ORIGINAL ARTICLE

CONGENITAL HEART DISEASES, A CONSEQUENCE OF CONSANGUINEOUS MARRIAGES IN PUNJAB, PAKISTAN

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Objectives: To find out the association of congenital heart diseases with inbreeding in Punjab, Pakistan.

Methodology: This case control study was carried out at Department of Paediatric Cardiology, Faisalabad Institute of Cardiology (FIC) Faisalabad, Pakistan, from December 2019 to February 2020. A total of 768 subjects, 384 cases suffering from congenital heart disease (CHD) and 384 controls having no CHD, both confirmed on echocardiography, were enrolled in the study. Their parents were interviewed regarding age, gender, residential area and data was collected including parental marriage type (consanguineous/ non related) and presence or absence of congenital heart disease through questionnaire.

Results: Among cases, 51.3 % were female with female to male ratio 1.05:1. As regard age, 85.7% (n=329) of the children among cases were below 5 years of age. As regard consanguinity, 66.4% (n=255) had consanguineous parents while 33.6% (n=129) of CHD children had parents who were un-related before marriage. Multivariate analysis showed parental consanguinity had strong association with CHD in children; odds ratio 5.84 (95% CI 4.2-7.99) with a P-value of <0.01. Acyanotic CHD was present in 76.8% children (n=295) while 23.2 % had cyanotic CHD (n=89). Ventricular septal defect (VSD) was the most common CHD (32%) followed by atrial septal defect (18.2%) and PDA (13.5%).

Conclusion: There is a remarkable association between inbreeding and CHD in Punjab, Pakistan.

Keywords: Congenital heart disease, consanguinity, ventricular septal defect

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INTRODUCTION

Congenital heart disease (CHD) is the most common birth defect with mean global prevalence of 8.2 per one thousand live births.[1] CHD constitutes 28 percent of all major congenital abnormalities.[2] Traditionally the etiology of CHD has been defined as a multifactorial model with some contribution of both genetic and external factors. The identification of genetic factors is of utmost significance in the clinical and surgical management of syndromic or non-syndromic congenital heart defects. Different types of non-syndromic congenital heart diseases (CHDs) are believed to be a consequence of integrated effects of numeral factors, probably both genetic and epigenetic.[3] The prevalence of cousin marriages is variable around the world and is about fifty percent in some countries of North Africa, South Asia and Middle Eastern.[4]

Pakistan is a multicultural country having huge number of various castes and different Islamic sects living in it resulting in a high number of consanguineous unions and their association with various recessively inherited disorders. In Pakistan the incidence of marriage with a first or second cousin is 50%, more than in any other country.[5] The important elements that encourage consanguinity include intermarriages, arranged marriages and lack of education. The problems that result from consanguineous marriages involve infant death, congenital disorders, rare genetic malformations, mental abnormalities, small birth size and congenital heart defects.[6] Consanguinity in parental marriages is an independent risk factor for presence of CHD in children. Despite the complexity of number of factors involved in CHD, the consanguinity may result in increased chances of CHD particularly if the disease has a multifactorial or recessive inheritance.

The trend of cousin marriages is widespread in Pakistan and out of the birth defects due to cousin marriages congenital cardiac malformations are the most common. The factors related to occurrence of CHD have not been studied at large in Pakistan and the data is scanty in this regard. The present study was conducted to find out the relationship of the consanguinity and pervasiveness of CHD.

METHODOLOGY

This was a hospital based, case control study aimed to determine the relationship of congenital heart diseases and consanguinity. The study was carried out at the Department of Paediatric Cardiology Faisalabad Institute of Cardiology (FIC) Faisalabad, Pakistan from December 2019 to February 2020. The approval of study from ethics committee of the Institute was obtained and there was no conflict of interest.

Cases were consecutive patients of congenital heart disease diagnosed on echocardiography, done by dedicated pediatric cardiologist, irrespective of gender (male, female, transgender) with age range from day one to 18 years, presenting in outpatient department (OPD) of pediatric cardiology. Similarly control group comprised of consecutive children presented for screening of congenital heart disease for first time but proved to be having no CHD confirmed by echocardiography. The patients who were diagnosed case of acquired heart disease like rheumatic heart disease or cardiomyopathy, had any conduction abnormality without structural heart disease, had bicuspid aortic valve with normal valve function and those with syndromic appearance were excluded from the study.

