Annals of Clinical and Analytical Medicine
Original Research

Incidence of congenital heart disease with consanguinity: 10 years of experience in a single-center

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Abstract
Aim: Congenital heart diseases (CHD) are inborn structural and functional anomalies of the heart and its great vessels. It is considered to have a multifactorial origin. This study aims to determine the frequency and types of CHD between siblings in Central Anatolia and investigate consanguineous marriages' contribution to this undesirable incidence.
Material and Methods: The study included 1916 children admitted to the pediatric cardiology outpatient clinic between 2009-2019. Congenital heart diseases were grouped as uncomplex CHD, complex CHD, heart muscle diseases and other heart conditions.
Results: There were 113 consanguineous parents. No relation was found between the types of consanguineous marriages and CHD incidence. Atrial septal defect (ASD) was the most common heart condition among consanguineous marriages seen in 73 patients. Parents with congenital heart diseases had ASD or Ventricular septal defect(VSD) type septal lesions. There was no relationship between the parents' consanguinity and the presence of CHD in any sibling ($p=0.169$). In 300 siblings, CHD was present in both patients. The older sibling having CHD increases the risk for the younger one ($p<0.05$). Of the patients, 827 had noncomplex cardiac lesions, 13 had complex cardiac lesions, and 136 had other cardiac pathological echocardiographic (ECHO) findings.
Discussion: Families who have a child with pre-existing CHD should be informed about the possibility of CHD recurrence before pregnancy, and these cases should be examined using fetal ECHO in the prenatal period. Those under risk should be followed up and treated in appropriate centers in terms of CHD.

Keywords
Consanguinity, Congenital Heart Defects, Sibling, Twins

DOI: 10.4328/ACAM.21468 Received: 2022-11-03 Accepted: 2022-12-24 Published Online: 2023-01-07 Printed: 2023-04-01 Ann Clin Anal Med 2023;14(4):306-310
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This study was approved by the Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (Date: 2020-06-19, No: 2020/2612)

Introduction

Congenital heart diseases (CHD) are structural and functional anomalies of the heart and large vessels emerging during embryogenesis in the first trimester. They are the most common anomaly among congenital abnormalities and constitute one-third of all malformations [1,2]. The cause of 80% of congenital heart diseases is still not fully understood. It is accepted to occur due to multifactorial determinants with the common interaction of genetic and environmental variables [3].

Consanguineous marriage increases the risk of babies with anomalies from 2-5% to around two folds [4]. Providing accurate and reliable counseling to families is of great importance for the health of the unborn child [1]. We aimed to determine the frequency and type of CHD among siblings in a set region and to investigate the contribution of consanguineous marriages to this health problem.

Material and Methods

A total of 1916 pediatric patients, 2 from each of the 958 families, who applied to the Pediatric Cardiology outpatient clinic between January 2009 and January 2019 with bruising, murmur, and a family history of heart disease, were included in the study. Since the number of applications for more than two siblings is low, families with more than two siblings were not included in the study. Demographic characteristics, presence of congenital heart disease in the family, consanguinity between the parents, the degree of consanguinity, echocardiographic findings, and diagnoses were extracted from the patient records. The frequency and type of congenital heart disease among siblings, parental consanguinity, and the effect of the presence of CHD in another family member were compared. Echocardiographic evaluation was performed with the GE Vivid S5 instrument using S3-6 sector probes.

Congenital heart defects were categorized into 3 main groups. The first group included those with noncomplex CHD: Conditions without cyanosis patent ductus arteriosus (PDA), ASD, VSD, and their combinations) were included. The second group included those with a complex CHD: Those with pathologies such as Tetralogy of Fallot (TOF), atrioventricular septal defect (AVSD), Ebstein's anomaly, and transposition of great arteries in which septal, valvular, or great vessels are affected together were included. Finally, the third group consisted of heart muscle and other valve diseases: Bicuspid aorta, mitral valve prolapse (MVP), cardiomyopathy, left ventricular outflow tract stenosis, etc.

The level of consanguinity between the parents was graded according to Thompson [5]. Consanguineous marriages were divided into 3 groups: the marriage of children of same-sex siblings, the marriage of children of different-sex siblings, and the marriage of distant relatives [6].

