Noncardiac malformations in congenital heart disease: A retrospective analysis of 305 pediatric autopsies

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Congenital heart disease (CHD) is one of the important groups of birth defects and contributes significantly to infant mortality. Extracardiac anomalies occur in 15-45% of cases with CHD. In this retrospective study, autopsies of cases born alive and diagnosed as CHD between 1977-2002 at Hacettepe University İhsan Doğramacı Children's Hospital, Pediatric Pathology Department, were investigated. In this period, a total of 3320 autopsies were performed and the incidence of CHD was 9.1%. The most commonly encountered CHD was ventricular septal defect (VSD) (15.3%).

In 45.9% of cases, one or more extracardiac malformations were present. The most commonly encountered extracardiac malformation was craniofacial malformations. Less commonly seen were malformations of genitourinary, musculoskeletal, respiratory, gastrointestinal, central nervous systems and spleen anomalies.

Ventricular septal defect, atrial septal defect (ASD), aortic coarctation, single ventricle, pulmonary stenosis, hypoplastic right heart syndrome, double outlet right ventricle, ASD+VSD, aortic arcus anomalies, and right and left atrial isomerism cases were often (>50%) accompanied by extracardiac malformations. No extracardiac malformations were detected accompanying pulmonary atresia with intact interventricular septum, Ebstein malformation, and mitral stenosis (MS). Spleen malformation was significantly high in cases with single ventricle ($p<0.002$). The anomalies of the gastrointestinal and genitourinary systems were found to be frequently associated with conotruncal heart defects ($p<0.001$). In the group with transposition of the great arteries, noncardiac malformations were present in only three cases (10%), differing from the rest of the material ($p<0.001$).

In conclusion, when a heart malformation is detected in a patient, a detailed investigation should be done on extracardiac malformations or vice versa. Proper identification and treatment of CHD early in the prenatal period will save the family from the economic and emotional burden caused by having such a child with CHD.

Key words: congenital heart defect, noncardiac malformation, association, necropsy examination, childhood.

Congenital heart diseases (CHD) represent one of the major groups of birth defects and make up approximately 1% of human malformations[1-3]. The total prevalence of CHD has been estimated at 3.9-11.9 per 1,000 live-born infants. The reported rates of CHD differ from one study to another because of variations in diagnostic and registration criteria and the percentage of prenatally diagnosed cases included[1,3]. CHDs contribute significantly to infant mortality because 10% of infant deaths are due to congenital malformations, and 50% of the latter are cardiovascular malformations[4].

In a substantial proportion of patients with CHD, an association with malformations in other organ systems has been identified[2-10]. A number of studies have attempted to unravel

the associations between specific cardiac defects and noncardiac malformations[3-10]. Among these associations, the only well-established ones are the association between Down syndrome and endocardial cushion defects (ECD) or ventricular septal defects (VSD), that between the agenesis of spleen and conotruncal anomalies and between limb reductions and septal defects in patients with autosomal dominant Holt-Oram syndrome[9,10]. Excluding the study by Lin and Perloff[11] reviewing all associations between upper limb defects and CHD in infants with chromosomal anomalies, the results of most of the studies were controversial and have yielded no clear-cut associations[12,13].

To our knowledge, there has been no series investigating the aforementioned associations in autopsies of children with CHD in Turkey. The main purpose of this study was to identify the noncardiac malformations associated with CHD and to determine if different types of CHDs are particularly related to a specific noncardiac malformation that would provide some additional knowledge about the pathogenesis of these associations. We also present our 25 years' experience on this subject as a referral center.

Material and Methods

During a 26-year period (1977 to 2002), 3,320 autopsies were studied in the section of, Pediatric Pathology at Hacettepe University İhsan Doğramacı Children's Hospital. Of these, 305 cases with CHD who were born alive were selected and evaluated retrospectively. Files of all cases were reviewed for age, gender, mother's age, consanguinity, history of a sibling with CHD, type and number of cardiac malformations, and extracardiac anomaly, and the relations between them were investigated. Clinical premortem diagnoses and, when available, the results of karyotyping were also evaluated. All external and internal anomalies of the cases were carefully detected, recorded and photographed. Following a gross systematic examination, the routine appropriate sections were done from all organs and the process was completed with the histopathological study and clinicopathological diagnosis.