Each group had equal number of subjects (384 each for either group). After informed consent and assurance of confidentiality about their personal data, the parents (mother, father or both) or guardians of the children (both case and control) were interviewed in a comfortable environment. Questionnaire was designed to collect data from the parents on different parameters like age, gender, residential status and the type of congenital heart disease.

As regard residential area of the study subjects, the urban areas included cities like Faisalabad, Jhang, Toba Tek Singh, Shahkot, Pindi bhatian, Sargodha, Mianwali, Bhakar, Khushab, Sheikhupura, Okara, Lahore, Gujranwala, Bahawalpur and Multan while rural areas were in the periphery of these cities. The cardiac diagnosis based on Echocardiography was reviewed in the entire study subjects and where more than one structural abnormality was present, the leading or main diagnosis was chosen. The spectrum of the heart diseases in children was assessed by categorizing them as acyanotic and cyanotic CHD. The history related to cousin marriage of parents of the subjects was also sorted out like first cousin, second cousin, distantly related and totally unrelated.

The data collected through questionnaires was entered on SPSS version-21 and analyzed while frequency and percentages were calculated for categorical variables. The odds ratio (OR) and 95% confidence interval (CI) were also calculated. The analysis was done by applying Chi square test to assess the association between inbreeding and CHD. Odds ratios and corresponding p-values were used for interpreting the results. A p-value of ≤ 0.05 was taken as significant.

RESULTS

A total of 384 subjects had CHD (Cases) while equal number of subjects (n=384) were having no CHD (controls). Among cases 51.3% were female with female to male ratio 1.05:1. As regard age, 85.7% (n=329) of the children among cases were below 5 years of age. Table 1 shows base line characteristics of both groups as regard gender, age and residential area (Table 1).

Table 1: Baseline characteristics

Characteristics	Cases (%)	Controls (%)
Total (N)	**n=384**	**n=384**
Gender		
Male	187 (48.7)	88 (22.9)
Female	197 (51.3)	296 (77.1)
Age		
1day to < 1month	104 (27.08)	46 (11.98)
1 Month to 1 Year	165 (42.97)	157 (40.88)
1-5 Years	60 (15.63)	95 (24.74)
5-12 Years	30 (7.81)	72 (18.75)
12-18 Years	25 (6.51)	14 (3.65)
Residential area		
Rural	200 (52.1)	226 (58.85)
Urban	184 (47.9)	158 (41.15)

As regard marriage type among cases, majority of CHD children (66.4%, n=255) had parents who were cousin before marriage while 33.6% (n=129) of CHD children had parents who were non-related before marriage. The odds ratio (OR) and 95% confidence interval (CI) were calculated [OR=5.84, 95% CI 4.2-7.99] with a P-value of <0.01 which is statistically significant and showed that occurrence of congenital heart disease in children with consanguineous parents was 5.84 times higher as compared to those with non-consanguineous parents. The distribution of marriage types in study subjects is shown in Table 2.

Table 2: Distribution of marriage types

Marriage Type	Cases (%)	Controls (%)
Total (N)	**n=384**	**n=384**
First Cousin	202 (52.6)	71 (18.5)
Second Cousin	21 (5.5)	2 (0.5)
Distantly Related	32 (8.3)	24 (6.3)
Non Related	129 (33.6)	287 (74.7)

Chi-square p-value <0.001

As regard distribution of cases according to area of residence, 65.9 % (n=253) subjects belonged to rural areas while 34.1% (n=131) belonged to urban area. The rate of consanguinity was also found to be remarkably higher in the rural areas than urban areas. The results showed a significant ($p<0.05$) rise in the incidence of consanguineous unions in the rural areas. From the total related/ consanguineous marriages in case group (n=255), subjects from rural areas accounted for 71.8% (n=183) of marriages whereas subjects from urban areas had 28.2% (n=72) consanguineous unions.

