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Original Articles

VACTERL associations in children undergoing surgery for esophageal atresia and anorectal malformations: Implications for pediatric surgeons☆,☆☆

Timothy B. Lautz [a,*], Ankur Mandelia [a], Jayant Radhakrishnan [b]

[a] Division of Pediatric Surgery, Department of Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University Feinberg School of Medicine, Chicago, IL, USA
[b] University of Illinois College of Medicine, Chicago, IL USA

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ABSTRACT

Purpose: The aim of this study was to compare the frequency and nature of VACTERL associations between children who underwent surgery for esophageal atresia/tracheoesophageal fistula (EA/TEF) and anorectal malformation (ARM).
Methods: We identified all children who underwent surgery for EA/TEF and/or ARM at hospitals participating in the Pediatric Health Information System (PHIS) database between 2004 and 2012. PHIS is an administrative database of free-standing children's hospitals managed by the Child Health Corporation of America (Overland Park, KS) that contains patient-level care data from 43 hospitals. The complete records of patients in this cohort were cross-referenced for diagnoses of vertebral, cardiac, renal and limb anomalies.
Results: 2689 children underwent repair of esophageal atresia. Mean gestational age was 36.5 ± 3.2 weeks and mean birth weight was 2536.0 ± 758.7 g. Associated VACTERL diagnoses included vertebral anomaly in 686 (25.5%), ARM in 312 (11.6%), congenital heart disease in 1588 (59.1%), renal disease in 587 (21.8%) and limb defect in 192 (7.1%). 899 (33.4%) had 3 or more anomalies and met criteria for a VACTERL diagnosis. 4962 children underwent repair of ARM. Mean gestational age was 37.4 ± 2.7 weeks and mean birth weight was 2895.2 ± 765.1 g. Associated VACTERL diagnoses included vertebral anomaly in 1562 (31.5%), congenital heart disease in 2007 (40.4%), EA/TEF in 348 (7.0%), renal disease in 1723 (34.7%) and limb defect in 359 (7.2%). 1795 (36.2%) had 3 or more anomalies and met criteria for a VACTERL diagnosis.
Conclusion: VACTERL associations are relatively common in children with EA/TEF and ARM and occur in specific clusters, with cardiac disease more common in EA/TEF and spinal and renal/urinary anomalies more common in ARM.

Anomalies of the spine or vertebrae (V), anorectal malformations (A), congenital cardiac anomalies (C), esophageal atresia/tracheoesophageal fistula (TE), renal and urinary abnormalities (R), and limb lesions (L) frequently occur together and are referred to as VACTERL anomalies. This association was first described by Quan and Smith in 1972 and 1973 [1,2], while the cardiac component was incorporated by Temtamy and Miller in 1974. In more recent years, a number of publications from single centers and birth defect registries have further delineated the patterns and frequency of these associations [3–12]. However, the diagnostic criteria for VACTERL, the list of specific diagnoses included within this spectrum, and the optimal evaluation of children born with one or more apparent components remain debated [13–15].

In the field of pediatric surgery, VACTERL associations are encountered most frequently in patients who require an operation for esophageal atresia/tracheoesophageal fistula (EA/TEF) or anorectal malformation (ARM). Pediatric surgeons play an important role in counseling parents of children with EA/TEF and ARM in the prenatal and early postnatal periods. A prenatal diagnosis of EA/TEF can now be established in approximately 25% of cases [16]. Prenatal diagnosis of ARM, though still rare, is increasingly possible, especially in high risk patients [17]. Comprehensive, modern, multiinstitutional data on the frequency and significance of VACTERL associations in these patients can better inform these conversations and guide the patients' diagnostic evaluations. To this end, this study was designed to compare the frequency of VACTERL anomalies between patients with EA/TEF and ARM using a national database of large children's hospitals and to determine predictors of mortality.

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* Corresponding author at: Division of Pediatric Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E. Chicago Ave, Box 63, Chicago, IL 60611. Tel.: +1 312 227 4210.
E-mail address: tlautz@luriechildrens.org (T.B. Lautz).

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1. Methods

We performed a retrospective cohort study to identify all patients who underwent surgery for EA/TEF or ARM at hospitals participating in the Pediatric Health Information System (PHIS) database between 2004 and 2012. PHIS is an administrative database of free-standing children's hospitals managed by the Child Health Corporation of America (Overland Park, KS) that contains patient-level care data. The PHIS hospitals are 43 of the largest children's hospitals in America. The participating hospitals are located in noncompeting markets in 27 states and the District of Columbia. Participating hospitals provide patient-level data including demographics, diagnoses, and procedures, as well as billing data which includes all medication, diagnostic imaging, laboratory, and supply charges. Data in PHIS are deidentified, but contain an encrypted medical record number that allows tracking of individual patients across multiple inpatient and outpatient encounters. In accordance with PHIS policies, analysis was blinded to the identity of the hospitals. The application of the PHIS database to important issues in the field of pediatric surgery has considerable precedent [18,19].

