Published in final edited form as:

J Pediatr Surg. 2015 May ; 50(5): 744–745. doi:10.1016/j.jpedsurg.2015.02.025.

The association between congenital diaphragmatic hernia and undescended testes

Kenneth S Azarow^{*,†,a}, Robert Cusick^{b,†}, Julia Wynn^c, Wendy Chung^c, George B Mychaliska^d, Timothy M Crombleholme^e, Dai H Chung^f, Foong Yen Lim^g, Douglas Potoika^h, Brad W Warnerⁱ, Gundrun Aspelund^j, and Marc S Arkovitz, MS^k

^aDivision of Pediatric Surgery, Department of Surgery, Oregon Health & Sciences University, Portland, OR

^bDivision of Pediatric Surgery, Department of Surgery, University of Nebraska College of Medicine/Children's Hospital and Medical Center, Omaha, NE

^cDepartment of Pediatrics and Medicine, Columbia University Medical College, New York, NY

^dDivision of Pediatric Surgery, Department of Surgery, University of Michigan School of Medicine, Ann Arbor, MI

^eColorado Fetal Care Center, Division of Pediatric General, Thoracic and Fetal Surgery, Children's Hospital Colorado and the University of Colorado School of Medicine, Denver, CO

^fDivision of Pediatric Surgery, Department of Surgery, Vanderbilt Children's Hospital, Nashville, TN

^gDivision of Pediatric General, Thoracic, and Fetal Surgery, Center for Molecular Fetal Therapy, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

^hDivision of Pediatric Surgery, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA

ⁱDivision of Pediatric Surgery, Department of Surgery, Washington University School of Medicine, St Louis Children's Hospital, St Louis, MO

^jDivision of Pediatric surgery, Department of Surgery, Columbia University Medical College, New York, NY

^kDivision of Pediatric Surgery, Department of Surgery, Shaare Zedek Medical Center, Jerusalem, Israel

© 2015 Published by Elsevier Inc.

*Author for Correspondence: Kenneth S. Azarow MD, FACS, FAAP, Surgeon-in-Chief, Doernbecher Children's Hospital, 3181 SW Sam Jackson Park Road, CDW 7, Portland, OR 97239, azarow@ohsu.edu.

†Co-First Authors

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies, with an incidence of 1 in 3000 live births (1). Undescended testes (UDT) is one of the more common congenital abnormalities evaluated and treated by pediatric surgeons with an estimated incidence between 1.5 and 3% (2,3,4). The current theory of testicular descent involves a 2 stage process with the first stage involving regression of the cranio-suspensory ligament (2). This ligament attaches in the exact location of the lateral pleuroperitoneal fold, which results in a posterior-lateral CDH when it fails to develop. In this study, we examine the relationship between treated UDT and CDH in a large prospective cohort of patients to determine if there is any association of these anomalies.

Materials and Methods

Subjects were recruited as part of the DHREAMS (Diaphragmatic Hernia Research & Exploration: Advancing Molecular Science) study (www.cdhgenetics.com). The DHREAMS study has a prospective cohort of neonates with a diaphragmatic defect identified at one of seven collaborating medical centers (1).

Eligibility criteria for this study were that the child was born or transferred into a participating institution within the first week of life, had radiological confirmation of CDH, and survived until at least 2 years of age. The study involves collecting tissue at the time of CDH repair for banking and genetic analysis, recording clinical and demographic data surrounding the time of initial hospitalization, and long term neurodevelopmental follow up. As part of this process, a health assessment was conducted by telephone interview with a parent at two years of age. Parents were asked if the child required orchiopexy within the first two years of life. UDT was defined as requiring orchiopexy by age two. The study was approved by the institutional review board at each of the participating institutions.

The incidence of UDT in our cohort was compared to the incidence of UDT in the general population using Chi-Square analysis with significance defined as $p < .05$. For the purposes of this analysis the incidence rate in the general population was estimated from the literature at 2.25% (2,3,4).

Results

Between March 2009 and February 2012, 174 patients met inclusion for this study. Of these, 65 males had full information recorded after their 2 year health assessment. 12 of 65 (18%) had an UDT repaired; which was significantly higher than that of the general population ($p < 0.05$). Children who had spontaneous descent not requiring surgery were not included in this analysis. Of the 12 who had a repair, no child had a unilateral UDT contralateral to the side of the CDH. 8 of 10 patients with a left CDH and UDT had a unilateral left UDT, 2 had bilateral. Both of the patients with a right sided CDH and an UDT had a unilateral right UDT.

We then further analyzed the data to see if the children with an associated UDT had any other differences in clinical parameters compared with the cohort that did not have UDT.

There was no difference between those patients with and without UDT without regarding need for ECMO, need for patch repair or oxygen dependence at 28 days of life.

There were no differences in the frequency of chromosome disorders or gene mutations between those male CDH cases with and without UDT. One of the patients with a bilateral UDT had a mosaic trisomy 18.

Discussion

We report an incidence of UDT requiring orchiopexy in CDH of 18% or about 9 times higher than that of the general population which is 1.5%–3% (2,3,4). In addition, none of the patients had a UDT contralateral to the side of the CDH. UDT can be associated with several congenital abnormalities including Prune Belly Syndrome, omphalocele and gastroschisis as well as multiple inherited intersex abnormalities (2,5).

