Original Article

Prevalence of Extracardiac Anomalies in Patients With Congenital Heart Defects

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ABSTRACT

Background: Various extracardiac disorders are associated with congenital heart defect (CHD) at varying prevalence rates (7%–50%). Over the years, numerous studies worldwide have investigated these associations. This study aimed to examine the prevalence of extracardiac anomalies in children with CHD in Isfahan, one of Iran's largest cities.

Methods: This cross-sectional study was conducted in Isfahan, Iran, from 2020 through 2022, involving 750 infants under 1 year old diagnosed with CHD. Pediatric cardiologists performed echocardiography to evaluate the cardiovascular system and detect CHD. Most participants were referred for cardiac examinations due to abnormalities detected during physical examinations of skin, cerebral, spinal cord, abdominal, and urinary tract regions. Patients exhibiting signs of a syndromic disorder were also referred for CHD evaluation.

Results: Out of 750 infants with confirmed CHD, 241 (32.13%) presented at least 1 extracardiac malformation. Ninety (37.7%) had craniofacial malformations, with 66.7% having cleft palate with or without cleft lip. Forty-eight patients (19.9%) had genetic syndromes, most commonly Down syndrome (56.5%), and 46 (19.8%) had gastrointestinal abnormalities, including intestinal or esophageal atresia.

Conclusions: The prevalence of extracardiac anomalies in patients with CHD is significant, and these patients are at an increased risk of mortality and morbidity throughout their lives. Implementing a screening program could effectively prevent further complications associated with the late diagnosis of these anomalies. ***(Iranian Heart Journal 2024; 25(3): 6-12)***

KEYWORDS: Extracardiac anomalies, Congenital heart diseases, Echocardiography

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Congenital heart defect (CHD) is a macroscopic structural disorder of the heart and blood vessels within the chest, potentially impacting cardiac function. This anomaly develops during the embryonic period, with a reported prevalence of 4 to 19 per 1000 live births. [1] CHD is the most common congenital disorder in humans (40%), and its prevalence is increasing due to improved

diagnostic capabilities. [2-4] Extracardiac anomalies (EAs) are macroscopic structural disorders of other organs outside the heart that develop before birth but may be asymptomatic in the early neonatal period. Several extracardiac disorders, such as intra-abdominal and cerebral anomalies with or without genetic syndromes, are associated with CHD at varying prevalence rates (7%–50%). [1] Timely and early diagnosis of these concurrent disorders may reduce mortality and morbidity.

Numerous studies worldwide have investigated these associations over the years. However, to our knowledge, no similar study has been conducted in Iran. Thus, we decided to examine the prevalence of EAs in children with CHD in Isfahan.

METHODS

This cross-sectional study was conducted in Isfahan, Iran, from 2020 through 2022. The study included 750 infants under 1 year old diagnosed with CHD. After the procurement of approval from the Ethics Committee at Isfahan University of Medical Sciences (Isfahan, Iran) (IR.MUI.MED.REC.1399.1079), informed consent was acquired from the parents of participating infants.

The inclusion criterion was infants under 1 year of age with CHD. The exclusion criteria were as follows:

1. Infants diagnosed with CHD before birth or immediately after birth who died before undergoing ultrasound and other necessary examinations.
2. Infants diagnosed with CHD before birth or immediately after birth whose parents declined participation in the research project.
3. Infants diagnosed with mitral valve prolapse, patent ductus arteriosus (PDA) in premature infants, and patent foramen ovale.

Pediatric cardiologists used echocardiography to assess the cardiovascular system and detect CHD in newborns and infants younger than 1 year of age. Most participants were referred to our heart clinic by general pediatricians, neonatologists, pediatric surgeons, neurologists, and nephrologists due to abnormalities detected during physical examinations at birth or later in the skin, cerebral and spinal cord, digestive system and abdomen, or urinary tract regions. Patients exhibiting signs of a syndromic disorder were also referred for CHD evaluation.

A smaller number of patients were directly and initially referred to our cardiology clinic for CHD evaluation. During their physical examinations, an abnormal sign was found after their CHD diagnosis, prompting further evaluation, including ultrasonography at Imam Hossein Children's Hospital in Isfahan. Patients with any EA were enrolled in our study. We investigated the prevalence of noncardiac anomalies in patients with CHD based on these findings.

