

## Case Report

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# 46XX testicular DSD SRY-Negative in a child with hypoplastic left heart syndrome

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### Abstract

Disorders of Sex Development (DSD) refers to biological differences between phenotypic sex, gonad morphology and chromosomal material. A full-term infant was born with Hypoplastic Left Heart Syndrome (HLHS) and ambiguous genitalia. Karyotype revealed 46XX with no evidence of Y chromosome or SRY. Biopsy of both gonads revealed testicular tissue. Parents decided to rear the child as male. The child underwent extensive cardiac repair and is currently awaiting decision regarding urological repair. This case emphasizes the need for multi-disciplinary care in the management of children with DSD associated with other complex medical conditions to ensure a timely diagnosis and multi-system, patient-centered treatment approach.

**Abbreviations:** DSD: Disorder of Sex Development; SRY: Sex Determining Region Y; HLHS: Hypoplastic Left Heart Syndrome; LH: Luteinizing Hormone; FSH: Follicle Stimulation Hormone; DHT: Dihydrotestosterone; NIPT: Noninvasive Prenatal Testing.

### Introduction

Disorders of Sex Development (DSD) represent a variety of congenital conditions with incongruence or atypical development of "chromosomal, gonadal, or anatomic sex" [1]. Specifically, 46XX testicular DSD is a rare subset of DSD with a reported prevalence of one in 20,000 [2]. Most patients with 46XX testicular DSD are diagnosed in adolescents due to abnormal pubertal development [3]. It is reported that amongst patients with 46XX DSD, 80% are SRY positive and 20% SRY-negative [3]. Grinspon et al. described two mechanisms that may explain the development of testes in patients with SRY-negative 46XX DSD: 1) overexpression of testes promoting genes such as SOX9 or SOX3 genes and 2) insufficient expression of ovary promoting

or anti-testes genes such as WNT4 or RSPO1 genes, leading to testicular development [4].

Hypoplastic Left Heart Syndrome (HLHS) is a congenital heart defect that results in underdevelopment of the left side of the heart and occurs in 2-3 cases per 10,000 live births [5]. This single ventricle physiology is considered fatal and often requires staged palliation during a child's life [6]. HLHS has known associations with chromosomal abnormalities and syndromes such as monosomy X (Turner), trisomy 18 (Edward), Trisomy 13 (Patau), 11q deletion (Jacobsen), CHARGE, Smith-Lemli-Opitz syndrome, and PAGOD [5,7].

We report a 5-year-old Hispanic child with 46XX, SRY-nega-

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tive testicular DSD and HLHS, an association which has not been previously reported. The purpose of this report is two fold: 1) To illustrate the association of a 46XX, testicular DSD and HLHS and 2) To emphasize the importance of multi-disciplinary care to ensure a timely diagnosis, collaborative treatment timeline incorporating cardiac and genital surgical repair needs, and patient-centered support regarding sex rearing and surgical repair in children with DSD.

### Case presentation

We report an infant who was born at 37 weeks gestation with prenatal diagnosis of left diaphragmatic hernia, HLHS with small aorta and ambiguous genitalia on fetal ultrasound. Noninvasive Prenatal Testing (NIPT) was normal for chromosomes 21,13,18, amniocentesis revealed a 46XX karyotype, and previous prenatal imaging suggested the presence of a phallus. The infant was born via vaginal delivery, weighed 2525 g, was stabilized in the delivery room and subsequently started on prostaglandin.

### Ambiguous genitalia evaluation

On day of life 0, the endocrinology team was consulted for work-up for ambiguous genitalia. The infant's initial physical exam findings were remarkable for low-set ears, webbed neck, small phallic structure with penoscrotal hypospadias, urethral orifice displaced to penoscrotal junction with bifid scrotum,

right gonad palpated in the right scrotum, but left gonad was non-palpable. The anus was patent in a normal location with no evidence of a vaginal opening. A karyotype confirmed 46XX with no evidence of Y chromosome or SRY gene on Fluorescence in Situ Hybridization (FISH). The endocrinology team recommended obtaining testosterone and anti-Mullerian hormone levels, a Congenital Adrenal Hyperplasia (CAH) panel, cortisol, and thyroid studies (Table 1). Parents were advised to avoid assigning sex for the infant until the work up was completed and were educated regarding gender-neutral language. The urology team was also consulted on the same day and recommended obtaining a scrotal ultrasound, which confirmed gonadal tissue in the right scrotum, but no gonadal tissue was identified in the left scrotum. Labs collected at 6 weeks of life were consistent with male minipuberty response with testosterone of 141 ng/dL (Table 1). Due to the need for more urgent cardiac repair, the remaining evaluation of the genital morphology was completed over the first year of life (Table 1). When he was one years old, ultrasound was repeated which showed the right testicle in the scrotum, a left gonad in the inguinal canal, and the presence of uterus in the pelvis. Gonadal biopsy, initially of the right gonad and followed later with biopsy of the left gonad, revealed testicular tissue. Following the completed endocrine and urological work-up, the diagnosis was confirmed to be SRY-negative 46XX testicular DSD.

