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46,XY Disorders of Sex Development and Congenital Diaphragmatic Hernia: A Case with Dysmorphic Facies, Truncus Arteriosus, Bifid Thymus, Gut Malrotation, Rhizomelia, and Adactyly

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Abstract

The association of 46,XY disorder of sex development (DSD) with congenital diaphragmatic hernia (CDH) is rare, but has been previously described with and without other congenital anomalies. Literature review identified five cases of 46,XY DSD associated with CDH and other congenital anomalies. These five cases share characteristics including CDH, 46,XY karyotype with external female appearing or ambiguous genitalia, cardiac anomalies, and decreased life span. The present case had novel features including truncus arteriosus, bifid thymus, gut malrotation, and limb anomalies consisting of rhizomelia and adactyly. With this case report, we present a review of the literature of cases of 46,XY DSD and CDH in association with multiple congenital abnormalities. This case may represent a unique syndrome of 46,XY DSD and diaphragmatic hernia or a more severe presentation of a syndrome represented in the previously reported cases.

Keywords

congenital diaphragmatic hernia; disorders of sex development; truncus arteriosus; bifid thymus; gut malrotation; polysplenia; rhizomelia; adactyly

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INTRODUCTION

46,XY disorder of sex development (DSD) is characterized by 46,XY karyotype, ambiguous external genitalia, and Mullerian structures ranging from absence to presence of a fully developed uterus and fallopian tubes [Ostrer, 2008; Lee et al., 2006]. 46,XY DSD is a rare condition with a prevalence of about 1:20,000 [Ostrer, 2008]. The association of congenital diaphragmatic hernia (CDH) and 46,XY DSD is also rare and has been previously described with associated congenital malformations in five patients [Meacham et al., 1991; Sogho et al., 1991; Maaswinkel-Mooij and Stokvis-Brantsma, 1992; Devriendt et al., 1995; Manouvrier-Hanu et al., 2000; Kent et al., 2004; Cho et al., 2006; Antonius et al., 2008].

There are additionally three cases of associated CDH and 46,XY DSD attributed to Denys-Drash syndrome with mutations in *WT1* [Devriendt et al., 1995; Cho et al., 2006; Antonius et al., 2008]. We report on a karyotypic male infant with 46,XY DSD and CDH notable for cardiac displacement to the left neck, truncus arteriosus, bifid thymus, gut malrotation, rhizomelia, adactyly as well as dysmorphic facial features. We compare the findings in this case with cases of 46, XY DSD and CDH with multiple congenital abnormalities in the literature. This patient may represent a unique syndrome of 46,XY DSD and CDH or a more severe presentation of a syndrome represented in the previously reported cases.

MATERIALS AND METHODS

Study Design

This project was reviewed by the Stanford Institutional Review Board (IRB).

DNA Extraction and Quantification

Following the manufacturer's protocol, genomic DNA was extracted from liver, spleen, adrenal, and kidney tissues from the patient using AllPrep DNA/RNA FFPE kit (Qiagen, Valencia, CA). The DNA concentrations were quantified using the Qubit fluorometer (Life Technologies, Carlsbad, CA).

Chromosome Microarray Analysis

Array comparative genomic hybridization (aCGH) was performed on the patient's genomic DNA using a NimbleGen 6-plex whole-genome array according to the manufacturer's protocol (Roche NimbleGen, Madison, WI).

CLINICAL REPORT

The patient was born at 35 weeks gestation to a 20-year-old G3P1SAB1 mother. A complex cardiac anomaly had been noted on 33 week ultrasound. Parents are nonconsanguineous and reported no family history of congenital abnormalities. At delivery, a heartbeat was present, but not spontaneous respirations. The patient expired within 10 min of birth. At autopsy, examination showed a small appearing nose with narrow nares, the appearance of widely spaced eyes, and a crescent shaped mouth. Thoracic abnormalities included a Bochdalek left posterior diaphragmatic hernia, herniation of stomach and spleen into the left hemithorax, and associated hypoplasia of the left lung. There was displacement of the heart to the left

neck region (Fig. 1A) with truncus arteriosus and ventricular septal defect (VSD). A bifid thymus was observed. Abdominal findings included malrotation of the gut and polysplenia. Genitourinary findings were ambiguous external genitalia with appearance of bifid scrotum versus redundant and thickened labial swellings, no identifiable phallus, and caudally displaced urethra near an atretic anus (Fig. 1B). The internal genitalia included bicornuate uterus, fallopian tube, prostate, seminal vesicles, and epididymis without evidence of gonads bilaterally. Skeletal exam showed rhizomelia and adactyly of the hands and feet with rudimentary thumbs (Fig. 1C and D).

