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Cincinnati Regional Incidence, Morbidity, and Mortality of Neonatal Foregut Defects and High Coincidence with Cardiovascular Malformations

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Abstract

The first trimester fetal foregut generates organs from larynx to ligament of Treitz. The incidence and clinical impact of many of the 29 congenital malformations arising from the foregut organs remain under characterized. We performed a retrospective chart review on patients from a geographically defined area born between 2006 and 2008 admitted to Cincinnati Children's Hospital Neonatal Intensive Care Unit with diagnoses consistent with one or more congenital foregut malformations.

We found foregut malformations occurred in 1 in 801 births and determined the incidence for each individual foregut malformation, including some that have not previously been reported. We report a high rate of multiple congenital foregut malformations within an individual with coincidence of foregut malformations of 51.5%, and a high association with cardiovascular malformations (40%). Hospital stay was prolonged (32 days versus 5days). Need for assisted feeding (51%) and respiratory support (27%) at discharge were higher when compared to control patients (12 and 6%, respectively). Mortality was 7% in patients with foregut malformations. These data provide needed quantitation of the incidence, morbidity, and mortality related to congenital foregut defects present in inpatient neonates. The coincidence of foregut malformations with cardiovascular malformations underscores the need for further research into their coordinated embryologic formation to aid their prevention and treatment.

Introduction

Congenital malformations remain the leading cause of neonatal death in the U.S. [1]. 3% of newborns present with congenital malformations; 1% require immediate surgical intervention after delivery [2,3]. Morbidity often continues beyond infancy, with subsequent need for hospitalizations and surgeries.

The embryonic foregut arises from endoderm progenitor cells established by 4 weeks (1-2 somites) of gestation and gives rise to many vital organs: thyroid, trachea, thymus, parathyroid, esophagus, lung, liver, biliary tract, pancreas, stomach, and duodenum [4-8]. Reciprocal signaling between the foregut endoderm and neighboring mesoderm (that later gives rise to the heart, major blood vessels, and diaphragm) mediates normal organogenesis [9-13]. Malformations of these structures arise from defective budding, differentiation or sub regionalization during the first trimester (Supplementary Table 1).

Population-based clinical genetic approaches have begun to establish new molecular insights into foregut malformations, e.g., Fog2 with congenital diaphragmatic hernia [14,15]. In addition, investigations using murine models have recreated certain well known human foregut defects such as esophageal atresia and tracheoesophageal fistula implicating specific molecular pathways in foregut organ development [4,16]; only some of these identified defects have been examined in relevant patients [17-23].

Here we report the incidence of foregut malformations among NICU admissions over a 3-year interval from a geographically defined Greater Cincinnati region. Our data defines the coincidence between distinct foregut malformations and the prevalence of accompanying congenital cardiovascular malformations. Of note we report a high coincidence of congenital cardiovascular defects with foregut organ defects. We also report the neonatal morbidity and mortality associated with these congenital foregut malformations. This study provides baseline data for future studies combining epidemiology and molecular embryology to advance our understanding of foregut birth defects.