Approval for this study was obtained from the hospital's local clinical research ethics committee (2020/2612).Statistical analysis was performed using the SPSS package program (SPSS for Windows, Version 18.0, SPSS Inc., USA). Descriptive statistics were used to classify the data. Categorical data were expressed as percentages. Skewed numerical data was indicated by the median. The Chi-square test was used to compare categorical data between groups, while the Mann-Whitney U test was used to compare numerical data. A p-value of <0.05 was considered significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Between January 2009 and January 2019, 22676 patients underwent ECHO in the pediatric cardiology outpatient clinic. 1916 children from 958 families, who were confirmed to be siblings, were included. Of the siblings, 1536(80.1%) were non twins, 380(19.9%) were twins. The flow chart of the study is given as a diagram (Figure 1).

Nine hundred and seventy-six (51.1%) of them had pathological findings in the ECHO. Of the patients with pathological ECHO findings, 827(84.7%) had noncomplex cardiac lesions, 13(1.3%) had complex cardiac lesions, and 136(13.9%) had other cardiac pathological ECHO findings.

There were 113 (11.8%) consanguineous parents. Of these, 106 (98.8%) were first-degree cousin marriages.When the types of consanguineous marriages were compared, although CHD was numerically higher in marriages between uncle/aunt's children, there was no statistically significant difference (p>0.05).There was no statistically significant difference between the types of consanguineous marriages concerning the incidence of CHD in the only child of the family or in siblings (p>0.05).

Children of families with consanguineous marriages had 102 noncomplex cardiac lesions, 2 complex cardiac lesions, and 18 valve and heart muscle diseases. These were: 73 ASD cases, 12 ASD/PDA cases, 7 ASD/VSD cases as noncomplex pathologies, and one TOF and one AVSD as complex cardiac lesions (Table 1).

Of the siblings' families, 23 (2.4%) had CHD. These were noncomplex septal lesions such as ASD/VSD.

CHD was found in one sibling in 676(69.2%) of the sibling cases and in both siblings in 300(31.8%) cases. In these cases, consanguinity was observed between the mother and father in 86 (13%) of those with CHD in one of the siblings and in 36 (22%) of those with CHD in both siblings. Also, There was no relationship between parental consanguinity and the presence of CHD in either or both siblings. (p=0.169). The information on the patients with pathological ECHO findings is schematically summarized in Figure 2

Of the sibling cases with at one sibling with CHD, 516 (76.3%) were normal siblings and 160 (23.7%) were twins. Of the sibling cases with at both siblings with CHD, 166 (55.3%) were normal siblings and 134 (44.7%) were twins When the status of having a normal sibling or a twin were compared, being a twin was riskier in terms of having CHD (p<0.05).

Of the normal sibling cases with a one sibling with CHD, 249(48.3%) were of different sex, and 267(51.7%) were of the same sex. Of the twins, with a one sibling with CHD 64(40.0%) were different sex, while 96 (60.0%)were same-sex. Of the non-twin cases where both siblings had CHD, 83 (50%) were of different sex, while 83(50%) were of the same sex. Of the twins who had CHD in both siblings, 58(43.2%) were of different sex, and 76(56.8%) were of the same sex. There was no relationship between the gender of the older and younger siblings being the same or different sex and the presence of CHD (p=0.941).

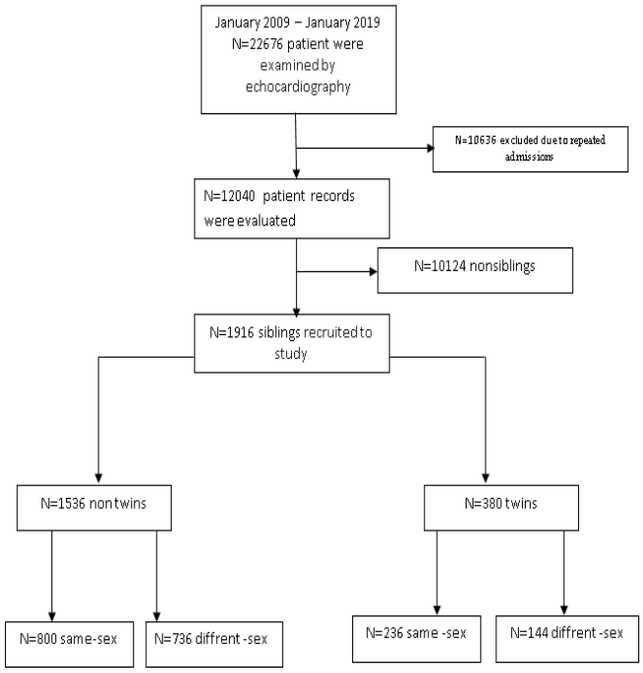

Figure 1. Flow chart of the patients included in the study (N=Number of people)

