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Risk factors related with congenital heart disease: a single center experience

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ABSTRACT

Aims: Many cases of congenital heart disease are multifactorial and result from a combination of genetic predisposition and an as-yet-to-be-determined environmental stimulus. The purpose of the study is to determine the patients who were diagnosed with CHD through echocardiography and to reveal the risk factors that may cause congenital heart anomalies in our center.

Methods: The medical records of pediatric patients applied to our pediatric cardiology clinic between January 2010 –December 2017 were retrospectively reviewed.

Results: 147 cases were diagnosed with CHD. 60 (52.6%) of the cases were female and 54 (47.4) were male. 77 of the 114 patients included in the study were acyanotic (67.5%) and 37 (32.5%) were cyanotic. Seventeen of the acyanotic patients had mixed CHD. The mean maternal gestational age was 28.2±5.78 years. 26 (22.8%) were born preterm. 17 (14.9 %) patients were born with low birth weight (under 2500 g). 8 (7%) patients were LGA (large for gestational age) (birth weight over 4000 g). Average birth weight was 2,98±740,8 gr. Consanguinity was found in the parents of 28 (24.5%) patients. There was a history of CHD in the relatives of 6 (5.2%) patients, siblings of 4 (3.5%) patients, and parents of 5 (4.3%) patients. Chromosomal abnormalities were found in 9 (7.9%) patients.

Conclusion: Our study is a valuable contribution to the existing literature in that it showed that the frequency and distribution of congenital heart diseases have not changed in recent years, and its findings are compatible with the literature findings.

Keywords: Congenital heart disease, risk factors, contemporary clinical practice

INTRODUCTION

The term congenital heart disease (CHD) includes congenital, structural or functional abnormalities in the cardiovascular system that can be identified at birth or later. Congenital heart disease occurs in approximately 0.8% of live births.[1] Many cases of CHD are multifactorial and result from a combination of genetic predisposition and an as-yet-to-be-determined environmental stimulus. Although CHD is one of the most common major congenital anomalies, we have the least information about its causes. There are many risk factors that can cause CHD. Among these, consanguineous marriage, congenital heart disease of the mother, father or one of the family members, the gestational age of the mother, the birth weight of the baby, the diseases the mother had during or before pregnancy (DM, SLE,etc.) the infections the mother had (rubella, mumps, toxoplasmosis,etc, the drugs used by the mother (thalidomide, lithium,etc.) the mother's exposure to radiation during pregnancy, the mother's smoking or alcohol use, the mother's substance abuse (marijuana, heroin, cocaine) and the mother's nutritional status.[2] The purpose of the study is to determine the patients who were diagnosed with CHD through echocardiography and to reveal the risk factors that may cause congenital heart anomalies in our center as contemporary clinical practice.

METHODS

The medical records of pediatric patients applied to our pediatric cardiology clinic between January 2010 – December 2017 were retrospectively reviewed. Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee approved the study (Date: 17.10.2017, Number: 18/07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patent ductus arteriosus (PDA), mitral valve prolapse, physiological peripheral pulmonary stenosis and bicuspid aortic valve disease in preterm newborns were excluded from our study. Transthoracic Echocardiography (TTE) was performed using "Vivid 3 Expert" and "Vivid 7 Pro ECO" devices of General Electric Medical Systems, Chicago, USA and probes of 3, 5, 7 MHz. All measurements were performed by the same pediatric cardiologist. In the measurements, images were taken in subcostal, parasternal long axis, short axis, apical four-chamber, five-chamber, and suprasternal positions, and hemodynamic functions were evaluated with M-mode, 2-dimensional and Doppler echocardiographic examinations. In addition, a tissue Doppler study was performed. American Society of Echocardiography recommendations[3] was taken as a reference for all measurements.

Statistical Analysis

The study data were analyzed using SPSS (Statistical Package for the Social Sciences) version 20.0 software (SPSS Inc.). The categorical variables were expressed as frequency and percentage, and continuous variables as mean and standard deviation (SD).

RESULTS

A total of 14,173 patients applied to our clinic between 2010-2017. One hundred and fourteen cases diagnosed with CHD by TTE performed by a pediatric cardiologist were detected. 60 (52.6%) of the cases were female and 54 (47.4) were male. Out of 114 patients, 64 (54.3%) presented with a murmur (detected by the pediatrician in our clinic) while the remaining 50 patients (45.7%) were admitted for other reasons (such as bruising, respiratory distress, routine examination, and positive familial risk factors). 29 patients (25.4%) were diagnosed antenatally. 77 of the 114 patients included in the study were acyanotic (67.5%) and 37 (32.5%) were cyanotic. 17 of the acyanotic patients had mixed CHD. Nineteen of the cyanotic patients were male (51.3%) and 18 were female (48.7%). 42 (54.6%) of the acyanotic patients were female and 35% (45.4%) were male.