Congenital heart disease is used to describe congenital structural anomalies of the heart and intrathoracic great vessels. Using the coding system of the International Society of Cardiology, 305 cases were classified into 23 groups: VSD, atrial septal defect (ASD), ECD, hypoplastic left heart syndrome (HLHS), hypoplastic right heart syndrome (HRHS), tetralogy of Fallot (ToF), patent ductus arteriosus (PDA), Ebstein anomaly (EA), truncus arteriosus (TA), pulmonary stenosis (PS), pulmonary atresia and intact interventricular septum (PA+IVS), pulmonary atresia and VSD (PA+VSD), ventricular septal defect + atrial septal defect (VSD+ASD), aortic stenosis (AS), coarctation of the aorta (CoA), transposition of great arteries (TGA), anomalies of pulmonary venous return (APVR), tricuspid atresia (TAt), mitral valve stenosis (MS), single ventricle (SV), double outlet right ventricle (DORV), and anomalies of the aortic arch, and malpositions[14]. Furthermore, a subgroup of conotruncal anomalies consisting of ToF, PA+VSD, TGA, DORV and anomalies of the aortic arch was separated.

Hearts with more than one lesion were classified according to the lesion with a higher morbidity and mortality. PDA was taken into consideration in cases born before 36 weeks of gestation and those under 14 days of age. Patients with VSD and mild PS were included in the VSD group. ECDs included both complete and incomplete forms. Malpositions covered situs inversus totalis, isolated dextrocardia, isolated levocardia and situs ambiguous.

Extracardiac anomalies were categorized in seven groups consisting of craniofacial anomalies, spleen anomalies, and malformations of respiratory, gastrointestinal, genitourinary, musculoskeletal and central nervous systems. Craniofacial anomalies were considered as microphthalmia, anophthalmia, optic nerve agenesis/hypoplasia, coloboma, corneal opacity, low-set ears, malformed ear helices, atypical facial appearance, cleft lip/palate, high-arched palate, and skin defects. Respiratory system anomalies included congenital diaphragmatic hernia, lung hypoplasia/agenesis, segment anomalies, tracheoesophageal fistula, and thymic anomalies. Gastrointestinal system malformations were Meckel's diverticula, duodenal/jejunal atresia, omphalocele, malrotation of the gut, duplication of the gut, biliary tract anomalies and anal atresia. Spleen malformations were evaluated as asplenia or polysplenia. Genitourinary system malformations were renal hypoplasia/agenesis, renal cortical cysts, dysplastic kidney, ureteropelvic junction stenosis/hydronephrosis, double ureters and collecting system, double renal arteries,

hypospadias, horseshoe kidneys and genital abnormalities (agenesis, micropenis, uterus bicornis). Microcephaly, hydrocephaly, agenesis of corpus callosum, meningomyelocele, encephalocele, olfactory nerve agenesis, Dandy-Walker malformation, lissencephaly and holoprosencephaly were detected as malformations of the central nervous system. Musculoskeletal malformations included anomalies of upper and lower extremities, hemivertebrae and joint dislocations.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) for Windows version 11.5 and Fisher's exact chi-square test.

Results

A congenital heart defect was found in 305 (9.1%) of the 3,320 autopsies performed during 1997-2002 in the Pediatric Pathology Unit at Hacettepe University İhsan Doğramacı Children's Hospital. The ages of the cases ranged from 1 day to 16 years with a median of 24 days. Of the patients, 186 (61%) were male, and 119 (39%) female.

