Congenital Heart Defects and Major Structural Noncardiac Anomalies, Atlanta, Georgia, 1968 to 2005

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Objective To identify the proportion of major structural noncardiac anomalies identified with congenital heart defects (CHDs).

Study design Records of infants with CHDs in the Metropolitan Atlanta Congenital Defects Program who were born during the period 1968 through 2005 were classified as having isolated, syndromic, multiple CHD (ie, having an unrecognized pattern of multiple congenital anomalies or a recognized pattern of multiple congenital anomalies of unknown etiology), or laterality defects. Frequencies of associated noncardiac anomalies were obtained.

Results We identified 7984 live-born and stillborn infants and fetuses with CHDs. Among them, 5695 (71.3%) had isolated, 1080 (13.5%) had multiple, 1048 (13.1%) had syndromic, and 161 (2.0%) had laterality defects. The percentage of multiple congenital anomalies was highest for case with atrial septal defects (18.5%), cardiac looping defects (17.2%), and conotruncal defects (16.0%), and cases with atrioventricular septal defects represented the highest percentages of those with syndromic CHDs (66.7%).

Conclusions Including those with syndromes and laterality defects, 28.7% of case infants with CHDs had associated major noncardiac malformations. Thus, infants with CHDs warrant careful examination for the presence of noncardiac anomalies. *(J Pediatr 2011;159:70-8)*.

Congenital heart defects (CHDs), which occur among approximately 3 to 9 of every 1000 live births, are the most common type of birth defects[1-3] and contribute significantly to infant morbidity and mortality.[4] Although in most instances the heart defects are isolated, an important proportion of patients with CHDs have additional noncardiac major malformations.[1] Some of these case patients have chromosomal or single-gene determined syndromes and others have not previously defined patterns of multiple congenital anomalies (MCAs).

In previously selected reports, proportions of additional structural noncardiac anomalies among children with CHDs range from 14.5% to 66.0%,[5,6] depending mainly on the type of ascertainment (Table I). The highest proportion of additional anomalies (45.9% to 66.0% in selected reports) has been identified in studies based on autopsy reports,[5,7] followed by clinical studies (14.5% to 30.1%)[8,9] and epidemiological studies (16.9% to 25.8%).[10-12] Also, the reported prevalence of the different types of cooccurring anomalies varies significantly. For example, Hanna et al[1] identified 5.2% of case patients with chromosomal and single-gene syndromes and 18.3% with undefined patterns of MCAs, and Ferencz et al[13] reported 17.3% of case patients with chromosomal and single-gene syndromes and 5.9% with MCAs. Regarding the type of additional noncardiac defects, Güçer et al[7] found that the most frequently occurring noncardiac defects were craniofacial (19.7%), genitourinary (15.1%), and musculoskeletal (13.4%); however, Calzolari et al[12] reported that the most frequently found noncardiac defects were musculoskeletal (25.3%), genitourinary (22.9%), and gastrointestinal (11.5%).

The wide variation in the proportion and type of MCAs reported in studies of CHDs has been due mainly to differences in the types of case ascertainment and defect classifications. Clarification of some of these differences could be obtained from a population-based study using data from an active surveillance system in which clinicians classify cardiac and noncardiac defects in a standardized manner. Findings from such a study might help to better guide studies of the etiologies of CHDs, which remain largely unknown[4]; to understand the pathogenesis of CHDs; to study health outcomes among people with CHDs; and to counsel affected families.

ASD	Atrial septal defect	MCA	Multiple congenital anomaly
AVSD	Atrioventricular septal defect	RVOTO	Right ventricular outflow tract obstruction
CHD	Congenital heart defect		
HLHS	Hypoplastic left heart syndrome	NTD	Neural tube defect
LVOTO	Left ventricular outflow tract obstruction	STS	Society of Thoracic Surgeons
		TOF	Tetralogy of Fallot
MACDP	Metropolitan Atlanta Congenital Defects Program	TOP	Termination of pregnancy
		VSD	Ventricular septal defect

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Table I. Selected literature review of congenital heart defects and associated noncardiac congenital anomalies