RESULTS

Out of 750 infants and babies with confirmed CHD, 509 (67.86%) had isolated CHD, while 241 (32.13%) presented at least 1 extracardiac malformation in addition to CHD. Among those with EAs, 90 (37.7%) had craniofacial malformations, with 66.7% having cleft palate with or without cleft lip. Forty-eight patients (19.9%) had genetic syndromes, with Down syndrome being the most common (56.5%). Furthermore, 46 patients (19.8%) had gastrointestinal abnormalities, including intestinal or esophageal atresia. Skin and nervous system malformations were the least prevalent defects observed. Table 1 summarizes the additional extracardiac malformations observed. Among these 241 cases, the most prevalent CHD cases were ventricular septal defect (VSD) and atrial septal defect (ASD), occurring in 50.2% and 49.4% of cases,

respectively. The least common types included Ebstein anomaly, anomalous pulmonary venous connections, aortopulmonary window, and double aortic arch. Table 2 depicts the overall prevalence of various CHD types. Table 3 outlines the frequency of extracardiac malformations in children with CHD.

Table 1: Extracardiac Malformations in 241 Cases With Congenital Heart Defects

Systems	Number	Percentage (%)
Craniofacial	91	37.7
Any syndrome	48	19.9
Gastrointestinal	46	19.8
Musculoskeletal	26	10.8
Genitourinary	22	9.1
Skin	8	3.3
Respiratory	7	2.9
Central Nervous System	7	2.9
Eyes	3	1.2

Table 2: The Distribution of Major Congenital Cardiac Defects in 241 Cases With 1 or More Extracardiac Anomalies

CHD Types	Number	Percentage (%)
VSD	121	50.2
ASD	119	49.4
PDA	59	24.5
PS	22	9.1
AVSD	13	5.4
TOF	11	4.6
COA	11	4.6
HLHS	8	3.3
DORV	6	2.5
PA	6	2.5
MS	4	1.7
PPS	3	1.2
Situs inversus totalis	3	1.2
DTGA	3	1.2
BAV	3	1.2
AS	2	0.8
Ebstein	1	0.4
Isolated dextrocardia	1	0.4
TAPVC	1	0.4
AP window	1	0.4
PAPVC	1	0.4
Double aortic arch	1	0.4

APW: aortopulmonary window, ASD: atrial septal defect, AS: aortic stenosis, AVSD: atrioventricular septal defect, BAV: bicuspid aortic valve, COA: coarctation of the aorta, DORV: double-outlet right ventricle, DTGA: dextro-transposition of the great arteries, HLHS: hypoplastic left heart syndrome, MS: mitral stenosis, PDA: patent ductus arteriosus, PA: pulmonary atresia, PAPVC: partial anomalous pulmonary venous connection, PPS: peripheral pulmonary stenosis, PS: pulmonary stenosis, TAPVC: total anomalous pulmonary venous connection, TOF: tetralogy of Fallot, VSD: ventricular septal defect

Table 3: The Frequency of Extracardiac Malformations in 241 Children With Congenital Heart Defects