Methods

Cincinnati Children's Hospital Medical Center serves as the only center providing specialized care in the referral area for neonates born in Cincinnati Children's Perinatal Outreach Program (CCPOP) Region I (Figure 1), yielding population-based numerators and denominators to determine the incidence of individual and aggregate congenital foregut malformations. Data was gathered through chart review on neonatal patients born alive and admitted to Cincinnati Children's Hospital Medical Center Neonatal Intensive Care Unit ('CCHMC NICU'). Presence of a foregut malformation was determined from diagnosis codes. Those matching known foregut malformations were
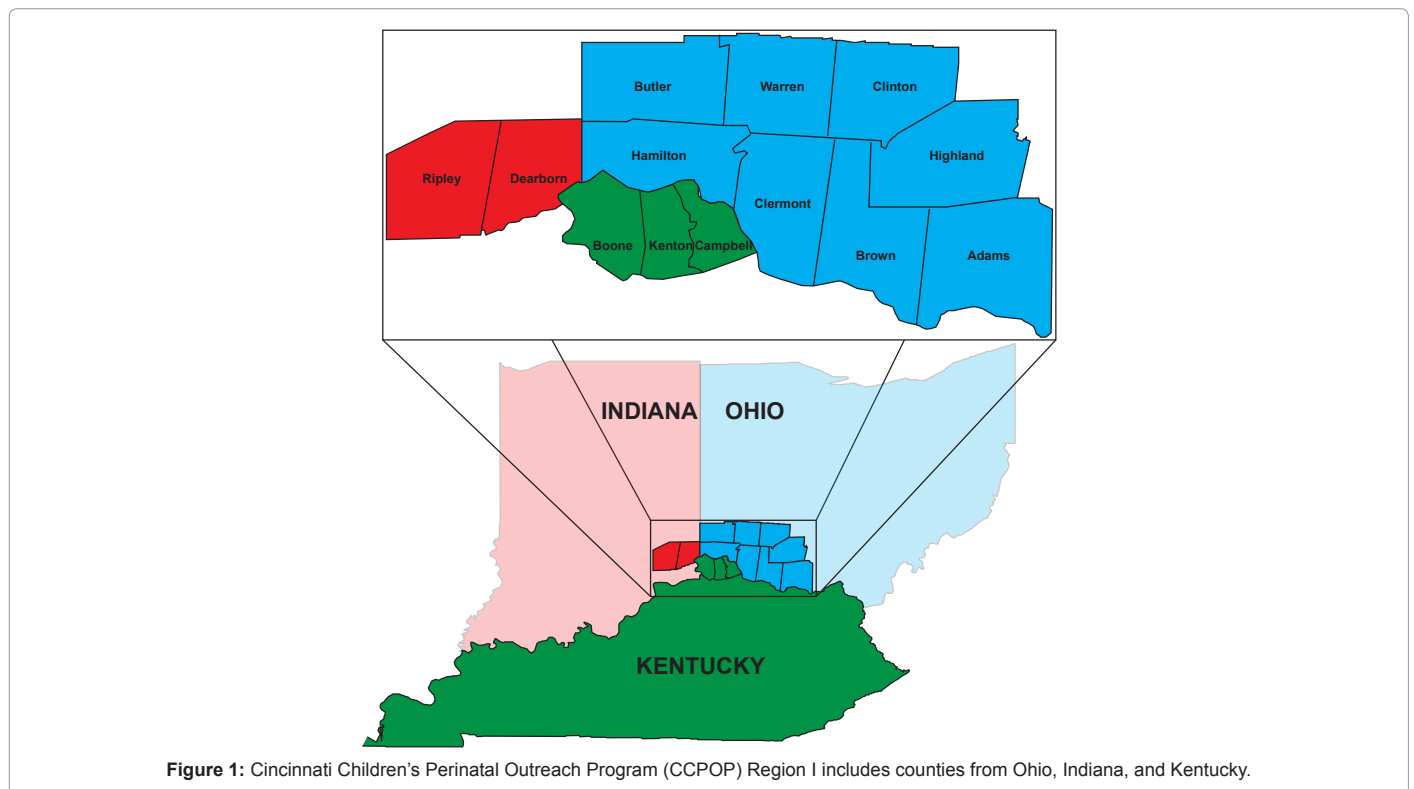
Figure 1: Cincinnati Children's Perinatal Outreach Program (CCPOP) Region I includes counties from Ohio, Indiana, and Kentucky.

included (Supplementary Table 1). Data was collected for the period between 1/1/2006 through 12/31/2008 from individuals residing in Zip Codes within CCPOP Region I.