The distribution of patients diagnosed with acyanotic, cyantoic, and mixed acyanotic CHD by type is shown on **Table 1**. Ventricular Septal Defect (VSD) was found to be the most common acyanotic anomaly (45 patients; 39.5%). Secundum type Atrial Septal Defect (ASD) was detected in 14 patients (12.2%), and PDA was detected in 12 patients (10.5%). Isolated VSD was also the most common acyanotic anomaly (n=29 patients, 25.4%).The most common mixed acyanotic anomaly was VSD-ASD (7 patients, 6.1%).

Tetralogy of Fallot (TOF) was the most common cyanotic anomaly (10 patients; 8.7%). Tricuspid atresia (TA) was detected in 5 patients (4.3%). Transposition of Great Arteries (TGA) was detected in 6 patients (5.2%), of which 4 were male.

Table 2 shows the risk factors that may be associated with congenital heart disease based on the patient's history. The mean maternal gestational age was 28.2±5.78 years. 88 (77,2%) patients were born at term, and 26 (22.8%) were born preterm. 17 (14,9 %) patients were born with low birth weight (under 2500 g). 8 (7%) patients were LGA (large for gestational age) (birth weight over 4000 g). The average birth weight was 2,982.8±740,87 gr. Consanguinity was found in the parents of 28 (24.5%) patients; and there was first-degree consanguinity in the parents of 18 patients (15.8%), and distant relatives (cousins, and second cousins etc.)in the parents of 10 patients (8.8%). There was a history of CHD in the relatives of 6 (5.2%) patients, siblings of 4 (3.5%) patients, and parents of 5 (4.3%) patients. Chromosomal abnormalities were found in 9 (7.9%) patients; 5 had Down syndrome, 2 had Di George syndrome, 1 Turner syndrome and 1 Edward syndrome. Two of Down syndrome patients had AV septal defect and 2 had VSD. Complicated ASD+VSD+PDA was detected in patients with Edward syndrome. 6 (5.2%) mothers had a history of chronic diabetes mellitus, 2 (1.8%) had a history of blood pressure disease and antihypertensive drug use, 4 (3.5%) had preeclampsia, and 8 (7%) had hypothyroidism with a history of levothyroxine use. Hashimoto's thyroiditis was detected in 5 patients with hypothyroidism. At least 57 (50%) patients had a history of regular folic acid and multivitamin use during pregnancy.

Table. Supposed risk factors for congenital heart disease

Risk factor	
Mean maternal gestational age (year)	28+/-5,8
Low birth weight n (%)	17 (14,9)
Consangiunity between parents n (%)	28 (24,5)
Family history of CHD n (%)	6(5,2)
Regular use of folic acid supplement n (%)	57 (50)
CHD in siblings n (%)	4 (3.5)
Chronic disease in mother (DM) n (%)	6(5,2)
Chromozomal anomaly n (%)	9 (7,9)

DISCUSSION

It is thought that 85-90% of CHD cases are multifactorial (which result from an interaction of genetic and environmental factors). In approximately 8% of cases, a congenital heart anomaly can be associated with a genetic defect; however, in most cases, a genetic etiology cannot be determined.[4]

In our patients there was a slight female preponderance (52,6%). The reason why acyanotic anomalies are more common in girls is the presence of anomalies such as VSD, PDA, ASD in this group, and these data are consistent with the information in the literature.[5] It has been reported that spontaneous septal defect closure is more common in males than females.[6] According to a meta-analysis, the female gender is a risk factor for the presence of CHD in Down Syndrome.[7] On the other hand, there are studies reporting cyanotic anomalies being more frequently detected in males.[2] Biological gender differences in the structure of blood vessels and androgenic hormones may be responsible for gender differences in this regard.[8]

Although the subjects included in the study presented due to reasons such as respiratory distress, cyanosis, familial risk factors or a routine examination, the most common reason for admission was cardiac murmur. 64 (54.3%) patients presented with a murmur. In previous studies, the most common reason for cardiological consultation was also cardiac murmur.[9,10]

Table 1. Distribution of congenital heart diseases in the study population

Isolated Acynotic Defects	N=60	Mixed Acyanotic Defects	N=17	Cyanotic Defects	N=37
VSD	29	VSD+ASD	7	Tetralogy of Fallot	10
Patents ductus arteriosus (PDA)	7	VSD+PDA	4	Transpoistion of great arteries	6
Aort stenosis (AS)	6	VSD+PS	2	Tricuspid atresia	5
Atrioventricular septal defect	5	VSD+ASD+AC	1	Hypoplastic left heart syndrome	4
Aort coarction (AC)	5	VSD+ASD+PDA	1	Hypoplastic right heart syndrome	3
Pulmonary stenosis (PS)	4	VSD+PS	1	Single ventricle	2
ASD	4	ASD+PS	1	Truncus arteriosus	2
				Double outlet right ventricle	2
				Total anomalous pulmonary venous return	2
				Pulmonary atresia	1