	Syndromes		Craniofacial System		Gastrointestinal System		Respiratory System		Central Nervous System		Musculoskeletal System		Genitourinary System		Skin		Eyes	
ASD	22	18%	40	34%	27	23%	2	2%	6	5%	11	9%	3	3%	5	4%	0	0%
AS	1	50%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	1	50%
VSD	23	19%	29	24%	34	28%	4	3%	2	2%	15	12%	7	6%	1	1%	1	1%
PDA	18	31%	11	19%	20	34%	2	3%	1	2%	10	17%	2	3%	2	3%	0	0%
MS	0	0%	2	50%	1	25%	0	0%	0	0%	0	0%	1	25%	0	0%	0	0%
PPS	0	0%	2	67%	1	33%	0	0%	0	0%	0	0%	0	0%	1	33%	0	0%
TOF	3	27%	3	27%	0	0%	1	9%	0	0%	1	9%	1	9%	0	0%	0	0%
Ebstein	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Situs inversus totalis	3	100%	1	33%	1	33%	0	0%	0	0%	1	33%	0	0%	0	0%	0	0%
HLHS	4	50%	4	50%	2	29%	0	0%	0	0%	3	43%	0	0%	0	0%	0	0%
DORV	1	17%	4	67%	1	17%	0	0%	0	0%	0	0%	0	0%	1	17%	0	0%
DTGA	0	0%	1	33%	1	33%	0	0%	0	0%	0	0%	1	33%	1	33%	0	0%
PA	0	0%	2	33%	3	50%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
COA	2	18%	1	9%	1	9%	0	0%	0	0%	1	9%	2	18%	2	18%	0	0%
Isolated dextrocardia	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
AVSD	10	77%	0	0%	5	38%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
TAPVC	1	100%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
AP window	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
PS	6	27%	5	23%	7	32%	0	0%	0	0%	1	5%	2	9%	0	0%	0	0%
BAV	2	67%	0	0%	0	0%	0	0%	0	0%	0	0%	1	33%	0	0%	0	0%
PAPVC	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Double aortic arch	0	0%	0	0%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%

APW: aortopulmonary window, ASD: atrial septal defect, AS: aortic stenosis, AVSD: atrioventricular septal defect, BAV: bicuspid aortic valve, COA: coarctation of the aorta, DORV: double-outlet right ventricle, DTGA: dextro-transposition of the great arteries, HLHS: hypoplastic left heart syndrome, MS: mitral stenosis, PDA: patent ductus arteriosus, PA: pulmonary atresia, PAPVC: partial anomalous pulmonary venous connection, PPS: peripheral pulmonary stenosis, PS: pulmonary stenosis, TAPVC: total anomalous pulmonary venous connection, TOF: tetralogy of Fallot, VSD: ventricular septal defect

DISCUSSION

In our study, the prevalence of EAs in CHD patients was 32%. Cleft palate with or without cleft lip was the most common EA associated with CHD. Genetic syndromes and gastrointestinal malformations were the next most prevalent EAs identified. Among genetic disorders, Down syndrome was most commonly associated with CHD. Isolated or combined VSD, ASD, and PDA were the most frequently observed CHDs associated with EAs.

Over the years, numerous studies conducted in various countries have highlighted the prevalence of EAs in association with CHD. These published results are presented in chronological order below.

A study conducted in Chile in 1986 by Julian and Farrú [5] estimated the prevalence of EAs in CHD patients at 31.9%, with 22.7% having some form of syndromic disorder. The most common associations were reported in the gastrointestinal, musculoskeletal, and genitourinary systems. Nonetheless, the authors did not specify which types of CHDs were more closely related to these EAs. Additionally, their diagnostic methodology was not described. In 1987, Ferencz et al [6] conducted a study in the United States, revealing that 26.8% of babies born with CHD had EAs, and only

8.3% of those cases were not associated with chromosomal anomalies or other syndromes. Central nervous system malformations and eye disorders were the most frequently observed anomalies.

In 1987, Kramer et al [7] in Germany found that 13.3% of CHD cases were associated with syndromic disorders, and in 7.7% of cases, EAs were associated with CHD without a syndromic disorder. Musculoskeletal, central nervous system, eye, and ear anomalies were more prevalent than other anomalies in this study. Tetralogy of Fallot (TOF) was the most common CHD associated with EA. In our study, TOF was detected in 4.6% of cases. In 1989, Stoll et al [8] in France reported that 25.7% of babies with CHD, including fetuses and stillbirths, had at least 1 type of EA, and 11.5% of CHD cases were associated with syndromic disorders. The most common EAs were related to the urinary system (21.4%) and the gastrointestinal system (19.6%). Murugasu et al [9] in Singapore reported a prevalence of significant urinary system disorders associated with CHD at 11.9%. In our study, these anomalies were detected in 9.1% of cases.

In 1998, Pradat [10] in Sweden reported that 25.7% of children with CHD had an EA, with the strongest association observed between atrioventricular septal defects and spleen abnormalities.

A study in Malta by Grech and Gatt [11] in 1999 reported a 17% prevalence of EA in CHD patients, including 9% with chromosomal disorders. The most common EAs were musculoskeletal abnormalities.

