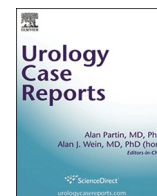


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Urology Case Reports

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Pediatrics

Hormonal suppression of mini-puberty in a neonate with mosaic 45X/46XY disorder of sexual development

Martin Kaefer^{*}, Erica Eugster

Pediatric Urology and Endocrinology, Riley Children's Hospital, Indiana University School of Medicine, USA



ARTICLE INFO

Keywords:

Disorder of sex development
Mini-puberty
GnRH agonist
Mosaicism
Testicle
Testosterone

ABSTRACT

Disorders of Sex Development (DSD) are some of the most controversial and challenging conditions that pediatric urologists treat. This may be especially true in mosaic 45X/46XY DSD, due to the inability to ascertain in the neonatal period which gender identity will best suit a given child with this condition. It has therefore been proposed to forgo any irreversible surgical interventions. In order to address the concern of early testosterone production in a nonsurgical manner we describe a case in which we treat a patient with a GnRH agonist to block the early physiologic rise in testosterone during the neonatal mini-puberty.

Introduction

Disorders of sex development (DSD) encompass a spectrum of conditions in which a discrepancy exists between a patient's chromosomal sex, gonadal histology and the appearance of the external genitalia. More than a decade after the Chicago consensus, there remains a wide disparity in opinion regarding treatment among physicians for nearly every category of DSD.¹

In the past, there existed a tendency to assign gender in the newborn period and thereafter proceed with surgical intervention in order to create an external appearance in keeping with this assigned gender. This strategy has largely been supplanted by a strategy to forgo early surgical intervention. This results in a number of potential social and physiological dilemmas that require the expertise of a multidisciplinary team. Parents and health care professionals justifiably fear that continued exposure to elevated testosterone levels during the mini-puberty of infancy could adversely affect the child's phenotypic appearance (e.g. increasing phallic size) and result in further brain imprinting. This may be particularly detrimental if the child ultimately declares their gender identity to be female. Borrowing from the paradigm of suppressing the onset of puberty in transgender children, we describe the successful treatment of a newborn with mosaic DSD with a GnRH agonist to block the physiologic rise in testosterone during the first 6 months of life.

Case report

The multidisciplinary DSD team was asked to consult on a full term newborn child for a chief complaint of ambiguous genitalia. The mother had received prenatal counseling and had undergone screening with cell-free DNA that revealed no identifiable Y chromosomal markers. The family had therefore anticipated the female gender.

Upon delivery, the child was noted to have a two-centimeter phallus with a proximal urethral meatus and labioscrotal fusion (Fig. 1). The left gonad was initially palpated in the high inguinal location and the right gonad could not be appreciated on physical examination. A pelvic ultrasound revealed a uterus with failure to identify either gonad. Serum testosterone on day 5 of life returned at 16 ng/dl. Karyotype returned as 45X/46XY and a diagnosis of mosaic DSD was made. A repeat serum testosterone obtained one week later revealed that the testosterone level had risen. An endoscopic evaluation at 21 days of life revealed a hemivagina that extended to the right of midline and laparoscopy confirmed the presence of a right hemi-uterus and fallopian tube with a streak like structure on the right and a left undescended intra-abdominal testicle with associated inguinal hernia (Fig. 2a and b).

Upon being presented with this information the parents demanded immediate gonadal removal in order to limit the child's exposure to endogenous androgens. The family was presented with the additional option of medically suppressing testosterone during the mini-puberty and agreed to the use of a GnRH agonist for this purpose. Treatment was initiated with depot Lupron 0.3 mg/kg IM monthly x 2 month. This

^{*} Corresponding author. Professor of Urology Riley Children's Hospital 705 Riley Hospital Drive, Suite 4230 Indianapolis, IN, 46202, USA.
E-mail address: mkaefer@iupui.edu (M. Kaefer).

<https://doi.org/10.1016/j.eucr.2020.101237>

Received 12 April 2020; Accepted 30 April 2020

Available online 3 May 2020

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Fig. 1. Appearance of external genitalia at birth.

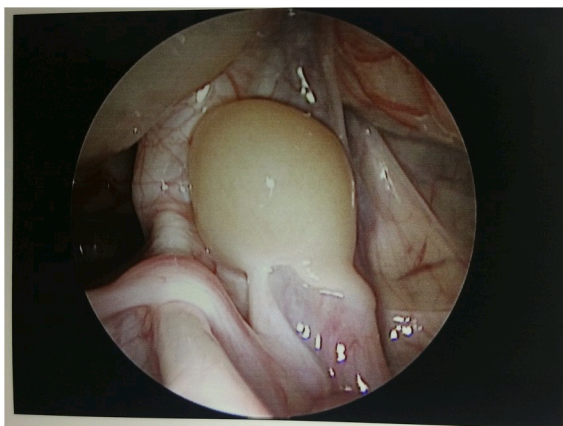


Fig. 2a. Laparoscopic appearance of Left Gonad: Testicle.

