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COUSIN MARRIAGES: ONE OF THE NEGLECTED CAUSES OF CONGENITAL HEART DISEASE: A CROSS-SECTIONAL STUDY

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Abstract

Background:
Congenital anomalies represent a significant global health concern, notably as a major contributor to birth defects and infant mortality. A primary factor implicated in their occurrence is marriage between blood relatives. The practice of cousin marriages across generations demonstrates a strong link to the development of congenital anomalies.

Objective:
This study aims to explore the association between parental consanguinity and CHD (congenital heart disease) among paediatric patients referred from nearby districts of Khyber Pakhtunkhwa to tertiary care hospitals in Peshawar.

Methods:
This descriptive cross-sectional study on 200 admitted paediatric patients with confirmed congenital heart disease from Khyber Pakhtunkhwa province was conducted over four months (March-June 2024) at a tertiary care hospital in Peshawar, Pakistan. Mothers of the enrolled children, receiving care at M.T.I. settings of Lady Reading Hospital and Hayatabad Medical Complex, Peshawar, were individually interviewed using a planned proforma after obtaining permission and providing study information in the local language.

Result:
In this cross-sectional study of CHD cases, a near-equal gender distribution was observed, with males comprising 50.5% and females 49.5%. A notable proportion of the study population (69%) reported consanguinity, with first-cousin marriages being the predominant form (64.5%). Ventricular Septal Defect (VSD) was identified as the most prevalent type of CHD, accounting for 32% of the cases, followed by Tetralogy of Fallot (TOF) at 17.5%. A statistically significant positive correlation ($r = 0.165$, $p < 0.05$) showed that increased parental consanguinity was linked to a higher chance of CHD diagnosis.

Conclusion:
This study highlights a significant association between multigenerational cousin marriages and congenital anomalies. Furthermore, it reveals a high prevalence of parental consanguinity within the study population, with first-cousin unions being

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the most common form. Notably, a statistically significant correlation was found, confirming a strong link between consanguinity and the occurrence of congenital heart disease (CHD).

INTRODUCTION

Consanguinity refers to marriage between individuals who share a common ancestor (1,2). The word "consanguinity" is rooted in Latin, where "con" implies similarity and "sanguineus" relates to blood, thus describing a bond between individuals with a common progenitor or blood relation (3). A significant portion of the global population, specifically one in eight individuals, one billion people, resides in nations where these practices are prevalent (defined as occurring at rates exceeding 20% – see Bittles, 2012). The risk of recessive genetic diseases is approximately doubled in children of consanguineous marriages when compared to children of non-consanguineous marriages (4).

In numerous Arab nations, cousin marriages are a common practice, with unions between first cousins being particularly prevalent, representing approximately 25-30% of all marriages. Furthermore, the incidence of cousin marriages is notably higher and reportedly increasing within the Western-affiliated populations of specific countries like Yemen, Qatar, and the United Arab Emirates (5). The closer the biological relationship between parents, the higher the likelihood that their offspring will inherit two identical copies of a detrimental recessive gene. This principle is particularly relevant in Arab Gulf countries and Pakistan, where a significant proportion of the population adheres to consanguineous marriage practices, with prevalence rates ranging between 40% and 60% (6).

A notable consequence of consanguineous marriages is the increased occurrence of congenital defects among offspring, a phenomenon particularly relevant in Pakistan, which exhibits one of the highest global trends in consanguineous unions (7). Marriages between closely related individuals, particularly first cousins, are a prominent factor in transmitting autosomal recessive disorders (8). They face an elevated likelihood of congenital heart defects, neural tube defects, cleft lip and/or palate, and various other physical abnormalities (9,10).

Congenital heart disease (CHD) is a significant global health concern, affecting millions of children worldwide (11). Congenital heart defects (CHDs) encompass a spectrum of cardiac malformations, ranging in severity from relatively simple conditions like septal defects and shunt lesions, such as Atrial Septal Defects (ASDs), to complex and critical presentations like single ventricle morphologies. The spectrum of risk factors contributing to congenital heart disease (CHD) varies geographically across the globe. Supporting the role of consanguinity in the development of CHD are inbreeding studies, which have elucidated an autosomal recessive inheritance pattern for certain congenital heart malformations (12).