There have been reports in the literature of an association between CDH and UDT (6,7,8). Fauza and colleagues described a large cohort of both male and female patients with CDH with an overall incidence of 3.6%, but did not exclude females from the cohort; therefore a more accurate estimate is approximately 7% (6). Benjamin et al described a 30% incidence of cryptorchidism in male CDH patients (7). Later, Lund et al described an incidence of approximately 26% in their high risk patients who were symptomatic within 6 hours of birth (8). In that cohort, 60% required ECMO.

There are several limitations of our study. The first is that an UDT was defined as a treated UDT, i.e. a child born with an UDT who died prior to their second birthday was not included in this study. A child who had a UDT that descended on its own and did not require orchiopexy was not included in the UDT group. Finally, children with UDT not repaired by age 2 may have been missed. Thus, our report of 18% of CDH males with UDT is likely an underestimate. Fauza and Lund both found a higher incidence of UDT with CDH. (6,8) In addition, we have no idea which type of UDT the patients had, i.e. an intra-abdominal or inguinal, palpable testes.

Though our sample size is modest, our results replicate those of others demonstrating an association of UDT with CDH. In addition, we are the first to emphasize the laterality of the UDT on the ipsilateral side of the CDH. We hypothesize that there is an association between these two birth defects because of the proximity of the urogenital ridge to the pleuro-peritoneal fold and a shared developmental processes. In the absence of diaphragm tissue, the first or trans-abdominal phase of the testicular descent between weeks 8–15 of gestation may be disrupted. During this phase, the testicle descends from the retroperitoneum to the internal inguinal ring. The abdominal phase involves regression of the craniosuspensory ligament, a structure that anchors the testis to the undersurface of the diaphragm. This process is under the control of both mullerian inhibiting substance (MIS) and insulin like hormone 3 (Insl3)(2). The lateral pleuroperitoneal folds are thought to develop medially around the fourth to sixth week of gestation, predating the first stage of testicular descent (9).

The second, or inguinal scrotal, phase of descent occurs between weeks 25–35 of gestation. During this phase the testis descends through the inguinal canal into the scrotum. This is under the control of the genitofemoral nerve and calcitonin gene related peptide (CGRP)(2). Developmental anomalies of the diaphragm result in abnormalities of the cranio-suspensory ligament and may disrupt normal testicular descent. The consistent association of the UDT on the ipsilateral side of the diaphragm defect supports this hypothesis. The subphenotype of both CDH and UDT may help to define a subset of CDH cases with shared developmental disturbances that are more likely to share similar etiologies, including genetic etiologies. As we identify specific genes for CDH, we will be able to test this hypothesis.

In conclusion, UDT is more common in CDH patients compared to the general population. There is a strong correlation between the side of the UDT and the CDH. This suggests a common embryologic origin for both defects.

Acknowledgments

Supported by: National Institute of Health grant number NIH R-01 HD057036-01 - Identification of Novel Genes for Congenital Diaphragmatic Hernia.

Supported in part by: Columbia University's CTSA grant UL1 RR024156 from NCATS-NCRR/NIH.

References

1. Wynn J, Krishnan U, Aspelund G, Zhang Y, Duong J, Stolar CJ, et al. Outcomes of congenital diaphragmatic hernia in the modern era of management. *J Pediatr*. 2013; 163:114–119. [PubMed: 23375362]
2. Hutson JM, Balic A, Nation T, Southwell B. Cryptorchidism. *Semin Pediatr Surg*. 2010; 19:215–224. [PubMed: 20610195]
3. Berkowitz GS, Lapinski RH, Dolgin SE, Gazella JG, Bodian CA, Holzman IR. Prevalence and Natural History of Cryptorchidism. *Pediatrics*. 1993; 92:44–49. [PubMed: 8100060]
4. Cortes D, Kjellberg EM, Breddam M, Thorup J. The True Incidence of Cryptorchidism in Denmark. *J Urol*. 2008; 179:314–318. [PubMed: 18006016]
5. Berkowitz GS, Lapinski RH, Godbold JH, Dolgin SE, Holzman IR. Maternal and neonatal risk factors for cryptorchidism. *Epidemiology*. 1995; 6:127–131. [PubMed: 7742397]
6. Fauza DO, Wilson JM. Congenital diaphragmatic hernia and associated anomalies: their incidence, identification, and impact on prognosis. *J Pediatr Surg*. 1994; 29:1113–1137. [PubMed: 7965516]
7. Benjamin DR, Juul S, Siebert JR. Congenital posterolateral diaphragmatic hernia: associated malformations. *J Pediatr Surg*. 1988; 23:899–903. [PubMed: 3069995]
8. Lund, Mitchell J, Kharasch V, Quigley S, Kuehn M, Wilson JM. Congenital Diaphragmatic Hernia: The Hidden Morbidity DP. *J Pediatr Surg*. 1994; 29:258–264. [PubMed: 8176602]
9. Ackerman KG, Greer JJ. Development of the diaphragm and genetic mouse models of diaphragmatic defects. *Am J Med Genet C Semin Med Genet*. 2007; 145C:109–116. [PubMed: 17436296]
10. Crane JP. Familial congenital diaphragmatic hernia: prenatal diagnostic approach and analysis of twelve families. *Clin Genet*. 1979; 16:244–252. [PubMed: 519894]
11. Jensen MS, Olsen LH, Thulstrup, Bonde JP, Olsen J, Henriksen TB. Age at cryptorchidism diagnosis and orchiopexy in Denmark: a population based study of 508,964 boys born from 1995 to 2009. *J Urol*. 2011; 186:1595–1600. [PubMed: 21855929]