**Table 1:** Case presentation timeline of work up, imaging, and surgical procedures.

TIME	LABS AND EVENTS	RESULTS	REFERENCE
0 DAY OF LIFE	Chromosome analysis, Fluorescence in Situ Hybridization (FISH)	46XX. No SRY gene signal. Cells counted 45, analyzed 5. 100% XX cells.	
	17-Hydroxyprogesterone	342 ng/dL	<330 ng/dL
	17-Hydroxypregnenolone	1289 ng/dL	<1546 ng/dL
	Androstenedione, serum	29 ng/dL	<98 ng/dL
	DHEA, Serum	210 ng/dL	43-245 ng/dL
	Testosterone, serum	29 ng/dL	Tanner 1: <7 ng/dL
	Progesterone level, serum	6.1 ng/dL	<7 ng/dL
	Pregnenolone, serum	436 ng/dL	<658 ng/dL
	11-Deoxycortisol	70 ng/dL	< 150 ng/dL
	Deoxycorticosterone (DOC), serum	< 16 ng/dL	<16 ng/dL
	Corticosterone B	50 ng/dL	< 125 ng/dL
	Cortisol Blood	51.2 mcg/dL	> 10 mcg/dL
	T4, Free	1.31 ng/dL	0.78-1.54 ng/dL
	TSH	3.24 uIU/mL	1.1-4.23 uIU/mL
	Scrotal ultrasound	Gonadal tissue in the right scrotum, but no gonadal tissue in the left scrotum. No evidence of uterus.	
1	17 Hydroxyprogesterone, LC/MS/MS	204 ng/dL	<225 ng/dL
	Testosterone, serum	55 ng/dL	
4	Inhibin A	1 pg/mL	
	Inhibin B	106 pg/mL	
5	Norwood procedure		
6	Anti-Mullerian	16.8 ng/mL	
12	Family meeting with NICU team, endocrinology, urology, medical genetics to discuss results. Family officially decides to rear infant as male.		

18	Chromosome microarray	No clinically significant genomic copy number gains and losses were detected.	
48	FSH	3.92 mIU/mL (H)	
	LH	1.54 mIU/mL	Prepubertal <0.02 mIU/mL
	Estradiol, serum	< 2 pg/mL	
	Testosterone Free	8.0 pg/mL	
	Testosterone Serum	141 ng/dL	
	DHT B	42 ng/dL	
60	Genitogram	Male appearing urethra	
67	Hernia repair and right gonadal biopsy		
	Gonadal biopsy during right open hernia	X3 benign testicular tissue, no definitive evidence of ovarian tissue or malignancy	
75	Discharged from initial hospitalization		
136	Estradiol, serum	< 2 pg/mL	
6 Months	Glenn procedure		
1 YEAR 2 MONTHS OLD	Pelvic ultrasound	Uterus found (1.8 x 0.5 x 0.8 cm). No evidence of ovaries.	
	Scrotal ultrasound	Right testis is normal in appearance and located within the right scrotum. Smaller left testis located within the left inguinal canal.	
3 YEARS 11 MONTHS	Fontan procedure		
4 YEARS 10 MONTHS	Left gonadal biopsy	Left gonad, superficial and deep biopsy: benign testicular tissue composed of immature seminiferous tubules. No evidence of ovarian tissue, fallopian tube, or malignancy.	

### Cardiac work up and treatment course

Post-natal echocardiogram showed a small mitral valve and left ventricle, small aorta, and hypoplasia of the aortic arch, which was consistent with HLHS. He eventually underwent a Norwood procedure during this hospitalization and transferred to the cardiothoracic intensive care unit. Post-operatively, the hospital course was complicated by supraventricular tachycardia and bacteremia, which required long-term management with propranolol and intravenous antibiotics. He subsequently underwent a Glenn procedure at 6 months of age and most recently a Fontan procedure at 4 years of age.