Demographic and clinical data were retrieved from existing medical records under an IRB approved protocol. Patients with a confirmed foregut malformation diagnosis were further evaluated for gestational age, birth weight, race, maternal age, zip code of residence, and APGAR scores. Outcome data gathered included length of stay (days), disposition (home, death, transferred to another care facility), discharge requiring feeding support (including nasogastric tube or percutaneous gastrostomy tube), discharge home requiring respiratory support (home ventilator, tracheostomy, or nasal cannula).

Two distinct populations of control patients were used to compare morbidity and mortality: 1) All CCHMC NICU patients born in the region during the same time period without a congenital foregut malformation diagnosis (patient characteristic data unavailable) and 2) patients admitted with a postnatal surgical foregut condition (a non-congenital foregut malformation), pyloric stenosis, for which patient characteristic data were gathered.

We compared morbidity and mortality for all patients with congenital foregut malformations and for the most common individual congenital foregut diagnoses to pyloric stenosis controls. Differences in admission day of life and length of stay were tested using the Wilcoxon Rank Sum test. Differences in proportions were tested using a chi-square test or Fisher's exact test. Significance was declared using an alpha level of 0.05. Among comparisons by diagnosis subgroup, we used a conservative critical significance level of alpha=0.002 to adjust for an inflated Type I error due to multiple testing. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

High total incidence of congenital foregut malformation patients requiring neonatal care

The total incidence of patients with foregut malformations has not been reported to date. We found 114Region I patients diagnosed with foregut malformations requiring care in CCHMC NICU. Since 91299 births occurred in the region, we determined an aggregate foregut malformation incidence of 1 in 801. Given that 2264 patients born within Region I received care at CCHMC NICU during this period, foregut malformations were associated with 1 in 20NICU admissions. Thus congenital foregut malformations as a whole are common in our region and in our referral NICU.

Individual incidence of congenital foregut malformations requiring neonatal care

Published incidences of foregut malformations and our regional incidence for each distinct foregut malformation are shown in table 1. Some conditions falling under the foregut malformation category were not observed during this period (congenital high airway obstruction syndrome, laryngotracheal cleft, bronchogenic cyst, congenital lobar emphysema, and choledochal duct cyst). The most common conditions include congenital malrotation at the Ligament of Treitz and the airway malacias (48 unique patients with at least one of the airway malacias [1:1902], laryngomalacia, tracheomalacia, and bronchomalacia). The least common presenting foregut diagnoses were esophageal web, lung lobe agenesis, diaphragmatic eventration, and congenital diabetes mellitus.

Coincidence of one foregut malformation with another

Embryonic stage signaling within and between distinct regions of the embryonic foregut might result in coincidence of one congenital

Foregut Region	Diagnosis	Incidence This Report (1:)		Reported (1:)	References
Esophagus	**EA-TEF**	4348		2500-3922	Depaepe and others, 1993
	Web	91299		No Reported Data	Robert and others, 1993
Airway	**Laryngomalacia**	3148			Holder and others, 1964
	Tracheomalacia	3512	1902	2100	Boogard and others, 2005
	Bronchomalacia	4565			
	Bronchus suis	45650		1000	Barat and Conrad, 1987
Thyroid	**Hypothyroidism**	15217		2900-3600	Alm and others, 1984
Lung	**CPAM**	45650		25,000-35,000	Laberge and others, 2001
	Sequestration	45650		666	Corbett and Humphrey, 2004
	Agenesis	91299		15,000	Bentsianov and others, 2000
	Pulm Hypoplasia	22825		714	Knox and Barson, 1986
Diaphragm	**CDH**	8300		2037	Stege and others, 2003
	Eventration	91299		1400-12875	http://www.fetalultrasound.com
Stomach	**Microgastria**	22825		No Reported Data	Kroes and Feston, 1998
Pancreas	**Diabetes Mellitus**	91299		400,000	von Muhlendahl and others, 1995
	Annular Pancreas	30433		6667-8173	Ravitch, 1975
Duodenum	**Duodenal Atresia**	8300		5,000-10,000	Fonkalsrud and others, 1969
Ligament of Treitz	**Malrotation**	3652		500	Welte and Grosso, 2007
Total Diagnoses		537		No Reported Data	
Total Patients		801		No Reported Data	
Unrepresented	**CHAOS**			No Reported Data	
	Laryngotracheal Cleft			625,000-2,000,000	Pezzettigotta and others, 2008
	Bronchogenic Cyst			No Reported Data	
	Hypoparathyroidism			No Reported Data	
	Thymic Hypoplasia			No Reported Data	
	Lobar Emphysema			25,000	Nayar and others, 2005
	Alagille Syndrome			70,000-100,000	Crosnier and others, 1998
	Choledochal Duct Cyst			13,000-2,000,000	deVries and others, 2002
	Nesidioblastosis			No Reported Data	
	Biliary Atresia			3125-19, 841	Zumkeller 1999

