported, given the rarity of DSD, it is an underexplored area [10]. Only few studies address this issue. The long-term outcomes should be evaluated on prospective studies with continuous follow-up of the subjects up until adulthood in order to provide information about long-term comorbidities and quality of life.

Ethical Approval

The institutional ethical committee approved the study protocol.

Funding

None.

Competing Interests

None.

Conflicts of Interest

None.

Abbreviations

DSD: Development Sex Disorder

UPB: Upper Pole Biopsy
LPB: Lower Pole Biopsy

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