

An unusual case of ambiguous genitalia

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ABSTRACT

Introduction: Mixed gonadal dysgenesis is most commonly associated with a mosaic 45X/46XY karyotype. The clinical phenotype may range from almost complete female or male external genitalia to ambiguous genitalia. The internal genitalia may be composed of dysgenetic testis on one side and a streak gonad on the contralateral side, however there can be varying configurations as well. The uterus and fallopian tubes are generally ipsilateral to the streak gonad and these retained Mullerian remnants are common. The presence of 45X may present with Turner like features including cardiac, renal anomalies and short stature. **Case Report:** We describe a case of ambiguous genitalia secondary to mixed gonadal dysgenesis where the sex assignment was made before the final diagnosis was reached. **Conclusion:** The diagnosis of mixed gonadal dysgenesis can be difficult for families. A multidisciplinary approach must be established for the patient and family while incorporating the psychosocial aspects also.

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INTRODUCTION

In 2005, the Chicago Consensus on Management of Intersex Disorders collaborated to change the nomenclature on conditions such as "intersex", "hermaphroditism", and "pseudohermaphroditism" for the term "disorder of sex development" [1]. This term defines congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical [1]. The classification is divided into sex chromosome DSD (e.g. Klinefelter syndromes and variants), 46XY DSD and 46XX DSD. Gonadal dysgenesis falls under the classification for both 46XY DSD and 46XX DSD. In this disorder, there are usually well formed testis on one side and a streak dysgenetic gonad on the contralateral side [2]. This is further divided into complete or pure XY gonadal dysgenesis, incomplete or partial gonadal dysgenesis and mixed gonadal dysgenesis. In the classification proposed by the Chicago Consensus, cases of testicular dysgenesis with a 45X/46XY karyotype have been termed mixed gonadal dysgenesis [3].

CASE REPORT

Our patient was a six-month-old Hispanic infant referred to our clinic for ambiguous genitalia. The patient was born at an outside institution via cesarean-

section for fetal bradycardia. He was born full term with birth weight of 3.2 Kg. Prenatal ultrasonography (USG) were indeterminate regarding fetal sex assignment. Amniocentesis was refused. In the neonatal intensive care unit, the patient was found to have a micropallus and an undescended testicle on the left side. An endocrine workup was done prior to discharge. Congenital adrenal hyperplasia was ruled out. A testosterone level on day-2 of life was 132 ng/dL and a karyotype revealed 46XY/47XYY. The decision had been made to raise this patient as a male. Family history was non-contributory including no maternal exposure to androgens or signs of virilization. The patient presented to us at six month of age for transfer of care. His physical exam was significant for a phallic structure with a length of three cm, a perineal hypospadias with chordee and incomplete fusion of labiosrotal folds. He had an underdeveloped left scrotum, no palpable left testicle, and a palpable right testicle in the inguinal canal, a right rugated scrotum, and an anal opening to base of scrotum measuring two cm. At six months of age, we did a work up to rule out partial androgen insensitivity syndrome and 5 α -reductase deficiency. Human chronic gonadotropin stimulation test showed an increase in testosterone levels pre HCG vs. post HCG (table 1).

The anti-Mullerian hormone was essentially unchanged and the testosterone/DHT ratio was normal for age at <10:1. An ACTH stimulation test was also done to rule out a congenital adrenal hyperplasia variant which was negative. The pelvic USG and MRI both revealed a right testicle in the inguinal region, no left testicle, and a blind ending vagina and uterus. The voiding cystourethrogram (VCUG) showed normal kidneys and a urogenital sinus. Cytogenetics confirmed 45X (41% interphase nuclei), 47XYY (45%) and 46XY (14%) of the 30 cells screened confirming our diagnosis of mixed gonadal dysgenesis. It is unclear why the first cytogenetics test did not confirm other cell lines on karyotype analysis. He is currently scheduled for surgery that will include an exploratory laparotomy to search for the gonad, which was not visualized via MRI on the left side.

Table 1: Results of HCG stimulation test.

	Pre HCG	Post HCG
Testosterone	2 ng/mL	162 ng/mL
Anti-Mullerian Hormone	18.06 ng/mL	16.2 ng/mL
Dihydrotestosterone	7 ng/dL	23 ng/dL

DISCUSSION

Three stages occur in fetal sex development: 1) an undifferentiated stage where identical primitive structures develop in XY and XX embryos, 2) gonadal differentiation into testis and ovaries and 3) differentiation of internal and external genitalia [4]. In the 7th week of fetal life, SRY expression occurs which promotes testicular formation [4]. SOX 9 stimulates

Sertoli cell differentiation in the testis where anti-mullerian hormone is produced. This glycoprotein hormone is then responsible for the regression of Mullerian ducts [4]. Leydig cells in the testis synthesize testosterone through the action of steroidogenic enzymes. Testosterone is then responsible for Wolffian duct differentiation into the epididymides, vas deferens and seminal vesicles. Testosterone is also converted by 5-alpha reductase to dihydrotestosterone which is responsible for the virilization of the urogenital sinus and external genitalia [4].