Table 1: Regional and Reported Incidences of Individual Congenital Foregut Malformation Diagnoses.

foregut malformation with another: e.g., esophageal atresia with tracheoesophageal fistula and, less commonly, pulmonary sequestration with cystic adenomatoid malformation [24,25]. We observed a total of 170 malformations (malformation incidence of 1:531) in 114 patients, and Supplementary table 2 demonstrates that two or more coincident foregut malformations were observed in 51.5% of patients (26.3% with two, 11.3% with three, 4.4% with four, 0.88% with five, and 0.88% with six coincident foregut malformations).

Coincidence of cardiovascular and foregut malformations

Embryonic stage signaling between endoderm and mesoderm play complementary instructive roles during early cardiovascular and foregut organ development [11,13,26,27]. Therefore, we investigated the frequency of foregut malformations with cardiac or major vascular malformations. Foregut malformations had a coincidence of 35.1% with either major vascular or cardiac defects.

13.2% of patients with foregut malformations had an associated major vascular malformation (compared to <1%reported in the general population, Table 2). These incidences exceed those reported in the general population for major vascular defects including subclavian artery and vena caval anomalies [28, 29].

Similarly we found excess incidence of cardiac malformations in foregut malformation patients above the general population (Table 2). Specific structural defects include: atrial septal defects [30-32],

ventricular septal defects [30-34], atrioventricular canal, dextrocardia, tetralogy of Fallot, and double outlet right ventricle [31,35,36].

Neonatal morbidity and mortality of patients with foregut malformations

The aggregate mortality for neonates with congenital foregut malformations was 7% (Table 3a, patient characteristic data in Supplementary Table 3), compared with no mortality for the control patients with pyloric stenosis. Of those neonates with congenital foregut malformation who survived to discharge, 51% required ongoing feeding support (nasogastric tube or percutaneous gastrostomy tube) compared with 12.5% of pyloric stenosis patients. Twenty-seven percent of patients with a congenital foregut malformation required respiratory support (nasal cannula or tracheostomy) at discharge compared with 6.3% of pyloric stenosis patient controls. Length of stay was also longer compared to the pyloric stenosis cohort (median [IQR] of 32 [18,87] days versus 5 [2,19] days versus 6.5 [3,26.5] days, respectively). Compared with controls, patients with a congenital foregut malformation diagnosis are at increased risk for considerably higher morbidity and mortality.

Table 3a summarized outcomes for the common foregut malformation diagnoses. Of these, malrotation had the lowest morbidity and mortality. Laryngomalacia, the next most frequent diagnosis had three times the median length of stay and a significantly increased proportion requiring feeding support at discharge when compared with pyloric stenosis controls. Esophageal