While the exact etiology of CHD is often multifactorial, several risk factors have been identified, including genetic mutations, maternal infections, environmental influences, and consanguineous marriages. Cousin marriages, a culturally prevalent practice in various regions, have been increasingly recognized as a significant risk factor for CHD. Numerous studies indicate a strong correlation between parental consanguinity and an elevated prevalence of congenital heart defects, particularly VSD and ASD. This association is particularly evident in regions with high rates of intra-family marriages, such as certain tribal areas of Khyber Pakhtunkhwa, where traditional norms prioritize marriages within close kinship networks.

Despite the increasing evidence of the link between consanguinity and CHD, there remains a significant gap in public awareness and healthcare interventions targeting this preventable risk factor. Many affected communities lack access to genetic counselling and education regarding the potential consequences of cousin marriages, leading to a persistently high incidence of CHD. Addressing this knowledge gap is crucial in reducing the burden of congenital heart disease and improving long-term health outcomes.

This study investigates the correlation between parental consanguinity and congenital heart disease (CHD) in paediatric patients referred to tertiary care hospitals in Peshawar, Khyber Pakhtunkhwa. The research aims to quantify the prevalence of cousin

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marriages as a modifiable risk factor for CHD and to highlight the importance of public health initiatives, including educational programs and genetic counselling, to mitigate associated risks. The goal is to reduce the incidence of CHD and enhance the quality of life for affected individuals and their families.

MATERIALS AND METHODS:

Study Design:

A descriptive cross-sectional study

Study Setting and Duration:

This cross-sectional study was conducted at two tertiary care hospitals in Peshawar, Pakistan: Lady Reading Hospital (LRH) and Hayatabad Medical Complex (HMC) and was conducted within a period of 4 months (from March 2024 to June 2024).

Participants:

The study enrolled 200 admitted paediatric patients with confirmed congenital heart disease from different areas of Khyber Pakhtunkhwa province who were receiving care at the M.T.I. settings of Lady Reading Hospital and Hayatabad Medical Complex, Peshawar. Eligibility criteria included ward-admitted patients, both surgically corrected and non-corrected, presenting with suggestive signs and symptoms of CHD such as cyanosis, tachypnoea, dyspnoea, cardiac murmur, chest infection, chest deformity, abnormal cardiac size on chest x-ray, or heart failure, admitted due to complications or as newly diagnosed cases; excluded were OPD patients and those received at the Accidents & Emergency department. All these patients were admitted for some reasons of complications or newly diagnosed cases. These observed signs & symptoms strongly determine the presence of congenital heart disease.

Diagnostics Procedures:

All patients' mothers were interviewed individually on a planned proforma after getting prior permission and necessary information about the current study in the local language. The history of CHD was confirmed from the admission file, which contains all the necessary information. Patient data includes the child's Name, age, sex, weight, address, current complaints, Investigations i.e. (ECG, X-ray, and Echocardiography), & Diagnosis.

Parents' data includes Consanguinity, Cousin Relations, i.e., (first or second), Previous family history, i.e., Number of children, affected or normal, were evaluated for clinical correlation. Standard Echocardiography examination reports already done at the hospital laboratory were evaluated for data collection.

After fulfilling all the criteria and clinical correlation of signs and symptoms, patients were recorded in a planned proforma. Patients fulfilling the inclusion criteria were selected randomly within wards. All those admitted patients who were not fulfilling the inclusion criterion were excluded.

Data sources:

Data for congenital heart lesion (CHL), the outcome variable, were sourced from patient admission files and standardized echocardiography reports, with diagnosis confirmed through echocardiographic findings supplemented by ECG and X-ray reports, ensuring a comparable assessment using established paediatric cardiology protocols within the tertiary care settings. Parental consanguinity, the primary predictor, was assessed through structured interviews with mothers using a standardized proforma in the local language, allowing for consistent categorization of relatedness and degree of cousin relationship. Previous family history of affected children was collected via maternal interviews, while child characteristics such as age and sex, along with presenting clinical signs and symptoms, were extracted from patient admission files, representing routine clinical data collection.