Distribution of CHD

Ventricular septal defect (VSD) was the most common cardiac malformation (15.3%), followed by ASD and TGA at rates of 10.8% and 9.8%, respectively. The majority of ASDs were secundum type (88%). Table I gives the distribution of heart defects diagnosed at autopsy. All cases with TGA were d-transposition type and no corrected TGA was detected in our series. CoA was noted in 23/305 cases (7.5%). The most commonly encountered CoA was preductal type (70%) followed by juxtaductal and postductal CoA in 22% and 8% of the cases, respectively. Single ventricle was determined in 21 cases (7%), and 16 of them were of left ventricular type. Total APVR was observed in 8 patients (2.6%), all of which were cardiac or supracardiac type.

Malposition was present in 9 of 305 cases. Of these, two revealed left or right atrial isomerism (Ivemark syndrome). The patient with lvemark syndrome showed atrioventricular canal defect, dextrocardia, bilateral three-lobed lungs, persistent left superior vena cava, asplenia, intestinal malrotation and symmetric liver, while the case with left atrial isomerism had high-set VSD, polysplenia, bilateral two-lobed lungs, and intestinal malrotation. There was no isolated levocardia.

Table I. Distribution of Major Congenital Cardiac Defects in 305 Cases

Cardiac defect	Case no.	(%)
VSD	47	15.3
ASD	33	10.8
TGA	30	9.8
CoA	23	7.5
Single ventricle	21	7
HLHS	20	6.6
ToF	18	5.9
PA+VSD	14	4.6
PDA	14	4.6
Endocardial cushion defect	10	3.3
Aortic stenosis	9	3
Truncus arteriosus	8	2.6
Pulmonary stenosis	8	2.6
Total APVR	8	2.6
HRHS	7	2.3
DORV	7	2.3
PA+IVS	6	2
Tricuspid atresia	6	2
VSD+ASD	6	1.6
Ebstein anomaly	5	1.6
Mitral stenosis	2	0.7
Anomalies of aortic arch	2	0.7
Right atrial isomerism	1	0.3
Left atrial isomerism	1	0.3
Total	305	100.0

VSD: ventricular septal defect, ASD: atrial septal defect, TGA: transposition of great arteries, CoA: coarctation of the aorta, HLHS: hypoplastic left heart syndrome, ToF: tetralogy of Fallot, PA+VSD: pulmonary atresia and VSD, PDA: patent ductus arteriosys, APVR: anomalies of pulmonary venous return, HRHS: hypoplastic right heart syndrome, DORV: double outlet right ventricle, PA+IVS: pulmonary atresia and intact interventricular septum.

Distribution of Additional Cardiac Anomalies

Eighty of 305 cases (26.2%) were associated with one or more additional cardiac anomalies. The most frequent additional defect was VSD, accounting for nearly half of these defects (42.5%). Fifteen cases revealed two additional anomalies. PDA was the most frequently found malformation followed in order by persistent left superior vena cava, VSD, aortic anomalies, ASD, pulmonary stenosis and dextrocardia. Dextrocardia was found in cases with PA+IVS, single ventricle, HLHS, VSD and Ivemark syndrome. When patients with HRHS, ToF, DORV and tricuspid atresia were taken into consideration together, the incidence of association of two or more cardiac anomalies was estimated to be 44%. Table II shows the distribution of additional cardiac anomalies detected.

Table II. Distribution of Additional Cardiac Defects

	Case no.	(%)
No extra defect	225	73.8
VSD	34	11.1
PDA	14	4.6
ASD	12	3.9
Dextrocardia	7	2.3
PLVCS	5	1.6
Endocardial cushion defect	4	1.3
Ectopia cordis	2	0.7
Anomalies of aortic arch	2	0.7

VSD: ventricular septal defect, PDA: patent ductus arteriosus, ASD: atrial septal defect, PLVCS: persistent left vena cava.