### Current medical course

The child is now 5 years old and doing well. He has had normal development to date attaining all milestones appropriately and continues to receive care by multiple subspecialties including endocrinology, urology, cardiology, medical genetics, ophthalmology, infectious disease, psychology, and hematology. Repeat serial ultrasounds have been performed which demonstrated the presence of a uterus with no ovarian tissue identified. Since day of life seven, the family has reared this child as a male. He identifies as male currently. Urology team and the family have been in continued discussion about possible options for corrective surgery and potential future fertility potential. The parents are interested in hypospadias repair, however, expressed that they would like to have their son decide for himself in the future so surgical correction is currently on hold.

### Discussion

We illustrated a unique timeline of a 5-year-old child with 46XX, SRY-negative testicular DSD and HLHS who survived his three-staged surgical palliation, and is now healthy after multiple, arduous hospitalizations, procedures, and complications. HLHS is a rare congenital heart disease, and the association with DSD is important to consider during the work-up of complex congenital heart disease. Early involvement of the DSD team in the NICU may be prudent given the potential delay of work up with other organ systems taking priority. This will allow early, established multidisciplinary care with sub-specialists and DSD team collaboration for timely DSD diagnosis and sex rearing decisions in the future.

Providing experienced multidisciplinary care for children with DSD has been recognized as standard of care for several years [1]. A specific DSD diagnosis is crucial in sex rearing decisions for newborns as the recommendation needs to factor in surgical options, fertility potential, need for hormone therapy, and family's perspectives and cultural views [1]. While in most cases a DSD evaluation is done promptly given the psychological urgency for families, this patient's case is unique as his work-up had to be delayed for several years due to his complex congenital heart disease and procedures. An accurate diagnosis is often difficult and time-consuming as it requires biopsies, genetic analysis, and complex lab and imaging result interpretations by multiple sub-specialty providers. Therefore, experienced multidisciplinary care is crucial in establishing the treatment priorities including an accurate diagnosis and allowing for the complete assessment of underlying endocrinopathies, reproductive potential, and surgical options to optimize long-term outcomes.

This patient example provides a concrete course on how this early collaboration was critical to identifying a diagnosis in a timely manner to establish a patient and family-centered treatment [8] plan. To date, this family continues to meet with all his sub-specialty providers every three months to review specialty specific components of his care as well as to provide support for the child and family. The family has received care from psychology and developmental pediatric specialists as they discuss the diagnosis, prognosis, and potential surgical options with the child.

As part of the patient and family-centered treatment plan, surgical correction of ambiguous genitalia is often part of the counseling process. There is growing controversy over timing and the specific surgical procedure offered for children with DSD. Early surgical correction may have better results and prevent living through the stigma associated with ambiguous genitalia [8]. However, there are ethical concerns whether the decision should lie on the patient, rather than the family, at a time when the child is able to express their gender identity and desires for or against surgical reconstruction [8]. There are continued conversations between DSD advocates and the medical community regarding these decisions. Evidence based practice guidelines for the initial gender rearing decisions for children with DSD and other complex multi-organ syndromes and long-term follow-up has not been well established [9] This is in part due to the more recent growing research in gender identity in general, but also due to the limited data on gender identity and rare syndromes [9].

For this patient, the parents did not want extensive genetic testing to be completed. However, in consideration of the child's clinical findings there are several genes that should be considered and have previously been associated 46XX DSD and congenital cardiac disease. The child is followed by medical genetics and the recommendation was made to obtain a focused exome sequencing of candidate genes which the family declined. Interestingly, there have been several reports out of France which have reported on various heterozygous frameshift mutations in NR2F2, encoding for COUP-TF2 in children with 46XX DSD and congenital heart disease [10]. This group's work has highlighted the importance of nuclear receptors in establishing human ovarian identity and the importance of sequencing these children to better understand the underlying genetic landscape that results in the associations of these rare syndromes [10].

## Conclusion

DSD management and gender rearing decisions in the newborn period is a difficult process given the psychosocial and cultural complexity. We report a 5-year-old Hispanic child with the rare association of 46XX, SRY-negative testicular DSD and HLHS to highlight the importance of collaborative, multi-disciplinary care to ensure a prompt diagnosis, appropriate treatment timeline and patient-centered approach. Further research is needed to investigate long-term health outcomes, quality of life and psychosocial health in children with DSD and other complex congenital syndromes to determine how to best support these children across their lifespan ensuring their quality of life is optimized.

**Table of contents summary:** 5-year-old child's challenging medical course leading to his DSD diagnosis in the setting of HLHS surgeries, which required extensive multidisciplinary care.

## Declarations

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