Study Size:

A total of 200 patients were included in the present study. OpenEpi software calculated a sample size of 200 participants, employing a 95% confidence interval and a 5% level of significance. Non-Probability Convenient sampling technique was used for the selection of the study samples.

Statistical Analysis:

Data analysis for this cross-sectional study was conducted using SPSS version 23. Descriptive statistics, including frequencies and percentages,

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were used to summarize the demographic and clinical characteristics of the study population, and tables were created for data visualization. Given that the data was not normally distributed, Spearman's Rank-Order Correlation, a non-parametric test assessing the monotonic relationship between the ranks of two variables, was performed to determine the correlation between consanguinity and congenital heart disease (CHD).

RESULTS:

The study analysed 200 confirmed congenital heart disease (CHD) cases, all of which were isolated non-syndromic CHD cases. The findings revealed significant insights into gender distribution, consanguinity, age distribution, and CHD lesion types. Additionally, a correlation between consanguinity and CHD development was observed.

The gender distribution of the congenital heart disease (CHD) cases was almost evenly split, with males comprising 50.5% (n=101) of the study population, as detailed in Table 1. This near 1:1 male-to-female ratio indicates no statistically significant sex-based susceptibility to CHD within this study. The age distribution of the 200 CHD patients revealed that the largest group (48.5%, n=97) was between 1 and 5 years of age. Infants under one year constituted 33.0% (n=66) of the cohort, while the smallest proportion (18.5%, n=37) was in the 6 to 10-year age range (Table 1). This distribution indicates that a significant number of CHD cases were identified in early childhood.

The prevalence of parental consanguinity among the studied CHD patients was notably high, with 69.0% (n=138) originating from consanguineous marriages, while the remaining 31.0% (n=62) were born to non-consanguineous parents (Table 1). This substantial proportion of consanguinity underscores its potential role as a significant factor in the etiology of CHD within this population.

Among the 138 CHD patients with a history of parental consanguinity, the majority (64.5%, n=129) were offspring of first-cousin marriages. A smaller proportion (4.5%, n=9) were from second-cousin unions. The remaining 31.0% (n=62) of the total cohort reported non-consanguineous parentage (Table 1). This detailed breakdown highlights the predominance of first-degree consanguinity within the affected population.

The most frequent CHD lesion was Ventricular Septal Defect (VSD) at 32.0%, followed by Tetralogy of Fallot (TOF) at 17.5% (Table 2). Combinations of defects, such as ASD with VSD and PDA, and VSD with PDA, also constituted a notable portion of the CHD diagnoses. Less frequent lesions included isolated ASD, PDA, TGA, and TGA with VSD.

A Spearman's correlation test revealed a statistically significant positive correlation between consanguinity and diagnosed CHD ($r = 0.165$, $p<0.05$), indicating that higher levels of consanguinity were associated with a greater likelihood of CHD development. Similarly, a significant positive correlation was observed between the nature of consanguinity and diagnosed CHD ($r = 0.157$, $p<0.05$), suggesting that closer degrees of consanguinity were related to a higher incidence of CHD.

The very strong positive correlation between consanguinity and nature of consanguinity ($r=0.956$, $p<0.01$) confirms the expected relationship that as consanguinity is reported, the nature of that consanguinity is also more likely to be specified and potentially closer. p-value=0.019, indicating a statistically significant correlation between consanguinity and CHD (Table 3).

DISCUSSION:

This study of congenital heart disease (CHD) in cousin marriage cases revealed a nearly equal distribution between male and female patients. A notably high prevalence of parental consanguinity was observed within this cohort, with first-cousin marriages being the predominant form. The largest proportion of affected individuals fell within the 1-5year age group. Ventricular Septal Defect (VSD) was identified as the most frequent CHD lesion, followed by Tetralogy of Fallot (TOF). Statistical analysis further demonstrated a significant positive correlation between parental consanguinity and the diagnosis of CHD, indicating that closer degrees of relatedness were associated with a higher likelihood of developing the condition.