Spectrum of Noncardiac Malformations

Of the 305 cases entered into the study, 140 (45.9%) revealed one or more noncardiac malformations (NM). The most frequent anomalies involved craniofacial malformations (CFM) (19.7%), and anomalies of the genitourinary system (GUS) (15.1%), muscle and skeletal system (13.4%), and respiratory system (13.1%). Less commonly, anomalies of the gastrointestinal system (GIS) (11.1%), central nervous system (CNS) (10.5%), and spleen (4.6%) were found. Table III gives the frequency of malformations of organs and systems associated with CHD.

Table III. Extracardiac Malformations in 305 Cases with Congenital Heart Disease

Extracardiac malformation	Case no. (%)
1. Craniofacial	60 (19.7)
2. Genitourinary	46 (15.1)
3. Musculoskeletal	41 (13.4)
4. Respiratory system	40 (13.1)
5. Gastrointestinal system	34 (11.1)
6. Central nervous system	32 (10.5)
7. Spleen	14 (4.6)

Fourteen cases (4.6%) had spleen anomaly (8 with polysplenia, 6 with asplenia). The remainder were cases with right atrial isomerism, HRHS, and VSD. Polysplenia was present in patients with VSD (2), HLHS (2), single ventricle (2), ECD (I), and left atrial isomerism. Spleen malformation was significantly high in cases with single ventricle ($p<0.002$). Table IV shows the distribution of NM associated with specific cardiac defect. There was no noncardiac anomaly

Table IV. The Frequency of Noncardiac Malformations in 305 Children with Congenital Heart Defects

Congenital heart disease	No of cases	Cases with NM (%)	Craniofacial (%)	Resp. system (%)	Spleen (%)	GIS (%)	GUS (%)	CNS (%)	Musculo-skeletal malf. (%)
VSD	47	27 (57.4)	18 (38.3)	7 (14.9)	3 (6.4)	15 (31.9)	12 (25.5)	19 (19.1)	13 (27.6)
ASD	33	20 (60.6)	8 (24.2)	5 (15.1)	0 (0)	3 (9.1)	6 (18.2)	5 (15.1)	5 (15.1)
TGA	30	4 (13.3)	0 (0)	2 (6.6)	0 (0)	0 (0)	0 (0)	1 (3.3)	1 (3.3)
CoA	23	13 (56.5)	8 (34.8)	3 (13)	0 (0)	3 (13)	7 (30.4)	4 (17.4)	2 (8.7)
SV	21	13 (62)	3 (14.3)	2 (9.5)	5 (23.8)	3 (14.3)	4 (19)	2 (9.5)	2 (9.5)
HLHS	20	7 (35)	1 (5)	2 (10)	3 (15)	2 (10)	1 (5)	1 (5)	2 (10)
ToF	18	7 (38.8)	2 (11.1)	3 (16.6)	0 (0)	2 (11.1)	3 (16.6)	1 (5.5)	2 (11.1)
Pa+VSD	11	7 (50)	3 (21.4)	4 (28.5)	0 (0)	0 (0)	1 (7.1)	1 (7.1)	2 (14.3)
PDA	14	4 (28.5)	2 (14.3)	0 (0)	0 (0)	2 (14.3)	0 (0)	2 (14.3)	0 (0)
ECD	10	4 (40)	1 (10)	1 (10)	1 (10)	1 (10)	2 (20)	1 (10)	2 (20)
AS	9	2 (22.2)	1 (11.1)	1 (11.1)	0 (0)	0 (0)	1 (11.1)	0 (0)	1 (11.1)
TA	8	4 (50)	1 (12.5)	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)
PS	8	5 (62.5)	2 (25)	1 (12.5)	0 (0)	0 (0)	2 (25)	1 (12.5)	4 (50)
TAPVR	8	3 (37.5)	0 (0)	2 (25)	0 (0)	0 (0)	2 (25)	0 (0)	0 (0)
HRHS	7	4 (57.1)	3 (42.3)	0 (0)	0 (0)	0 (0)	2 (28.5)	2 (28.5)	1 (14.3)
DORV	7	5 (71.4)	2 (28.5)	2 (28.5)	0 (0)	0 (0)	1 (14.3)	1 (14.3)	0 (0)
PA+IVS	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ta	6	2 (33.3)	1 (16.6)	0 (0)	0 (0)	1 (16.6)	0 (0)	0 (0)	1 (16.6)
VSD+ASD	5	5 (100)	2 (40)	1 (20)	0 (0)	1 (20)	2 (40)	1 (20)	1 (20)
Ebstein anomaly	5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MS	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AAA	2	2 (100)	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)
RAI	1	1 (100)	0 (0)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
LAI	1	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Total	305	140	60	40	14	34	46	32	41