As regard congenital heart diseases, ventricular septal defect (VSD) was the most common CHD (32%, n=123) followed by 18.2% cases of Atrial Septal defect (ASD) and 13.5% cases of Patent ductus arteriosus. The relative frequency of each congenital heart disease among cases with reference to cousin or unrelated marriage type is shown in Table 3.

Among 384 cases, 76.8% had acyanotic CHD (n=295) while 23.2% had cyanotic CHD (n=89). Similarly 69.6% cases of cyanotic CHD had cousin marriage and 65.4% of acyanotic CHD cases had cousin marriages as described in Table 4.

Table 4: Distribution of marriage types in cyanotic and acyanotic congenital heart diseases

Consanguinity	Cyanotic CHDs (%)	Acyanotic CHDs (%)	Total (%)
Total (N)	**n=89**	**n=295**	**n=384**
First cousins	51 (57.3)	151 (51.2)	202 (52.6)
Second cousins	5 (5.6)	16 (5.4)	21 (5.5)
Distantly related	6 (6.7)	26 (8.8)	32 (8.3)
Non-related	27 (30.3)	102 (34.6)	129 (33.6)

Table 3: Distribution of marriage types in congenital heart diseases

Type of Disease	Related/ consanguinity with %			Non-related N (%)	Number	% CHD n=384
	First cousin n (%)	Second cousin n (%)	Distantly related n (%)			
VSD	67 (54.5)	8 (6.5)	8 (6.5)	40 (32.5)	123	32
ASD	38 (54.2)	2 (2.9)	9 (12.9)	21 (30)	70	18.2
PDA	28 (53.8)	1 (1.9)	5 (9.6)	18 (34.6)	52	13.5
AVSD	6 (37.5)	2 (12.5)	1 (6.2)	7 (43.8)	16	4.2
PS	6 (37.5)	2 (12.5)	2 (12.5)	6 (37.5)	16	4.2
AS	3 (25)	1(8.3)	1(8.3)	7 (58.3)	12	3.1
CoA	3 (50)	-	-	3 (50)	6	1.6
TOF	36(62.1)	5 (8.6)	6 (10.3)	11 (19)	58	15.1
TGA	11 (61.1)	-	-	7 (38.9)	18	4.7
SV	4 (100)	-	-	0 (0)	4	1.0
PA	-	-	-	3 (100)	3	0.8
TA	-	-	-	2 (100)	2	0.5
TAPVC	-	-	-	2 (100)	2	0.5
CCTGA	-	-	-	1 (100)	1	0.3
TAr	-	-	-	1 (100)	1	0.3

Abbreviations: VSD (Ventricular septal defect), ASD (Atrial septal defect), PDA (Patent ductus arteriosus), AVSD (Atrioventricular septal defect), PS (Pulmonary stenosis), AS (Aortic stenosis), CoA (Coarctation of aorta), TOF (Tetralogy of Fallot), TGA (Transposition of great arteries), SV (single ventricle), PA (Pulmonary atresia), TA (Tricuspid atresia), TAPVC (Total anomalous pulmonary venous connections), CCTGA (Congenitally corrected transposition of great arteries), T Ar (Truncus arteriosus)

DISCUSSION

The present study was carried out to determine the relationship of CHD with consanguineous marriages. In Pakistan inbreeding could be a potential risk factor for CHD as majority of marriages are consanguineous.[6] According to 2017-18 Pakistan Demographics and Health survey (PDHS 2017-18), 63.9% of marriages in Pakistan are related with highest prevalence of first cousin inbreeding (48.1%) in heavily populated province Punjab.[7] Consanguineous union was noted in 58.4% , 56.72% and 44.1% of the study population of Rahim Yar Khan, Sargodha and Mardan districts of Pakistan respectively.[8-10] In our study 45.8% of total subjects (cases and controls) were product of cousin marriage which is also significantly high but less than above studies. The reason of relatively less number of

consanguineous unions in study subjects could be less number of total study population presenting to our institute during the study period and predominant urban population as compared to above studies.