	N	%	Incidence (1:) This Report	Previously Reported	References
All CV Defects	**40**	**35.1**	**3**	**123-168**	Bound and Logan, 1977
All Major Vessel	**15**	**13.2**	**8**		
Aberrant Right Subclavian Artery	5	4.4	23	50-250	
All Vena Cava	6	5.3	19		
Left SVC only	0	0.0	NA	333	Mowery and others, 2006
Bilateral SVC	6	5.3	19	333	Albay and others, 2006
Left IVC	1	0.9	114	145	
Double IVC	0	0.0	NA	97	
Interrupted IVC+Azygous Continuation	1	0.9	114	1250	Ueda and others, 1983
AP Collateral	2	1.8	57	NA	
PAPVR	1	0.9	114	12500	http://emedicine.medscape.com
Hypoplastic Aortic Arch	1	0.9	114	NA	
All Valves	**3**	**2.6**	**38**		
Pulm Valve Stenosis	3	2.6	38	1000-2000	http://www.pediatricheartspecialists.com
All Septal Defects	**31**	**27.2**	**4**		
ASD	15	13.2	8	167-2122	Bound and Logan, 1977
VSD	14	12.3	8	19-422	Meberg, 2008
AVC	2	1.8	57	2222	Bound and Logan, 1977
All Other CHDs	**3**	**2.6**			
Dextrocardia	1	0.9	114	12019	Bohun, 2007
Tet of Fallot	1	0.9	114	238-2518	Bound and Logan, 1977
DORV	1	0.9	114	11222	Mitchell and others, 1971
All patients with foregut malformations	**114**				

Table 2: Incidence of cardiac or major vascular anomalies in the foregut malformation population.

atresia-tracheoesophageal fistula, duodenal atresia, and congenital diaphragmatic hernia all had considerably higher length of stay as well as higher proportions requiring feeding and respiratory support at discharge.

We further compared the outcomes for the diagnoses in table 3a separated in two subgroups: foregut malformations in combination ("multiple") and those that occur as the patient's sole foregut malformation ("isolated"; Table 3b). Length of stay and need for respiratory and/or feeding support were highest for CDH and lowest for malrotation (Table 3b). Patients with any isolated foregut defect had shorter length of stay as well as lower need for feeding and/or respiratory support at discharge compared to patients with multiple congenital foregut defects (Table 3b). Length of stay was significantly increased for multiple categories of malrotation and laryngomalacia when compared to patients with these diagnoses in isolation. Trends toward increased feeding and respiratory support were seen in the multiple diagnosis category for malrotation, laryngomalacia, EA-TEF, CDH, and duodenal atresia. Thus foregut defects in isolation convey less morbidity than when present in combination for patients.

Discussion

We took advantage of our population-based, geographically defined service area to generate the incidence and associated morbidity and mortality of congenital foregut malformations. We are the first to report the aggregate foregut malformation incidence of 1 in 801, which places aggregate foregut field defects among the more common congenital birth defects such as cleft lip/palate (1 in 940) and Down syndrome (1 in 737) [37]. We found airway malacias to be the most common congenital foregut malformations and provide previously unreported incidences of other less common malformations (esophageal web, bronchus suis, sequestration, microgastria, and annular pancreas).

We note that the majority of foregut malformation incidences

fell below published frequencies (Table 1). This is likely due to our inclusion of foregut diagnoses (e.g., congenital hypothyroidism) that do not always obligate admission tertiary care center NICU. It is also possible that our region may have generally lower incidences for at least some of these conditions. In addition, we only included neonates who survived birth and transfer for admission to the CCHMC NICU; thus more severe, lethal malformations were likely missed. Two exceptions found to this study trend were: (1) duodenal atresia which had an incidence similar to those previously published by other epidemiologic studies [38, 39] and (2) congenital diabetes mellitus, which occurs once in 400,000 patients (which exceeds the number of patients evaluated by this study) [40]. The incidences reported here may be most relevant in terms of estimating the size of the clinically significant patient populations needed for future molecular studies.

Some conditions (particularly the airway malacias–laryngomalacia, tracheomalacia, and bronchomalacia) have been argued to reflect postnatal airway injury rather than primary fetal malformation [41]. This study revealed several instances, however, where the clinical symptoms and diagnosis preceded any possible airway trauma (e.g., intubation and mechanical ventilation, data not shown). Future work will focus on the aggregate incidence of these conditions as well as on establishing whether or not their diagnosis preceded any observable postnatal airway injury.