NM: Noncardiac malformation, GIS: gastrointestinal system, GUS: genitourinary system, CNS: central nervous system, VSD: ventricular septal defect, ASD: atrial septal defect, TGA: transposition of great arteries, CoA: coarctation of the aorta, SV: Single ventricle, HLHS: hypoplastic left heart syndrome, ToF: tetralogy of Fallot, PA+VSD: pulmonary atresia and VSD, PDA: patent ductus arteriosus, ECD: endocardial cushion defect, AS: aortic stenosis, TA: truncus arteriosus, PS: pulmonary stenosis, TAPVR: total anomalies of pulmonary venous return, HRHS: hypoplastic right heart syndrome, DORV: double outlet right ventricle, PA+IVS: pulmonary atresia and intact interventricular septum, Ta: tricuspid atresia, MS: mitral stenosis, AAA: anomalies of aortic arch, RAI: right atrial isomerism, LAI: left atrial isomerism.

in six cases with PA+intact interventricular septum, in five cases with EA and in two cases with MS, whereas noncardiac malformations were found in all cases with VSD+ASD. The anomalies of GIS and GUS were found to be frequently associated with conotruncal heart defects ($p<0.001$). In the group of TGA, noncardiac malformations were present in only three cases (10%), which differs from the rest of the material ($p<0.001$).

Specific recognizable malformation syndromes were considered in 36 cases (Table V). Most were associated with chromosomal abnormalities including trisomy 18, trisomy 21 and trisomy 13 in order of decreasing frequency. Unfortunately, chromosomal analysis was available in only 16 of the present cases. Of these, eight were normal, while the remaining eight revealed trisomy 13 (3), trisomy 21 (2), trisomy 18 (2) and 15/18 translocation (1).

Table V. Clinical Genetic Diagnoses of the Cases

No.	Case no.	(%)
Trisomy 18	10	3.3
Trisomy 21	7	2.3
Trisomy 13	6	2
Fryns syndrome	2	0.7
Meckel-Gruber syndrome	2	0.7
Asplenia syndrome	2	0.7
Beckwith-Wiedemann syndrome	1	0.3
Alagille syndrome	1	0.3
Cornelia de Lange syndrome	1	0.3
18q deletion	1	0.3
Pena-Shokeir syndrome	1	0.3
DiGeorge syndrome	1	0.3
Goldenhar's syndrome	1	0.3

The ages of mothers of the cases ranged from 16 to 45 years, with a median of 25, and there was no history of consanguineous marriage in the majority of the cases (78%). A history of a sibling with CHD was found in only 15 (4.9%) of 305 cases studied.

Discussion

Congenital malformations are known to be one of the leading causes of death in newborns[15-20]. CHDs are an important subgroup of these since they carry a high risk of mortality and morbidity. The causes of CHD are complex and could be considered as chromosomal, single gene mutations or multifactorial[19]. Though the prevalence has been reported to vary from 3.9 to 11.9 per 1,000 live births, the rate may be as high as 10-fold in the series including primarily the autopsy materials[1,3,21].

In a recent study, Tennsted et al.[3] found a CHD in 129 fetuses of the 815 fetuses examined (16%), which is slightly higher than the incidence reported for CHD in necropsies on newborns varying between 6%-13%. In the present study, we found an incidence of 9.1% of CHD in 3,320 necropsies, which is in parallel with most studies in the relevant literature.