A separate study in Al Madinah city, also conducted in the same year, indicated that a substantial proportion of the respondents acknowledged the

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link between consanguineous marriages and increased health risks in their children, with 39.6% agreeing and an additional 23.5% strongly agreeing with this assertion (13).

Both the Qatar study (Sidra Medicine/Weill Cornell Medicine-Qatar) and our study reveal a high prevalence of first-degree cousin marriages among parents of children with congenital heart disease (CHD), with our study showing a notably higher proportion (64.5%) compared to the Qatar study (41.4%). In contrast, the prevalence of second-degree cousin marriages was notable in the Qatar study (12.1%) but considerably lower in our study (4.5%). Despite these differences in the degree of consanguinity, both studies consistently identified Ventricular Septal Defect (VSD) as the most frequent CHD lesion. However, the second most frequent lesion differed, with Patent Ductus Arteriosus (PDA) being more common in the Qatar cohort and Tetralogy of Fallot (TOF) in our study, suggesting potential population-specific variations in the spectrum of CHD associated with consanguinity (14).

Both studies show first-cousin marriage is the most common type of consanguineous union among parents of patients (Kabul: 61.8%, Quetta:32.1% and our study: 64.5%), highlighting its significance in populations with prevalent consanguinity and its potential contribution to genetic risks. This consistent prevalence of first-cousin marriages across geographically distinct populations suggests it is a common practice in communities where consanguinity is prevalent and likely contributes significantly to the observed genetic risks (15)(16).

A study conducted in the TRoCA region reported that congenital heart defects (CHDs) arising from first-cousin marriages constituted 12.5% of their cases. In contrast, our study reveals a considerably higher proportion, with 64.5% of CHD cases having a history of parental first-cousin marriage (17). Similarly, a study revealed a notably elevated child mortality rate under the age of 5 years among offspring of close biological kin (16.62%) in comparison to children from non-consanguineous unions (5.77%)(18).

Studies from the Department of Paediatric Cardiology (FIC) Faisalabad, Dhaka Shishu Hospital (focusing on offspring of consanguineous parents), Maiwand Hospital, a pediatric teaching hospital in Kabul, Aghanistan, and Sidra cardiac registry in Qatar consistently identify Ventricular Septal Defect (VSD) as the most common congenital heart defect. While the Faisalabad data reports VSD (32%) followed by Atrial Septal Defect (18.2%) and Patent Ductus Arteriosus (13.5%), and both the Dhaka and Qatar studies also highlight VSD as the most frequent acyanotic lesion, the subsequent order of prevalence for ASD and PDA varies. The Dhaka study found ASD and PDA equally prevalent as the second most common acyanotic lesions, whereas the Qatar study and our own demonstrate a different distribution, suggesting that while VSD is a consistently prevalent CHD, the relative frequency of other common defects like ASD and PDA might differ across populations and in relation to factors such as parental consanguinity (19-23).

A relevant frequency of the major congenital heart 1esions reported in this study was comparable to other work done in the same title. The frequency of VSD (32%) reported in this study was high as compared with Shafqat eta (21%) (24), Rahimtoo la et al (25) (39.46%) & Rehan et al (42.2%). All the four trials reported the same high frequency of VSD followed by TOF & ASD.

CHD is the most common infant disorder. This may because of widespread rate of consanguinity present inside our community. Well approach to antenatal care is cost effective and may be a key to Success over this burden. Social awareness is the need of the day. Inside hospitals proper parents counseling in this manner may play better role in guidance of community and upcoming generations in society. In this regard inside wards setups there should present parents counsel centers who should provide literatures and counseling in local language to avoid cousin marriages in the families, so that to minimize the rate of CHDs in society.

Congenital heart diseases are an increasing issue of current era. Number of newborns with defects is increasing with the passage of time. There are multiple factors discussed early on, which are consider contributing factors to the development of Congenital Heart Defects. These factors may be either modifiable or un-modifiable. New researches are in progress to minimize this burden on parent's economic status.