Author	Type of study	Sample size	MCA* %	Syndrome† %	Total‡ %
Hoffman et al (1978)	Clinical series 1959–1966	194	NA	NA	30.1
Kramer et al (1987)	Clinical series 1981–1982	1016	7.7	13.3	NA
Greenwood et al (1975)	Clinical series 1968–1972	1566	16.8	8.4	25.2
Eskedal et al (2004)	Clinical series 1990–1999	3527	NA	NA	20.3
Wojtalik et al (2005)	Clinical series 1997–2002	1856	4.5	NA	NA
Dilber and Malćić (2009)	Clinical series 2002–2007	1480	NA	NA	14.5
Stoll et al (1989)	Epidemiological 1979–1986	801	14.2	11.5	25.7
Ferencz et al (1997)	Epidemiological 1981–1987	3834	5.9	17.3	23.3
Hanna et al (1994)	Epidemiological 1974–1978	388	18.3	5.2	23.5
Pradat (1997)	Epidemiological 1981–1990	2618	14.1	13.3	NA
Grech and Gatt (1999)	Epidemiological 1990–1994	231	6.5	10.4	16.9
Calzolari et al (2003)	Epidemiological 1980–1994	1549	11.6	9.8	25.8
Bosi et al (2003)	Epidemiological 1980–2000	2456	10.0	9.1	24.0
Stephensen et al (2004)	Epidemiological 1990–1999	740	12.0	4.9	16.9
Meberg et al (2007)	Epidemiological 1982–2005	662	10.1	8.5	22.0
Tennstedt et al. (1999)	Postmortem 1991–1997 (induced abortions, spontaneous abortions, stillbirths)	129	NA	33.0	66.0
Güçer et al (2005)	Postmortem autopsy of live born infants 1977–2002	305	NA	NA	45.9

*Multiple congenital anomalies.
†Chromosomal syndromes, single-gene disorders, and recognized conditions.
‡Total percent is the summary of multiple congenital anomalies, chromosomal syndromes, single-gene disorders, and recognized conditions.

Our study identified the proportion of infants with additional noncardiac anomalies and characterized the types and distributions of these entities among case infants with CHDs in a large, population-based birth defects surveillance system.

Methods

We identified all live-born and stillborn infants and elective terminations of pregnancy (TOPs) with diagnosed CHDs delivered during the period 1968 through 2005 that were ascertained by the Metropolitan Atlanta Congenital Defects Program (MACDP). MACDP was granted authority to conduct birth defect surveillance in the five central counties of metropolitan Atlanta in collaboration with and on behalf of the Georgia Division of Public Health by the Georgia Department of Human Resources and has CDC's Institutional Review Board approval. MACDP is an ongoing, population-based birth defects surveillance system established in 1967 to actively monitor birth defects among the offspring of women living in any of the five central counties of metropolitan Atlanta, Georgia, at the time of delivery. The program routinely collects data on clinical and demographic characteristics of live-born and stillborn infants and pregnancies terminated at or after 20 weeks of gestation that present with structural birth defects. Major structural defects, chromosomal abnormalities, and clinical syndromes diagnosed within 6 years of delivery are included in MACDP. The defects are coded using a modified 6-digit code from the *International Classification of Diseases, Ninth Revision, Clinical Modification* and the *British Paediatric Association Classification of Diseases* developed for MACDP. Further details about this system have been published elsewhere.[14]

All MACDP records of infants with cardiac defect 6-digit codes were reviewed and classified by experts in pediatric cardiology, according to a standard clinical nomenclature adapted from the Society of Thoracic Surgeons (STS) and a morphogenetic three-level classification system previously described.[15] The grouping of CHDs into higher-order aggregation levels aids in monitoring and research; in the current study, nine major broad categories were used—cardiac looping defects, conotruncal defects, atrioventricular septal defects (AVSDs), left ventricular outflow tract obstructive defects (LVOTOs), right ventricular outflow tract obstructive defects (RVOTOs), atrial septal defects (ASDs), ventricular septal defects (VSDs), cell growth defects, and Ebstein anomaly.[16] Specific cardiac defects included in the broad STS categories are presented in the **Appendix** (available at www.jpeds.com). Newborn conditions and those of prematurity were not considered structural abnormalities; patent ductus arteriosus was only counted as a CHD if occurring in nonpremature infants, persisting beyond 6 weeks of life, and not maintained patent for another cardiac condition. Inlet-type VSDs were included in the AVSD category and malaligned or conoventricular-type VSDs in the conotruncal category. Using STS nomenclature, most case infants had only one CHD. However, if a case infant had more than one independent lesion, each CHD was counted separately.[15]

Clinical information was reviewed by a clinical geneticist (J.F.), who classified cases as having isolated, MCA, or syndromic CHDs based on etiology and the presence and pattern of major structural noncardiac anomalies. Noncardiac anomalies were defined as "major" if they had surgical, medical, or serious cosmetic importance.[17] Cases were considered "isolated" when no noncardiac major malformations were present; cases were considered MCAs when at least one major additional noncardiac malformation was found. Also, cases with known associations (eg, the vertebral, anal, cardiac, tracheo-esophageal, renal, and limb association) were classified as having MCAs. Those with