Ventricular septal defect was the most commonly encountered malformation (15.3%), which is compatible with the rates reported in other necropsy studies[22]. VSD was perimembranous in nearly half of the cases and associated with other cardiac anomalies (ToF, PA, TA, ASD, CoA, persistent left superior vena cava).

The incidence of NM in cases with CHD has been reported to vary between 15-45% in the literatures[5,7,23]. Greenwood et al.[5] diagnosed NM in 25.2% of their study population, whereas in the Baltimore-Washington Infant Study (BWIS), NM was observed in 27% of the cases[7]. In the present study, the rate of NM was found as 45.9%. The difference in rates could be attributed to the composition of cases selected [clinical studies, autopsy studies, cases of death only to CHD, necropsy (death from any cause), live births or stillborns and abortions]. Differences in definitions of NM may also have contributed to the discrepancy. The association of CHD with NM is considered the result of common insult, possibly environmental.

Craniofacial malformations (CFM) were the most frequently encountered NM in the present study (19.7%). This was followed by anomalies of GUS (15.1%), musculoskeletal system (13.4%), respiratory system (13.1%), GIS (11.1%), CNS (10.5%), and spleen (4.6%). This is in contrast to the BWIS, in which CNS anomalies were reported to be the most frequent[7]. We found a higher occurrence of CFM in the present cases than in the literature since some anomalies, including cleft lip-palate, high-arched palate, etc. were included in G1S malformations instead of CFM in the reported series. Excluding CFM in the present study, GUS malformations were the leading anomalies (15.1%) including horseshoe kidney, cortical cysts, renal agenesis/hypoplasia, cystic dysplasia,

and genital anomalies. The rate of GUS malformations is compatible with results from the other studies reported by Wallgren et af[23].

Central nervous system anomalies were found to be less common (10.5%) in our study. This figure is quite different from that reported by Tennstedt et al.[3], who found CNS anomalies in 31% of their cases, which consisted of only 815 fetal necropsies and no live births. However, our figure is slightly higher than those from Greenwood et al.[5] and Wallgren et al[23]. This may reflect that our cases were all autopsy cases and a more detailed investigation could be done with clinical studies. No significant relationship has been reported between CHD and CNS malformations in the literature[5,23,24]. Of our cases with CNS malformations, 40.6% revealed VSD, which is in line with the study by Gallo et a1[24].

While the cases with malpositions, SV, ASD,VSD, HLHS, DORV, anomalies of aortic arch or ASD+VSD revealed an incidence of NM reaching more than 50%, it was below 13% in patients with TGA, PA+IVS, MS and EA.

We found respiratory system malformations in 40 cases (13.1%). Previous reports have revealed its incidence varying from 3.8% to 11%[3,5,23]. Nearly half of our cases with respiratory tract malformations showed segment anomalies in the lungs.

Structural defects of the trachea and esophagus are usually concurrent because of their close embryologic development. Several studies on patients with tracheoesophageal fistula (TEF) have shown CHD present in 15%-40% of cases[25,26] Greenwood and Rosenthal et al.[25] and Gallo et al.[24] reported the incidence of TEF in 0.5% and 1% of their cases, respectively. In the present study, we found seven cases with TEF (2.3%), which is slightly higher than reported in the literature.

Omphalocele is one of the abdominal wall defects which is the consequence of the failure of normal infolding process of the borders of the embryonic disc. There have been a number of reports on the association of omphalocele with CHD[25,27]. Greenwood et al.[25] and Carpenter et al.[27] found the incidence of CHD as 9.5% and 32% of their cases, respectively. TOF was the most common defect in their series. Of 305 cases, eight (2.6%) had omphalocele and revealed no particular but rather various types of cardiac malformations, including ASD,VSD, ToF, single ventricle, HLHS and CoA.