Two studies conducted in Italy in 2003 by Bosi et al [12] and Calzolari et al [13] reported the prevalence of EAs as 24% and 26%, respectively. Similar to our findings, VSD, ASD secundum, and complex cardiac walls were most frequently associated with EAs. The most common EAs included musculoskeletal system abnormalities (25.3%), genitourinary abnormalities (22.9%), and gastrointestinal system abnormalities (11.5%). Additionally, 9.1% of babies had chromosomal disorders.

In 2004 and 2007, Eskedal et al [15] and Meberg et al [14] in Norway reported the prevalence of EAs as 20% and 22%, respectively. The most common EAs were gastrointestinal disorders, particularly small intestine anomalies and esophageal atresia. The most frequent associations were observed with atrioventricular septal defects, ASD, TOF, and single ventricles.

In Iceland, Stephensen et al [16] demonstrated a 12% prevalence rate of EAs in 2004, with the urinary, genital, and digestive systems being most commonly affected.

Güçer et al [17] conducted a study in Turkey in 2005 on 3320 autopsies and reported a 1.9% prevalence rate of CHD, with at least 1 EA present in 45.9% of the cases. VSD was the most commonly observed CHD (15.3%). Craniofacial anomalies were the most common (19.7%), and 15.1% of cases involved the genitourinary system. Spleen malformations were significantly more prevalent in single ventricle cases, while arterial trunk defects were predominantly associated with urinary, genital, and digestive system disorders.

Miller et al [18] conducted a study in the United States in 2011 involving 7984 patients with CHD. They found that 13.5% of cases were associated with EAs, and 13.1% had some form of syndrome. The prevalence of multiple congenital disorders was higher in patients with interatrial communication (18.5%), cardiac malrotation (17.2%), and conus arteriovenous defects (16%). The most common EAs involved the skeletal (35%), gastrointestinal (25.2%), and urinary (23.1%) systems. The authors reported a higher prevalence of hydronephrosis or urethral atresia in association with cardiac malrotation, obstruction of the right ventricular outflow

tract, and interatrial and interventricular communication.

In Saudi Arabia in 2012, Alabdulghader [19] reported that 28% of CHD patients had EAs. The most common anomaly was atrioventricular wall defect (72%). Syndromic disorders were the most prevalent EAs associated with CHD (37%). Ahmadi et al [20] evaluated the early results of the Persian Registry of Cardiovascular Disease, Congenital Heart Disease (PROVE, CHD) in Isfahan, Iran in 2020. Among 1252 patients with CHD, the most common cardiac diagnoses were VSD (39.3%), ASD (29.7%), PDA (25.4%), pulmonary stenosis (11.0%), TOF (6.1%), coarctation of the aorta (5.4%), and aortic stenosis (5.1%). Their findings align with our study concerning the prevalence of CHD types; however, the authors did not assess the presence or absence of any EAs.

As previously mentioned, several studies have employed various diagnostic methods, including cardiac catheterization and computed tomography angiography, resulting in a range of findings. In our study, we utilized noninvasive and more readily available techniques, such as echocardiography for detecting CHDs and physical examination and ultrasonography for identifying EAs. Despite these differences in methodology, our final results are consistent with those of other studies. Notably, only 1 study [17] found craniofacial anomalies to be the most common EAs, chiming with the findings of our study. Nevertheless, the prevalence and types of EAs varied across different regions. Therefore, conducting region-specific studies is crucial to better understand these variations.

Our study had some limitations. Firstly, we examined only infants and children under 1 year of age, resulting in a relatively small study population. Secondly, we did not perform genetic testing on all patients suspected of having chromosomal abnormalities, as the high cost of testing was a barrier for some parents.

CONCLUSIONS

The prevalence of EAs in patients with CHD is substantial and varies across different countries. Patients with both CHD and EAs face a higher risk of mortality and morbidity throughout their lives, including during cardiac surgery. Thus, early screening and identification of these disorders using common noninvasive methods, such as abdominal ultrasound, is crucial and cost-effective. This is not only due to the prevalence of EAs but also because many of these disorders may be asymptomatic. Developing a screening program could be beneficial in preventing further complications associated with late diagnosis of these anomalies.

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Conflict of Interest: None

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