All the associated foregut malformations noted in our cohort have been previously noted in other research. Airway malacias (laryngomalacia, tracheomalacia, bronchomalacia) coincided: (1) with one another [42], (2) with esophageal atresia and tracheoesophageal fistula [43], and (3) with congenital diaphragmatic hernia [44]. We also observed esophageal atresia with tracheoesophageal fistula frequently as expected from previous reports [45], and annular pancreas in 18% of the eleven duodenal atresia patients [39, 46]. We conclude that foregut malformations often coincide, although no new associations were identified here. These data support the idea of

a) Aggregate Congenital Foregut Malformation Neonatal Morbidity and Mortality with Diagnosis Subgroup[a] Comparison to Pyloric Stenosis.

	All congenital foregut malformations N=114	Most common congenital foregut diagnoses[a]					Pyloric stenosis N=16
		Malrotatio N=20	Laryngomalacia N=18	EA-TEF[b] N=12	Duodenal Atresia N=5	CDH[b] N=4	
Admission Day of Life, median [IQR]	1 [0,9]	1.5 [1,5]	3.5 [1,23]	0 [0,2][d]	0 [0,1]	0 [0,0.5]	26 [13,55]
Length of stay, median [IQR]	32 [18,87]	17 [7,27]	21.5 [9,44]	24 [20,31.5]	43 [36,64]	20.5 [12.5,27]	6.5 [3,26.5]
Mortality, n (%)	8 (7)	1 (5)[c]	0	1 (8.3)[c]	1 (20)[c]	2 (50)[c]	0
Discharged with:							
Feeding support, n (%)	53 (51)	0[c]	11 (61.1)[d]	3 (27.3)[c]	1 (25)[c]	1 (50)[c]	2 (12.5)
Respiratory support, n (%)	28 (27)[c]	0[c]	3 (16.7)[c]	1 (9.1)[c]	0[c]	1 (50)[c]	1 (6.3)

[a]Diagnosis subgroups do not include infants with multiple foregut diagnoses
[b]Abbreviations: EA-TEF=Esophageal Atresia and Tracheoesophageal Fistula, CDH=Congenital Diaphragmatic Hernia
[c]Fisher's Exact test
[d]Significantly differs from Pyloric stenosis after adjusting for multiple comparisons, p ≤ 002

b) Congenital Foregut Malformation Neonatal Morbidity and Mortality: Isolated vs Multiple Malformations.

	All congenital foregut malformations		Malrotation		Laryngomalacia		EA-TEF[a]	
	Isolated	Multiple	Isolated	Multiple	Isolated	Multiple	Isolated	Multiple
N	76	38	20	5	18	11	12	9
Admission Day of Life, median [IQR]	2 [0,10]	1 [0,8]	1.5 [1,5]	0 [0,1]	3.5 [1,23]	8 [0,35]	0 [0,2]	0 [0,0.5]
Length of stay, median [IQR]	24 [11.5,43.5]	99 [49,164][c]	17 [7,27]	62 [46,78][c]	21.5 [9,44]	98 [50,193][c]	24 [20,31.5]	67 [46,111]
Mortality, n (%)	5 (6.6)	3 (7.9)[b]	1 (5)	1 (20)[b]	0	0	1 (8.3)	1 (11.1)[b]
Discharged with:	70	34						
Feeding support, n (%)	24 (34.3)	29 (85.3)[c]	0	3 (75)[b]	11 (61.1)	11 (100)[b]	3 (27.3)	4 (57.1)[b]
Respiratory support, n (%)	11 (15.7)	17 (50)[c]	0	1 (25)[b]	3 (16.7)	8 (72.7)[b]	1 (9.1)	1 (14.3)[b]

[a]Abbreviations: EA-TEF=Esophageal Atresia and Tracheoesophageal Fistula, CDH=Congenital Diaphragmatic Hernia
[b]Fisher's Exact test
[c]Significantly differs from isolated diagnosis after adjusting for multiple comparisons, p ≤ 002