Heterotaxia syndromes include a constellation of congenital abnormalities of the spleen (asplenia or polysplenia), variable degrees of visceral malpositions and complex heart disease. Although there are some case reports on the sequence of right laterality with spleen, asplenia is usually associated with right atrial isomerism, i.e., viscera take on a bilateral right-sidedness with bilateral tri-lobed lungs and a midline liver with intestinal malrotation[28,29]. CHD is commonly seen in these cases and often consists of atrioventricular septal defects, TGA and anomalies of pulmonary and systemic venous return. Though there was one case with right atrial isomerism in the present series, he had ECD, which supports the reported findings in the literature.

Polysplenia is usually associated with left laterality, showing two-lobed lungs and left atrial isomerism and complex CHD including atrioventricular septal defects and APVR. We also had one case with left laterality with total APVR. Suprisingly, we observed the rate of splenic malformations to be significantly higher in cases with single ventricle than in those with other heart defects ($p<0.002$).

Musculoskeletal malformations were seen in 13.1% of our cases, and a significant number of those (32.5%) had VSD. Greenwood et al.[25] and Gallo et al.[24] found skeletal anomalies in 8.8% and 4.6% of their cases with CHD, respectively. However, Wallgren et al.[23] noted musculoskeletal malformations in 161 of 1,000 children with CHD (16.1%), in whom the most frequent cardiac defect was ToF. It is interesting that we found no extracardiac anomaly in six cases with PA+intact interventricular septum, in five cases with EA and in two cases with MS, whereas NMs were found in all cases with VSD+ASD.

In recent years, the important causative role of genetic factors has become more apparent thanks to a considerable technical advance in molecular genetics and a developmental approach to cardiac embryology. A number of genes have been suggested to be involved in laterality, septation and vascular morphogenesis of the heart[19]. Cardiac malformation can occur not only in cases with full trisomy but also in those with a tiny microdeletion in autosomal chromosomes. In the last few years, a microdeletion on chromosome 22, as a typical example, has been found to be associated with conotruncal heart defects such as ToF, TA, DORV, anomalies of aortic arch and

TGA with several types of VSDs[30,31]. Unfortunately, the results of chromosomal analysis were only available in 16 of our cases. Of these, eight were normal while eight revealed trisomy 13 (3), trisomy 21 (2), trisomy 18 (2) and I5/18 translocation[1]. Chromosomal abnormality has been found in 5-12% of liveborn infants with CHD, and an even higher rate has been shown in fetuses with CHD or stillbirths, as these fetuses often die before birth and are not included in statistical data by pediatric cardiologists'. We found chromosomal abnormality in only 2.6% of the cases since the present cases were all livebirths and because only a small number of cases were investigated for a chromosomal anomaly due to the limited technical facilities in early years.

The role of consanguinity as a risk factor in CHD is controversial. However, in a recent report, Nabutsi et al.[32] showed a rate of parental consanguinity as high as 34.7% compared to the overall rate of 12.8% found in all newborns. They suggested that aortic anomalies, ASD, DORV, PA, PDA, PS, ToF and VSD were significantly associated with parental consanguinity. There was a parental consanguinity in 22% of our cases. The rate was not significant since the overall incidence of marriages between relatives in our country is similar. A history for a sibling with CHD was obtained in 4.9% of our cases, in parallel with reported rates varying from 3.5% to 17.6%[32].

In the latest decades of the 20th century, considerable progress has been made in recognizing congenital malformations, including heart defects, with high-resolution fetal echocardiography. Therefore, there was a significant decrease in the number of newborns with CHD. In most cardiac centers, fetal echocardiography is performed in all cases with extracardiac anomalies[33]. Also, a cardiac defect should prompt the physician to investigate any other congenital malformation. A full delineation of all fetal malformations will, in turn, provide us with an oppurtunity to make an optimal approach to affected pregnancies. Furthermore, a proper identification and treatment of CHD early in the prenatal period will protect the family from the economic and emotional burden caused by having such a child with CHD.

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