RESULTS

Amniocentesis karyotype was 46,XY. Subsequent chromosome microarray analysis using aCGH, with resolution adequate to detect chromosome deletions and duplications greater than 20 kb in size [Haraksingh et al., 2011], found 25 copy number variants (CNVs), ranging in size from 22.5 to 714 kb and impacting a combined 35 genes. Analysis identified 14 genes where one allele is deleted and 21 genes where one allele is duplicated; however, no known pathogenic CNVs were observed. Parental chromosome microarray and fluorescence in situ hybridization (FISH) analyses were not performed.

DISCUSSION

The combination of 46,XY DSD and CDH is rarely associated with multiple additional congenital abnormalities. However, no molecular etiology has been determined for this association, an effort complicated in part by its rarity. The current patient presented with characteristics previously observed in association, including ambiguous genitalia in the absence of testes, left CDH, lung hypoplasia, VSD, and shortened lifespan. This patient appears unique in presenting with cardiac displacement to the left neck, truncus arteriosus, bifid thymus, gut malrotation, polysplenia, rhizomelia, adactyly, and distinct facial features including a small appearing nose with narrow nares, the appearance of widely spaced eyes and a crescent shaped mouth. Microarray analysis of the CNVs in the genome of this patient identified 14 genes where one allele is deleted and 21 genes where one allele is duplicated. However, no known pathogenic CNVs were found and the number of observed CNVs is not necessarily different from the number one would expect to find in a control genome with the given resolution of the aCGH platform that was used here [Haraksingh et al., 2011; Mills et al., 2011].

Etiologies of CDH

The prevalence of CDH is estimated at 1:3,000 live births, and a number of molecular etiologies have been associated with it, including aneuploidy (i.e., trisomy 18 and trisomy 21), chromosome micro-deletion and microduplication as well as single gene disorders [Pober et al., 2006]. About 10% of patients with CDH have a chromosome aberration [Pober et al., 2006; Holder et al., 2007]. Among the monogenic syndromes which can associate with CDH are Cornelia de Lange syndrome (up to 5%), Fryns syndrome (>80%), Donnai-Barrow syndrome (approximately 70%), and Matthew-Wood syndrome (approximately 50%; [Pober et al., 2006]). While each of these have been associated with genitourinary tract abnormalities, none have been associated with 46,XY DSD [Pober et al., 2006].

46,XY DSD With Other Congenital Anomalies

Among the syndromes associated with 46,XY DSD are campomelic dysplasia, Frasier syndrome, and Denys–Drash syndrome [Ostrer, 2008]. Of these, only Denys–Drash syndrome, caused by mutations in *WT1*, has been rarely noted to associate with CDH [Ostrer 2008; Devriendt et al., 1995; Royer-Pokora et al., 2004; Cho et al., 2006; Antonius et al., 2008]. However, Denys–Drash syndrome does not account for this patient’s multiple congenital anomalies including truncus arteriosus and ventricular septal defect, bifid thymus, malrotation of the gut, polysplenia, and adactyly of the hands and feet [Dome and Huff, 1993; Pober et al., 2006].