	Duodenal Atresia		CDH[a]	
	Isolated	Multiple	Isolated	Multiple
N	5	6	4	7
Admission Day of Life, median [IQR]	0 [0,1]	0 [1,2]	0 [0,0.5]	0 [0,0]
Length of stay, median [IQR]	43 [36,64]	67 [34,256]	20.5 [12.5,27]	187 [119,255]
Mortality, n (%)	1 (20)	1 (16.7)[b]	2 (50)	0[b]
Discharged with:				
Feeding support, n (%)	1 (25)	4 (80)[b]	1 (50)	7 (100)[b]
Respiratory support, n (%)	0	3 (60)[b]	1 (50)	4 (57.1)[b]

[a]Abbreviations: EA-TEF=Esophageal Atresia and Tracheoesophageal Fistula, CDH=Congenital Diaphragmatic Hernia
[b]Fisher's Exact test
[c]Significantly differs from isolated diagnosis after adjusting for multiple comparisons, p ≤ 002

Table 3: Patient characteristics, morbidity and mortality.

"field defect"[47,48]; that foregut malformations arise early in the first trimester from defective development of a common progenitor tissue that gives rise to more than one foregut organ [12, 49]. In our study, only two foregut malformations occurred exclusively as isolated defects in our population: Congenital Pulmonary Adenomatoid Malformation (CPAM) and bronchopulmonary sequestration. They have been associated with other congenital foregut malformations in previous epidemiologic studies [50,51], and are not reported here here likely due to their low coincidence in our relatively small study population. However, molecular and developmental links between these associations will be a ripe area for future investigation [52].

We observed an increased coincidence of cardiovascular malformations with congenital foregut malformations, particularly vena caval anomalies (bilateral SVC or Left SVC) and septal defects (ASD and VSD). 43% of 21 patients with esophageal atresia-tracheoesophageal fistula had cardiovascular malformations (ASD, VSD, aberrant subclavian, aberrant vena cava), consistent with

previous reports [53]. Fifty-five percent of the 11 patients with duodenal atresia had coincident cardiovascular malformations (including ASD, VSD, aberrant subclavian, aberrant vena cava, anomalous pulmonary venous return); these patients all had trisomy 21 (data not shown), which has well established associated cardiovascular anomalies [54].

Nearly one third (29%; 14/48) of NICU patients with a diagnosis of airway malacias had a concurrent cardiovascular defect (ASD in 6, VSD in 7, aberrant subclavian artery in 3, aberrant superior vena cava in 4, tetralogy of Fallot in 1), and these associations have not previously been reported. This was surprising given the perception that these anomalies might arise not as congenital malformations but as a consequence of incidental airway injury or trauma which would come from the respiratory management required for these patients [41]. The observed coincidence instead provides clinical evidence supporting a possible developmental association between these different organ malformations.

Other foregut malformation diagnoses observed to be

associated with cardiovascular malformations included congenital diaphragmatic hernia [55], bronchus suis, annular pancreas [56], and congenital hypothyroidism [57, 58]. We conclude that cardiovascular malformations have a high coincidence with congenital foregut organ malformations, consistent with the concept that these malformations may well be linked through a shared developmental mechanism [4, 59].

Neonatologists are often the first physicians to care for many patients with congenital foregut malformations. Their prompt recognition and treatment as well as the provision of objective outcome data for anticipatory guidance will be of great value to the patients and their families. This study is the first of its type to quantify the morbidity and mortality of congenital foregut malformations in the neonate. In the outcome analysis undertaken here, we quantified the increased neonatal morbidity with these conditions. This work underscores the severe phenotype and clinical course of these conditions and highlights the increased burden to the health care system in general from neonatal foregut malformations. In conclusion, we have provided both anticipatory guidance related to these malformations as well as impetus for further research into their cause, management, and prevention.

Acknowledgments

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