Aydogdu et al.[11] showed that VSD was the most common anomaly with a prevalence of 42.9%, and ASD was in the second most common anomaly with a prevalence of 37.5%. In our study, VSD was the most common anomaly (39.5%) followed by ASD (12.2%), a finding which was partially consistent with the literature.[12] The most common cyanotic anomaly was tetralogy of fallot (10 patients; 8.7%); tricuspid atresia was found in 5 (4.3%) patients, and TGA in 6 (5.2%). The fact that 4 of these 6 patients were male is in accordance with literature data indicating that serious and complex heart defects are more common in males.[2]

In our study, consanguinity was found between the parents of 28 (24.5%) patients; It was determined that there was first-degree consanguinity among the parents of 18 patients (15.7%), and distant consanguinity between the parents of 10 patients (8.8%). In a study conducted by Al Mamun et al.[13] on CHD, it was found that 8.85% of children with CHD had a family history of consanguineous marriage between their parents. They found that children who born to consanguineous parents had 2.5 times risk of developing CHD. Having a higher rate of consanguinity, 15.7% of our patients' parents were first-degree relatives. Our data suggest that first-degree consanguineous marriage may be influential in the etiology of CHD.

The recurrence risk for CHD increases two- to threefold when there is a family history.[14] This shows that CHD can be transmitted by Mendelian inheritance.[15] In the literature, it has been shown that having CHD in the family is a risk factor for CHD in subsequent children.[16] In our study, 6 (5.2%) patients had a history of CHD in their relatives, 4 (3.5%) in their siblings, and 5 (4.3%) in their parents.

Congenital heart disease is seen more frequently in some single gene defects and chromosomal abnormalities; for example, approximately 40% of children with Down Syndrome have overt heart disease, 50% of which can be congenital heart diseases such as endocardial cushion defect, VSD, PDA, and TOF.[17] In our study, a chromosomal anomaly was found in 9 (7.9%) patients. Of these patients, 5 had Down syndrome, 2 had Di George syndrome, 1 had Turner syndrome and 1 had Edward syndrome. In a study by Park et al.[18] endocardial cushion defect (43%) was the most common anomaly in patients with Down syndrome, followed by VSD (32%). In a study by Meberg et al.[19] Edwards syndrome was detected 2.1% (58%), in the study of Dorfman et al.[10] 0.5%. In our study, Edwards Syndrome was found at a rate of 0.87%. In Down syndrome patients, there is overexpression of the DSCAM (Down syndrome cell adhesion molecule) gene that creates an imbalance in the epithelial-mesenchymal transformation that leads to a defect in mesenchymal migration and proliferation that causes CHD.[20]

Compared to normal babies born in the same gestational week, low-birth-weight babies are more likely to have ASD, VSD, tetralogy of Fallot, hypoplastic left heart syndrome, pulmonary stenosis, or aortic coarctation.[21,22] In a study performed by Kadivar et al.[9] the mean gestational age was 38 weeks, the mean birth weight was 2812 g, and the number of prematurity was 41 (16.9%). In the study of Aydoğdu et al., the mean birth weight was 2961 g, and 18% of the cases were prematüre.11 In our study, 26 (22.8%) patients were preterm, 17 (14.9%) were low birth weight (under 2500 g), and the mean birth weight was 2.982±740 g. The high rate of low-birth weight and high mean maternal gestational age suggests that these two factors may be influential in the etiology of CHD. Besides comorbidities are also effective risk factors. Maternal diabetes increases the incidence of congenital heart disease. If the mother has insulin-dependent diabetes mellitus, anomalies such as VSD, TOF and great vessel transposition may develop. In the study of Kadivar et al.[9] 9% of patients diagnosed with CHD were born to diabetic mothers. In our study, 6 of the patients (5.2%) had a maternal history of insulin-dependent diabetes mellitus, 2 (1.8%) had a maternal history of hypertension and antihypertensive drug use, and 4 (3.5%) had a maternal history of preeclampsia. Both maternal hypertension and diabetes affect maternal metabolism and cause endothelial dysfunction, which leads to CHD.

It has been shown that folic acid deficiency increases the risk of cardiovascular anomalies in the fetus.[23] Therefore, it is recommended that folic acid supplements be administered to mothers starting one month prior to pregnancy and for two months after the start of pregnancy.[23] In our study, although the mothers of at least 57 (50%) patients regularly used iron, folic acid, and multivitamins during pregnancy, it was determined that many mothers either used folic acid irregularly or did not use it at all.

CONCLUSION

Our study is a valuable contribution to the existing literature in that it showed that the frequency and distribution of congenital heart diseases have not changed in recent years, and its findings are compatible with the literature findings. Families who have a child with a congenital heart anomaly should receive genetic counseling due to a possible cardiac anomaly in the next child; in addition, people who will get married should be informed about CHD, and a good maternal care should be provided before pregnancy.

ETHICAL DECLARATIONS

Ethics Committee Approval: Kırıkkale University Faculty of Medicine Clinical Researches Ethics Committee approved the study (Decision No: 18/07 Date: 17.10.2017).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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