CDH and 46,XY DSD

CDH and 46,XY DSD with multiple congenital abnormalities have been described in five cases in the literature without an attributable etiology (Table I). In three cases, testes were present with feminized or ambiguous external genitalia [Meacham et al., 1991; Maaswinkel-Mooij and Stokvis-Brantsma, 1992; Kent et al., 2004], the remaining two had no observable gonads [Sorgo et al., 1991; Manouvrier-Hanu et al., 2000]. Four out of five prior cases had left sided diaphragmatic abnormalities, four out of five were reported to have some degree of lung hypoplasia, and all had one or more cardiac abnormalities including dextrocardia, VSD, and hypoplastic left heart, among others [Meacham et al., 1991; Sorgo et al., 1991; Maaswinkel-Mooij and Stokvis-Brantsma, 1992; Manouvrier-Hanu et al., 2000; Kent et al., 2004]. It is difficult to determine if the dextrocardia reported in some cases refers to developmentally derived orientation or mechanical cardiac displacement to the right as described by Kent et al. [2004], and implied by Manouvrier-Hanu et al. [2000]. Four out of five previously reported cases demonstrated shortened lifespan ranging from 4 days to 19 months [Meacham et al., 1991; Sorgo et al., 1991; Maaswinkel-Mooij and Stokvis-Brantsma, 1992; Kent et al., 2004]. Individual cases demonstrated unique features such as double vagina [Meacham et al., 1991], rhabdomyomatous dysplasia [Meacham et al., 1991], horseshoe kidney [Maaswinkel-Mooij and Stokvis-Brantsma, 1992], and curved clavicles ([Manouvrier-Hanu et al., 2000]; Table I). Polysplenia in the present patient, defined by the presence of more than one splenic mass [Peoples et al., 1983; Zhu et al., 2006], was also observed in a previous patient with reported extra spleen, spleen adherent to liver, and spleen tissue in the tail of the pancreas [Maaswinkel-Mooij and Stokvis-Brantsma, 1992]. The number of cases describing significant visceral findings may be under-represented as only three patients underwent autopsy [Meacham et al., 1991; Sorgo et al., 1991; Maaswinkel-Mooij and Stokvis-Brantsma, 1992] with only one of these specifically commenting on the splenic morphology [Maaswinkel-Mooij and Stokvis-Brantsma, 1992].

SUMMARY

Overall, the present patient and the previously reported cases of CDH and 46,XY DSD with multiple congenital anomalies, are not adequately described by a currently recognized syndrome. While this patient shares a number of features with prior cases, including feminized or ambiguous external genitalia, left CDH, lung hypoplasia, cardiac anomalies, polysplenia, and shortened lifespan, several characteristics in the patient have not been previously reported, specifically truncus arteriosus, bifid thymus, gut malrotation,

rhizomelia, and adactyly. The rare association of 46, XY DSD and CDH with additional congenital abnormalities in this patient may represent a unique syndrome, or a severe presentation of a syndrome that encompasses the prior cases.

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FIG. 1. Patient post mortem. (A) Heart displacement to the left neck. (B) Ambiguous external genitalia. (C) Adactyly of the hands and (D) feet. (E) Radiographs of the thorax and upper extremities and (F) lower extremities.

TABLE 1

Cases of 46,XY DSD and CDH

	Diaphragmatic hernia	Reproductive/genital	Pulmonary	Cardiac/vascular	Visceral	Musculo-skeletal	Lifespan
Present patient	Left posterior	Ambiguous external genitalia, bicornuate uterus, seminal vesicles, no gonads observed bilaterally	Left lung hypoplasia	Cardiac displacement to left neck, TA, VSD	Bifid thymus, stomach and spleen in left hemithorax, gut malrotation, polysplenia	Rhizomelia, adactyly	10 min
Manouvrier-Hanu et al. [2000]	Left (almost total absence of left diaphragm)	Completedly feminized external genitalia, uterus, fallopian tubes, no gonads observed bilaterally	NR	Dextrocardia	Normal renal function	2-3 toes syndactyly, curved clavicles	Alive at 1 year
Maaswinkel-Mooij et al. [1992]	Muscular defect in diaphragm	Female external genitalia, bicornuate uterus, epididymal and right testicular tissue, no left gonad	Left lung aplasia	hypoplastic left heart, MV and AV atresia, hypoplastic AA, persistent left superior vena cava	Liver in right hemithorax, horseshoe kidney, extra spleen	Bilateral single palmar creases	4 days
Kent et al. [2004]	Left (minimal diaphragm for closure)	Clitoromegaly with normal introitus, uterus, fallopian tubes, testes	Pulmonary hypoplasia	Cardiac displacement to the right	NR	NR	3 months
Meachem et al. [1991]	Left	Ambiguous external genitalia, double vagina, left uterine fundus, left fallopian tube, prostatic tissue, bilateral testes	Right lung hypoplasia, RLL sequestration, rhabdomyomatous dysplasia	Dextrocardia, ASD/ single atrium, PDA, total anomalous pulmonary vascular return	NR	NR	9 months
Sorgo et al. [1991]	Right	Female external genitalia, mild clitoromegaly hypoplastic uterus, no gonads observed bilaterally	Right lung hypoplasia	Dextrocardia, VSD, PDA, persistent left superior vena cava, right pulmonary artery hypoplasia	NR	No skeletal deformities	19 months

AA, ascending aorta; ASD, atrial septal defect; AV, aortic valve; MV, mitral valve; PDA, patent ductus arteriosus; RLL, right lower lobe; TA, truncus arteriosus; VSD, ventricular septal defect; NR, not reported.