Table 1. Congenital heart diseases among the types of consanguineous marriages. ASD: Atrial septal defect, AVSD: Atrioventricular septal defect, BAV: Bicuspid aortic valve, CHD: Congenital heart disease CoA :coarctation of the aorta ,MVP: Mitral valve prolapse ,PDA:Patent ductus arteriosus, PFO: Patent foramen ovale, ,TOF: Tetralogy of Fallot , VSD: Ventricular septal defect.

	Nonconsanguineous parents	(Maternal) Aunt/ Uncel	(Paternal) Aunt/ Uncel	Distant relative
Normal	834	40	59	5
Non complex CHD	725	44	51	7
Complex CHD	11	1	-	1
Valve and heart muscle disease	118	8	9	1
PFO/ASD	564	28	41	4
VSD	22	2	2	-
ASD/VSD	39	2	4	1
PDA	22	2	2	-
ASD/PDA	52	5	5	2
ASD/VSD/PDA	8	2	-	-
BAV	28	-	3	-
TOF	1	1	-	-
Complex CHD	4	-	-	-
AVSD	4	-	-	1
PDA/BAV	2	-	-	-
ASD/BAV	14	-	-	-
Dextrocardia	2	-	-	-
Ebstein anomaly	2	-	-	-
CoA	2	-	1	-
MVP	83	7	5	1
Cardiomyopathy	5	1	-	-

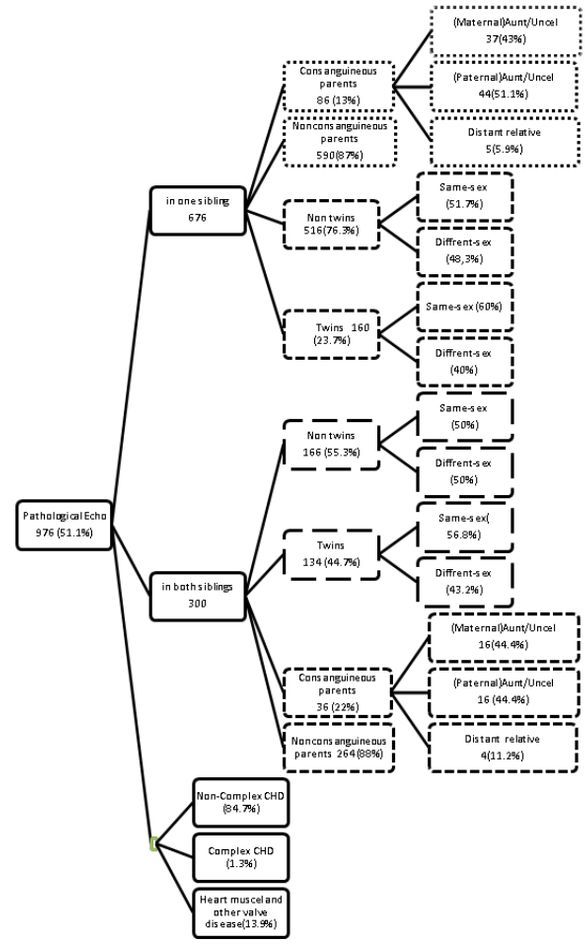

Figure 2. Schematic distribution of pathological ECHO findings according to maternal/paternal vulture status, sibling type, gender, and Congenital Heart disease types. CHD: Congenital heart disease Echo: Echocardiography

Table 2. Types of congenital heart diseases among the children included in the study and their incidence in one or both siblings in the family. ASD: Atrial septal defect, AVSD: Atrioventricular septal defect, BAV: Bicuspid aortic valve CHD: Congenital heart disease, CoA: Coarctation of the aorta, MVP: Mitral valve prolapse, PDA: Patent ductus arteriosus, PFO: Patent foramen ovale, TOF:Tetralogy of Fallot, VSD: Ventricular septal defect