Patients were identified based on *International Classification of Diseases 9th Revision* (ICD-9) diagnosis codes for the various VACTERL anomalies shown in Table 1. Inclusion in the study was limited to patients who also had an ICD-9 procedure code indicative of surgery for EA/TEF (31.73 or 42.89) or ARM (48.49, 49.79, 46.11, 46.10, 46.03, 46.13). All hospital encounters for these patients were captured, regardless of whether a VACTERL diagnosis was addressed during that encounter. Data were aggregated across all encounters for a given patient to determine the total number of visits (inpatient, emergency department, ambulatory surgery or outpatient) and the range of time (and age) between those visits. Not all types of encounters were captured for all hospitals in every year.

Table 1
ICD-9 codes used to identify VACTERL associations.

Spinal and vertebral anomalies	
Congenital absence of vertebra	756.13
Hemivertebra	756.14
Spina bifida	741.X
Tethered cord	742.59
Absent rib	756.3
Congenital vertebral fusion	756.15
Other	756.10, 756.19
Anal atresia	751.2
Cardiac anomalies	
ASD	745.5
VSD	745.4
Tetralogy of Fallot	745.2
Anomalies of the great veins	747.4X
Transposition of the great vessels	745.1X
Congenital anomalies of the aorta	747.2X
Truncus arteriosis	745.0
Hypoplastic left heart	746.7
Endocardial cushion defect	745.6X
Common ventricle	745.3
Other	745.8, 745.9
Esophageal atresia	750.3
Renal anomalies	
Agenesis/dysgenesis	753.0
Obstructive uropathy	753.2
Vesicoureteral reflux	593.7X
Dysplastic kidney	753.15
Posterior urethral valves	753.6
Other	753.3, 753.4
Limb deformities	
Reduction deformity upper limb	755.2X
Reduction deformity lower limb	755.3X
Polydactyly	755.0X
Syndactyly	755.1X
Other anomalies	
Trisomy 21	758.0
Single umbilical artery	747.5
Duodenal atresia	751.1

Demographic data and birth information (birth weight and gestational age) were captured from the patient's earliest encounter. Birth weight and gestational age were generally only available for patients whose first admission was in the neonatal period. The median age at first encounter was 0 days (interquartile range 1 day) for those with a birthweight reported compared to 151 days (interquartile range 454 days) for those whose birth weight was not recorded. Race was summarized as white, black, Asian, and other/unknown. The complete records of patients in this cohort were searched for ICD-9 diagnosis codes indicative of the other VACTERL anomalies listed in Table 1.

Selection of the exact diagnoses meeting criteria for inclusion as a VACTERL association was based on review of prior literature. The "vertebral" category was broadened to include both bony vertebral anomalies and spinal dysraphisms [7,20]. The "anorectal malformations" category was limited to atresia of the rectum and not expanded to include other intestinal atresias as has been suggested by some [7]. For purposes of comparing to other studies, these more proximal gastrointestinal atresias were reported separately. "Cardiac" defects included major structural anomalies of the heart, but not a patent ductus arteriosus or noncardiac aortic anomalies. The "renal" anomalies category was broadened to include all renal and internal urinary anomalies but not external defects such as hypospadias. Finally the "limb anomalies" included both upper and lower extremity reduction deformities, polydactyly and syndactyly.

The study was approved with exempt status by the Institutional Review Board of the Ann & Robert H. Lurie Children's Hospital of Chicago (#2013-15531). Statistical analysis was performed using IBM SPSS Statistics v20. Q-Q plots were examined to determine variation from a normal distribution in this large sample. Variables with a clear nonnormal distribution were reported as a median (interquartile range [IQR]). Otherwise, continuous variables were reported as a mean ± standard deviation. A logistic regression was performed to identify factors associated with mortality. For all analyses, statistical significance was set at a two-tailed $p < 0.01$ because of the large sample size.

2. Results

2.1. Esophageal atresia/tracheoesophageal fistula

2689 children underwent repair of EA/TEF. Demographics are shown in Table 2. The majority of patients (n = 1429, 53.1%) were admitted to their respective PHIS hospital on the day of birth, while 708 (26.3%), 113 (4.2%), and 48 (1.8%) were admitted/transferred on the 1st, 2nd, and 3rd days of life, respectively. For the remaining 391 (14.5%) patients, the first admission was at a later age. Mean gestational age was 36.5 ± 3.2 weeks among the 1649 (61.3%) patients in whom it was

Table 2
Patient demographics.

	EA/TEF	ARM
Gender		
Male	55.4%	54.0%
Female	44.6%	46.0%
Race		
Caucasian	67.9%	62.5%
African-American	9.6%	12.0%
Asian	1.3%	3.8%
Other	16.5%	16.5%
Unknown	4.6%	5.1%
Ethnicity		
Hispanic	15.8%	19.4%
Not Hispanic	36.0%	28.9%
Unknown	48.2%	51.6%
Birth weight (mean ± SD)	2536.0 ± 758.7 g (n = 2287)	2895.2 ± 765.1 g (n = 3267)
Gestational age (mean ± SD)	36.5 ± 3.2 weeks (n = 1649)	37.4 ± 2.7 weeks (n = 2443)
Hospital encounters, median (interquartile range)	4 (IQR 8)	4 (IQR 7)