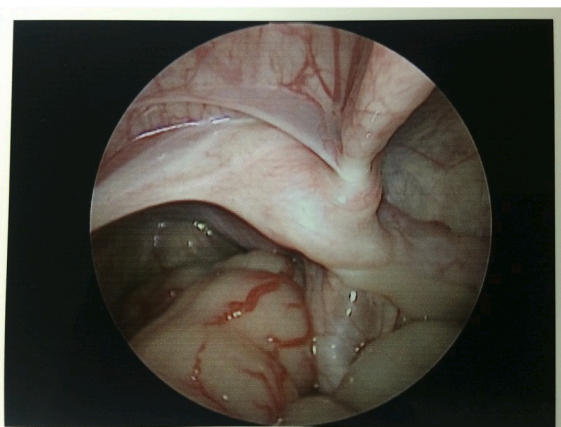


Fig. 2b. Laparoscopic appearance of Right Gonad: Streak Gonad.

suppressed testosterone levels to pre-pubertal levels (<2.5 ng/dl). At one year of age the right streak gonad was removed, the left hernia repaired and the left testicle biopsied and secured in a supra-facial location.

As per the parent's wishes, the patient continues in the female sex assignment. Frequent visits to our multidisciplinary clinic have helped to reinforce the value of an observational approach and manage the unique stressors that come with having a child with genital ambiguity.

Discussion

Patients with DSD may present in a number of different ways. Genital ambiguity is commonly the manner in which children are identified. The combination of hypospadias with one or bilateral undescended gonads, inguinal hernias in a phenotypic female and amenorrhea in a teenager are other common ways in which these patients present for medical evaluation.² Prenatally, DSD may be suspected if the results of amniocentesis do not correlate with ultrasound images of the genitalia. Recently, with the advent of maternal cell-free DNA testing an additional mode of presentation has emerged. Although one can accurately predict the gender of the newborn from the PCR amplification of fetal DNA, the prediction of fetal gender can be in error in as many as 4% of cases.³ In our patient the family was informed that their child was likely female and was subsequently found to have mosaic DSD. This case serves to underscore the continued need for caution with this diagnostic modality.

The appearance of a child with mosaic DSD presents as a spectrum ranging from phenotypic males with a completely formed male urethra and bilaterally descended gonads to phenotypic females with bilateral streak gonads (so called Turners syndrome). Patients may also present with genitalia that is ambiguous.⁴ In the past, early gender assignment was frequently made based on size of the phallus and levels of measured serum testosterone. However, cases in which the patient later identified with a gender other than that which was assigned has brought this paradigm of management into question.

In the case presented, our multidisciplinary team explained to the family that it is not possible to know the gender identity of a child with mosaic DSD. The family, having anticipated a female, chose to raise the child in the female gender role. After explaining that their child had a rise in testosterone consistent with neonatal mini-pubertal surge, the family insisted that the gonads be immediately removed in order to minimize additional masculinizing effects. Faced with this dilemma, we proposed the use of a GnRH agonist to suppress this rise in postnatal testosterone.

The use of GnRH agonists to suppress testosterone in children has precedent. The World Professional Association of Transgender Health's standards of care has recommended suspending puberty by this means in certain gender non-conforming minors. By suppressing hormone levels it is possible to obviate the development of secondary sexual characteristics that are not in keeping with the individuals chosen gender.⁵

We have successfully suppressed testosterone in our patient with mosaic DSD with the monthly delivery of depot Lupron. The potential advantage of this is clear, minimizing the effect of additional androgens on genital appearance without performing irreversible surgery to remove the gonads in the neonatal setting.

References

1. Lee PA, Houk CP, Ahmed SF, Hughes IA, et al. Consensus statement on management of intersex disorders. *Pediatrics*. Aug 2006;118(2):e488–e500.
2. Kaefer M, Diamond D, Hendren WH, et al. The incidence of intersex in children with cryptorchidism and hypospadias: stratification based on gonadal palpability and meatal position. *J Urol*. Sep 1999;162:1003–1007.
3. Ho SS, Barrett A, Thadani H, Asibal CL, Koay ES, Choolani M. Application of real-time PCR of sex-independent insertion-deletion polymorphisms to determine fetal sex

- using cell-free fetal DNA from maternal plasma. *Clin Chem Lab Med.* Jul 2015;53(8): 1189–1195.
4. Kaefer M. 45,X/46,XY mosaicism: a spectrum of phenotypic expression and management. *Dialogues Pediatr Urol.* 2000;23(6).
 5. Mahfouda S, Moore JK, Siafarikas A, Zepf FD, Lin A. Puberty suppression in transgender children and adolescents. *Lancet Diabetes Endocrinol.* Oct 2017;5(10): 816–826.