Gonadal dysgenesis results in defective embryonic development of the gonads. It can be divided into complete or pure XY gonadal dysgenesis, incomplete or partial gonadal dysgenesis and mixed gonadal dysgenesis. Complete gonadal dysgenesis is usually complete phenotypic sex reversal in an XY female. There is normal female genitalia at birth but breast development is delayed at puberty. Uterus and fallopian tubes are present, but Wolffian duct remnants are not found [2]. Histology reveals streaked gonads. The incomplete form is any evidence of masculinizing effects such as ambiguity of genitalia at birth or virilization at puberty.

Mixed gonadal dysgenesis, which our patient has, is of sporadic inheritance. It is associated with a mosaic 45X/46XY karyotype, although additional karyotypes such as 45X/47XXY and 45X/46XY/47XYY can also occur. The clinical phenotype may range from almost normal female external genitalia with mild clitoromegaly, ambiguous genitalia, isolated hypospadias or normal male external genitalia. The internal genitalia may be composed of dysgenetic testis on one side and a streak gonad on the contralateral side, however there can be varying configurations as well. The uterus and fallopian tubes are generally ipsilateral to the streak gonad and these retained Mullerian remnants are common. The presence of 45X may present with Turner like features and include cardiac, renal anomalies and short stature. Due to the risk of malignancy in the streak gonad, it is usually removed during early childhood.

Management is based on sex assignment. Factors in deciding whether to raise the infant as male or female includes genital appearance, surgical options (both cosmetic and functional), need for lifelong replacement therapy, potential for fertility and views of the family [5]. It involves a multidisciplinary approach and psychosocial involvement. In one study from Sweden that looked at males with 45X/46XY, the management included removal of the streaked gonad as well as orchiopexy if necessary [6]. The risk of malignant transformation of the streaked gonad is 70% by the third decade. They recommend a testicular biopsy when puberty is complete to determine if there is normal v.s. dysgenetic tissue. A USG of the testes should be performed yearly from age 10 year onwards and a follow up ultrasound and biopsy until age 20 [6]. If carcinoma is not detected, they recommend follow up with a yearly ultrasound and a new biopsy after three years [6]. Controversy exists for the necessity of testosterone therapy for DSD patients. Therapy may be expected to

induce puberty, growth, sexual function and support psychosexual maturation, however there are no large studies conducted on long term follow up of infants with mixed gonadal dysgenesis with respect to growth, pubertal development, fertility and risk of gonadal tumors. One study did look at long term physical, hormonal, and sexual outcomes of males with disorders of sex development over a median of 19.8 years [7]. Four out of twelve included in the study had mixed gonadal dysgenesis [7]. Out of men four men, one was treated with testosterone therapy because of a bilateral gonadectomy [7]. In this study, most patients with testis did not have hormonal therapy because of the desire to not have any further treatment and because puberty and sexual function developed without therapy.

In a case report from Brazil, a 41-day-old infant was referred before sex assignment was established due to sex ambiguity [8]. This was different from our patient because sex assignment was already decided prior to diagnosis. This infant had a 1.3 cm phallus (our patient had 3 cm) with chordee, penoscrotal hypospadias, scrotum with rugae and pigmentation and a palpable left gonad in the scrotal fold. This infant also had normal levels of gonadotropin, testosterone, 17-OH progesterone and androstendione at 41 day of age. The karyotype was 45X/46XY and the decision was made to raise this patient as a male. This patient was treated with three injections of testosterone resulting in increased phallus size [8]. He had a laparoscopy at eight months of age revealing a small right gonad that was removed. Turner Screening was also done for this patient. Our patient was not treated with testosterone due to phallic size sufficient for surgery.

CONCLUSION

In conclusion, it is apparent that the diagnosis of mixed gonadal dysgenesis can be difficult for families. Management must be individualized. A multidisciplinary approach must be established for the patient with the help of a psychologist who can help support the parents and deal with the psychosocial aspects of the disorder. This expertise will help facilitate team decisions based on sex assignment, surgery and hormone replacement therapy.

Author Contributions

Marianna Nicoletta-Gentile – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Leslie Lam – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Mariam Gangat – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Yelena Kogelman – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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