Cousin marriage is a known risk factor of CHD all over the world. In a study done in Saudi population 50.9% cases of neonatal CHD were associated with parental cousin marriage.[11] In another study done in Andhra Pradesh India 28.3% of the CHD subjects were product of consanguineous marriage.[12] A study in Bangladesh showed that 45.51 % of CHD patients were product of consanguineous marriage.[13] In a study by Dev D et al. 83% of children having CHD were product of consanguineous marriages and these all were Muslims highlighting religion based trend of cousin marriage.[14] The above four studies describe the significant association of parental cousin marriages and incidence of CHD in children. The consanguineous unions in our study case group was 66.4% ($p<0.01$) which shows significant association of CHD with cousin marriages and variability in incidence of such cases in different parts of the world as seen in above studies. Unrelated marriages are significant factor for freedom from CHDs. In our study we had 25.3% of children in control group whose parents were cousin that means most of the control subjects had parents who were unrelated to each other.

Congenital heart disease has been more commonly seen in patients whose parents were first cousin before marriage. According to Yunis K et al., there is 1.8 times higher risk of having a CHD diagnosed at birth in infants born to first cousin marriage as compared to those born to unrelated parents.[15] A study conducted in Karachi by Haq FU et al showed that CHD was seen in 74 % of children whose parents were first cousin before marriages.[16] The results of our study showed that, in the case group among the consanguineous unions, 79.2% were first cousin unions thus making the marriages more susceptible to have a CHD baby.

At present, 63.6 % of total population of Pakistan lives in rural areas while 52.2% of Faisalabad district population lives in rural areas.[17] In our study among cases from rural areas, 72.3% belonged to parents having consanguineous unions which show that CHD is more common in rural areas due to the same reason. Consanguineous marriages are preferred in these areas to strengthen the family relations, due to decreased demand of dowry by the relatives, tradition of marrying in the same caste and within the family without taking into account the negative impacts of consanguineous unions.

The spectrum of CHD is almost similar as we look at the different studies on cousin marriage. Fazeriandy A et al reported VSD (30%) as the most common CHD followed by ASD (25%), PDA (24%), TOF (12%) and TGA (6%).[18] Haq FU et al study shows VSD as the common defect followed by PDA, ASD and TOF.[16] The results of Al-Ani Z also are not too much different.[19] In our study VSD was the most common CHD (32%) followed by ASD (18.2%), TOF (15.1%), PDA (13.5%), TGA (4.7%), AVSD (4.2%) and PS (4.2%), thus the spectrum of CHD in our set up is almost similar to above mentioned studies

In our study the overall incidence of cousin marriage was slightly dominant in cyanotic CHD cases (69.6%) as compared to acyanotic CHD cases (65.4%). The reason could be small number of cyanotic CHDs (n=89, 23.2%) found in the study as compared to acyanotic CHDs (n=295, 76.8%). A study done by Yunis K et al.[15] showed a significant association of VSD, ASD, Single ventricle for first-cousin marriages. In a recent study from Peshawar, there was increased incidence of VSD, PDA, complex congenital heart diseases and ASD in children whose parents had cousin union.[20] A study from Egypt showed a significant association of parental cousin marriages and incidence of CHDs like ASD (16.5%), PDA (13.5%) and VSD (11%).[21] An other study by Gul M et al. described the incidence of CHD with cousin marriage while commonly associated CHDs were VSD(43%), ASD (29%), PDA (16%) and TOF (12%).[22] The results of our study are very much similar to these studies as consanguinity was commonly associated with VSD, ASD, PDA, TOF and TGA.

This is the first study of its kind from a pediatric cardiology department of Punjab, Pakistan. There is need to conduct more studies on cousin marriages association with congenital heart diseases as well as other contributing factors leading to CHD in Pakistan so that public awareness can be created to avoid such birth defects.

Our study has a few limitations as well. The study was focused only on congenital heart disease association with parental consanguineous marriages while many other factors are involved in CHD as a whole. The marital data was entirely based on parent's interview and we could not visit the residences of the family and could not check pedigree of each parent through NADRA certificate.

CONCLUSION

The present study findings strongly suggested a remarkable association between inbreeding and CHDs. In Pakistan where the consanguinity rate is extremely

high, this association might be a big problem. Cousin marriage is a custom in our population and most of the public is unaware of its detrimental outcomes. Thus there is an urgent need to make the people aware of this independent risk factor of CHDs.

AUTHORS' CONTRIBUTION:

ARM: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. AB, SH, SM: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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