	1.sibling N/ CHD	2.sibling N/ CHD	In both sibling N/same CHD
PFO-ASD	266 (27.2%)	371 (38%)	152 (15.9%)
VSD	18 (1.9%)	8 (0.8%)	1(0.1%)
ASD-VSD	19 (2.0%)	27 (2.8%)	1(0.1%)
PDA	13 (1.4%)	13 (1.4%)	-
ASD-PDA	24 (2.5%)	40 (4.2%)	10 (1.0%)
ASD-VSD-PDA	3 (0.3%)	7 (0.7%)	1 (0.1%)
BAV	16 (1.7%)	15 (1.6%)	2 (0.2%)
TOF	1 (0.1%)	1 (0.1%)	-
Complex CHD	3 (0.3%)	1 (0.1%)	-
AVSD	3 (0.3%)	2 (0.2%)	-
PDA-BAV	2 (0.1%)	-	-
ASD-BAV	6 (0.6%)	8 (0.8%)	1 (0.1%)
Dextrocardia	1 (0.1%)	1 (0.1%)	-
Ebstein anomaly	2 (0.2%)	-	-
CoA	2 (0.2%)	1 (0.1%)	-
MVP	60 (6.3%)	36 (3.8%)	6 (0.6%)
Cardiomyopathy	5 (0.5%)	1 (0.1%)	-

In older siblings, ASD was the most common with 266 (27.2%) cases, followed by MVP with 60 (6.3%), and both ASD and PDA in 24 (2.5%).There were complex cardiac lesions in 9 older siblings (0.9%), including 3 AVSD , 2 Ebstein anomaly/ ASD, 1 TOF, 1 double inlet left ventricule/AV-VA discordance/ VSD, 1 great artery transposition of great arteries/ASD/VSD, and 1 total abnormal pulmonary venous return anomaly/High venosum ASD.

In younger siblings, the most common diagnosis was ASD with 371 (38%) cases, 40 (4.2%) cases of ASD/PDA coexistence, and 36 (3.8%) cases of MVP. There were also 4 (0.4%) patients with complex cardiac lesions in younger siblings. These were 2 atrioventricular septal defects, 1 Tetralogy of Fallot, and 1 case of transposition of the great arteries/ASD/VSD.

ASD, ASD-PDA, MVP, and BAV were observed in two children of 152 families, ten families, six families, and two families, respectively. In addition, VSD, ASD-VSD-PDA, and ASD-BAV were found in 3 families consecutively. The older sibling having CHD poses a risk for the younger sibling to also have CHD ($p<0.05$). There was no family with complex cardiac lesions in both siblings. These findings are summarized in Table 2.

Discussion

As a result of developing technology and surgical techniques, most patients with congenital heart diseases can survive until reproductive age. Hence, there is a comprehensive and reliable counseling need in terms of CHD heredity [7] . Due to the varying severity of congenital heart disease types, an important factor to consider when counseling families is the estimation of the type of lesion that can recur [8] . It is stated that the risk of recurrence varies between 1% and 3% for different types of heart defects [9] .

Although people with a family history of CHD have an increased risk of also having CHD, mostly only one individual in these families is affected. Thus, the increased risk may not be easily detected in clinical practice [10]. Familial recurrence and the association with some environmental factors support that CHD occurs with polygenic inheritance. In people with genetic predispositions, drugs, environmental factors, and viruses can initiate events and cause cardiac anomalies [11].

It has been reported that recurrence in first-degree relatives is between 2-5%, and these results mathematically fit the model of polygenic transmission [12].

Family Structure in Turkey 2016 survey data indicates that consanguineous marriage is 23% across Turkey, which is 26.7% in Central Anatolia, where our center is located. When these marriages are analyzed according to the type of kinship, it is seen that 28.5% of the individuals who have had consanguineous marriages are married to the children of their father-side aunts/uncles and 20.9% to the children of their mother-side aunts/uncles [13] .

In our study, the rate of consanguineous marriage was 11.8%. The low rate of marriages between relatives may have led to the lower incidence of diseases such as CHD. We think that the relatively low number of CHD patients in our study may be related to this factor of consanguineous marriages.

Ertoy Karagöl et al.were conducted their study in Konya among 651 children having consanguineous parents where most were married to first-degree cousins, reported 16 (3.3%) CHD cases in the relatives, and there was no significant difference in CHD between them and the control group [14].

In the comparison between 1585 non-syndromic CHD cases and 1979 control cases, Chehab G et al., reported that the rate of consanguineous marriage was 19.4% in the CHD group and 14.4% in the control group. Furthermore, some specific heart lesions such as Tetralogy of Fallot, valvular aortic stenosis, and ASD were seen at higher rates in consanguineous marriages, and there was no increase in cardiac malformations such as atrioventricular canal defect and transposition of great arteries with consanguineous marriages [15].