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Because in this observational study, most of the patients were from such areas where traditional are followed. They have strong beliefs on their grandparents. They can't even think about outside family. Their culture didn't accept the advancement of science and the latest literature. In this respect approach to the local Masharan and Ulma may contribute the maximum to change their false belief and negative thinkings. As our beloved Prophet Hazrat Muhammad (PBUH) also gives the message of building relationships from outside families. In many of Ahadees, it has been revealed that you people should try to enhance your relationships through marriages from other tribes and families. This will enhance love and relations amongst your upcoming generation.

As discussed earlier about the risk factors may be minimized by avoiding maximum drugs during the first trimester of pregnancy. Gonads and fetus should be protected from overexposure to X-ray radiation. Proper vaccinations against rubella to mothers should offer during childhood.

The prevalence of CHDs will be dramatically reduced if preventive strategies are implemented by local physicians/obstetricians personally in their locality community during routine check-ups. Because local awareness may minimize the prevalence rate.

LIMITATION:

Due to the cross-sectional nature of the study, causal relationships between variables cannot be determined, and the sample size was small for generalizability.

SUGGESTIONS:

Main suggestions that need emergency considerations are,

1. Awareness programs to be planned at affected areas through involving local focal persons along with awareness campaigns through social and print media from health facilitators.

2. Counselling provision to the affected family regarding care and management of the child suffering from congenital heart disease.

3. Proper diagnostic facilities in the remote areas of the province.

4. Properly trained staff (Specialist, Echo-Cardiographer) availability in remote centers.

CONCLUSION:

Parental consanguinity was significantly associated with an increased risk of congenital heart disease among paediatric patients in Peshawar, with first-cousin unions being most prevalent. The findings emphasize the critical need for targeted genetic counselling and public health interventions to address consanguinity-related genetic risks. Further research is recommended to explore causal pathways and preventive strategies.

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CONFLICTS OF INTEREST:

The author declares that there are no conflicts of interest.

ETHICAL COMMITTEE APPROVAL:

This study received ethical approval from the Institutional Review Board (IRB) committee of the Institute of Paramedical Sciences, Khyber Medical University (Reference No IRC/IPMS/24/00101).

AUTHOR CONTRIBUTIONS:

BA conceived the idea, designed the study, supervised the project, analysed the data, and reviewed the manuscript. SG and HU performed the clinical workup, wrote the initial draft of the manuscript, KK and AU collected clinical data.

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Table 1: Demographic and Clinical Characteristics of Patients (N = 200)

Variable	Category	Frequency (n)	Percent (%)
Sex	Male	101	50.5
Age Group	Less than 1 year	66	33.0
	1–5 years	97	48.5
	6–10 years	37	18.5
Consanguinity	Yes	138	69.0
Nature of Consanguinity	First Cousin	129	64.5
	Second Cousin	9	4.5
	Non-Cousin	62	31.0

Table 2: Frequency of Congenital Heart Disease (CHD) Types (N = 200)

CHD Type	Frequency (n)	Percent (%)
Atrial Septal Defect (ASD)	18	9.0
Ventricular Septal Defect (VSD)	64	32.0
ASD + VSD	25	12.5
Tetralogy of Fallot (TOF)	35	17.5
Transposition of Great Arteries (TGA)	5	2.5
Patent Ductus Arteriosus (PDA)	23	11.5
ASD + PDA	9	4.5
VSD + PDA	16	8.0
TGA + VSD	5	2.5
Total	**200**	**100.0**

Table 3: Pearson Correlation Matrix Between Study Variables

Variables	Age	Diagnosed CHD	Consanguinity	Nature of Consanguinity
Age	1.000	0.096	0.065	0.085
Diagnosed CHD	0.096	1.000	0.165*	0.157*
Consanguinity	0.065	0.165*	1.000	0.956**
Nature of Consanguinity	0.085	0.157*	0.956**	1.000

*p < 0.05, **p < 0.01, *CHD = congenital heart disease*

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