In our study, there was consanguinity in 113 (11.8%) of the 958 families and similar to the study performed by Ertoy Karagöl et al. in the same region, there was no significant difference between the children of related parents and children of non-consanguineous parents regarding CHD ($p=0.169$) [14].

The increased risk of CHD in siblings descending from parents with CHD is explained by genes, shared environmental factors, or their combined effects. The increased risk may be associated with a single strong risk factor in some families. For other families, it may be the result of familial aggregation of multiple interacting risk factors, each of which carrying a low risk of CHD [16].

The fact that consanguinity did not affect the development of CHD in our study suggests that the genetic predisposition for CHD in this region may be lower and the effect of environmental factors may be less. Relatives of consanguineous parents having no CHD and the previous study in the same region showing similar results support this idea.

Brodwall et al. reported that the risk of CHD among siblings was significantly associated with the presence of CHD in the older sibling, and reported that the risk of CHD in the younger sibling was 411.8 per 10,000 if the older sibling had CHD; if the older sibling did not have CHD, this rate was 112.8 per 10,000 [17]. In the same study, the risk of CHD recurrence was 14.0 in twins of the same sex and 11.9 in twins of different sexes, and this risk increased 10 times in individuals with two older siblings who had CHD. Furthermore, the risk of recurrence between siblings was higher in severe CHD types.

It has been reported that if one of the parents has CHD, the same type of cardiac lesion can be seen in children with a rate of 1/3 or 2/3, and this lesion is more serious in the second and third siblings [18]. In our study, 19 cases with CHD had 3 members of the family with the disease, including both siblings and at least one parent with CHD. These lesions were similar in all family members and were septal lesions such as ASD and VSD.In our study, having CHD in the older sibling was a risk in terms of CHD in the younger sibling ($p<0.05$). When we compared the status of having a non-twin and having a twin, it was seen that being a twin was riskier in terms of having CHD ($p<0.05$). In addition, there was no relationship between the gender of the older and younger siblings being the same or different sex and the presence of CHD ($p=0.941$).In the study performed by Atalay et al., the most common CHD siblings were VSD, ASD, and TOF, and 40% of their siblings had the same type of cardiac lesion [19]. It has been reported that the rate of similar CHD was 71.44% in the children of relatives with

consanguinity.

In their study on the risk of CHD among siblings, Brodwall et al. reported that the same type of CHD is 33.3% in twins of the same sex, 20% in twins of different sexes, and 16% among non-twins [17]. Among siblings, similar CHD was detected in 30% and different type of CHD in 54%. Therefore, the increased risk of CHD in siblings may be largely due to the increased risk of having the same type of CHD. However, in this study, unlike ours, the recurrence of septal lesions was less common among siblings. In our study, the most common was ASD, followed by ASD/PDA association in both sibling groups; this being more common in younger siblings. Although VSD is most common in the pediatric age group, the reason why ASD was more common in our study may be that families who are worried bring their children to the pediatric cardiology department in the early period because most families have a history of CHD, and that small ASDs and PDAs are also seen and diagnosed earlier.

In the current literature, we see that the studies are mostly conducted in the general population; there are few studies in which only siblings are evaluated [15]. In the studies conducted in Turkey, the data collection period is mostly short, and they cover a small number of siblings and families. In this respect, our study differs from other investigations in that it took 10 years and included 958 families and 1916 siblings [14,19].

The limitation of our study is covering only the Central Anatolia region. Therefore, these data will not fully reflect the general population. However, the relatively high rate of consanguineous marriage where the study was conducted may affect the evaluation of the effects of consanguinity on CHD. The low rate of consanguinity among the patients in our study may also be considered among the limiting factors.

Conclusion

As a result, the concerns of families with a child with CHD should be taken seriously, and these families should be informed about the possibility of CHD recurrence before pregnancy. Due to the risk of recurrence of CHD in relatives, these cases should be screened for CHD with fetal ECHO in the prenatal period, and high-risk pregnant women with complex CHD should deliver in a center where first interventions can be made after birth.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Hüseyin Yılmaz, Mehmet Burhan Oflaz. *Incidence of congenital heart disease with consanguinity: 10 years of experience in a single-center. Ann Clin Anal Med 2023;14(4):306-310*

This study was approved by the Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (Date: 2020-06-19, No: 2020/2612)