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Original Article

The Frequency of Congenital Heart Disorders among Children Issued from Consanguineous Marriages in Khorasan Province, Northeast of Iran

Mahdieh Daliri Ghouchan Atigh[1], Hassan Motaghi[2], Atieh Eslahi[1], Zahra Jafari[1], Sara Shahidi[1], Mahdi Keyvanlou[2], Mohammad Hassanzadeh Nazarabadi[1*]

1. Department of Medical Genetics, Mashhad University of Medical Sciences, Mashhad, Iran.

2. Department of heart, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.

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Congenital heart disorders (CHDs) are an important health issue due to heavy costs and emotional effects they impose to families and society. In general, the prevalence of CHDs is approximately 8 in 1000 newborn, with a multifactorial origin. On the other hand, previous studies have shown that the prevalence of CHDs is high among the children of parents with consanguineous marriage. The aim of this investigation was to determine the frequency of CHDs among the children of parents with consanguineous marriage in comparison with non-consanguineous parents. 605 medical records of children with CHD admitted at Imam Reza's hospital, Mashhad, Iran during the years 2001 to 2005 were examined and questionnaires were completed and data were analyzed using a statistical software. The mean age of affected children was 1.25± 4 years. The average age of left obstructive acyanotic group was significantly higher than others (P< 0.001). Acyanotic disease with left to right shunt (%49) and cyanotic with decreased pulmonary flow (%19) were the most common defects. Other most common lesions were ventricular septum defects (VSD), atrial septum defects (ASD) and patent ductus arteriosus (PDA). Our data revealed that the risk of CHD increases with parental inbreeding, but there was no significant relationship between parents inbreeding and the type of CHD.

Keywords: Congenital heart disease (CHD), consanguinity, children

Congenital defects are defined as a physical abnormality that is present at the time of birth up to few weeks after birth (1). Heart development in humans is complex and starts very early, from the third to eight weeks of gestation. Development begins with a primitive tube that beats at 25th day of gestation and ends in the four-chamber heart (2, 3). Congenital heart disorders (CHDs) are caused by defects in one or more structure of the heart or blood vessels that occur during the 3rd- 8th weeks of the first trimester of pregnancy when the heart is being formed (4). Approximately about 8 infants per 1000 live births have congenital cardiovascular malformations (5-7) and CHD accounts for one third of deaths due to congenital malformations (8). Almost 90% of CHDs are reported as being

*Correspondence: Department of Medical Genetics, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: NazarabadiM@mums.ac.ir

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multifactorial in origin (9). These disorders include ventricular septal defects (VSD), atrial septum defects (ASD), patent ductus arteriosus (PDA), atrioventricular septal defect, pulmonary atresia, tetralogy of Fallot, etc… (10-13). CHD is associated with multiple risk factors including a variety of maternal ailments such as infections, smoking, and gestational diabetes mellitus. Fetal risk factors such as prematurity, low birth weight and stillbirth are also associated with CHD (14, 15). Consanguinity may be another significant risk factor (16-18). Endogamy, the marriage of individuals with a common ancestor is still a common practice in the Middle East (19). Among the European populations, the consanguinity rate is generally less than 0.5%, while the rate of consanguineous marriages in Southern and Western Asia, North Africa and Saudi Arabia is 22–55% (20, 21). Consanguineous marriages are favored in the Iranian populations with a prevalence rate of 58.2% and an average inbreeding coefficient of 0.0185, which is relatively high compared with many other countries (22). It is believed that these types of marriages, offer strong social, cultural and economic advantages. On the other hand, consanguinity increases the risk of autosomal recessive conditions, stillbirths, perinatal mortality and morbidity, birth defects as well as CHDs (23-26). Worldwide, parental consanguinity confers a two to three fold increase in risk for a broad range of CHD phenotypes, as reported in Saudi Arabia, Lebanon and South India (7, 11, 12, 26). Consanguinity often has genetic implications for offspring. A clinical study in Iran showed a mean prevalence of 12.30 CHD per 1000 live births between 1998 and 2007 but there are very limited studies on determining effective factors of these diseases in Iran and available data identifying effective factors have mainly been obtained from studies of other countries (22, 27, 28). The aim of this study was to determine the frequency of CHDs among the children of parents with consanguineous marriage in northeast of Iran.

Materials & Methods

This descriptive investigated and 605 patients (mostly children) with CHD who were referred to Imam Reza hospital, Mashhad, Iran, during 2001-2005. The recorded variable factors included the age, sex, the number of affected offspring, family history, other congenital diseases, andf parents familial relationship. Data were collected from patients' medical records and questionnaires. The results of data processing are reported as mean± SD. ANOVA and X^2 tests were used to determine the relationships between the variable factors. SPSS version 15 was used for data analyzing.

Results

In total 605 patients with CHDs were studied and have been classified into 7 groups according to the type of CHD (Table 1). Acyanotic with left to right shunt disease was the most frequent lesion. In the present study the youngest patient was a newborn and the oldest one was 21 years old. The mean age was 1.25± 4 years. The mean age of left obstructive acyanotic patients was significantly higher than others (15.02 years, $P< 0.001$). The sex distribution was 53% male and 47% female. Acyanotic with left to right shunt (%49) and cyanotic with decreased pulmonary flow (%19) were the most frequent lesions (Table 1). 13% of patients had positive familial history (except siblings) and only 2 cases had a brother/sister with CHDs. Consanguineous marriages are favored in the

Table 1. Classification of CHDs

Group1	**acyanotic with left to right shunt**
Group2	acyanotic with left shunt
Group3	acyanotic with right shunt
Group4	Cyanotic with decreased pulmonary flow
Group5	Cyanotic with increased pulmonary flow
Group6	others

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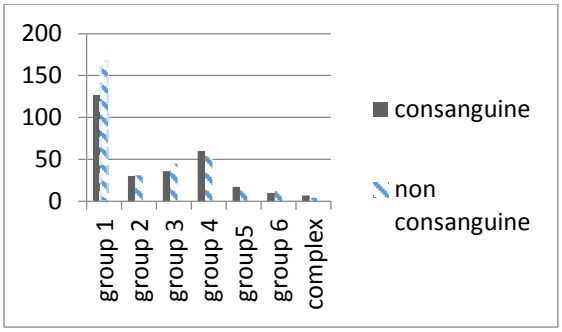

Figure1. Distribution of consanguineous parents.

Iranian populations and the distribution of consanguineous marriages in Khorasan province during 2001-2005 is illustrated in Table 2. 46% of patients were issued from consanguineous marriages: third-degree relatives for 33% of the cases and fourth or higher-degree relatives for 13% of them. Figure 1 shows the distribution of consanguineous and non consanguineous marriages among parents of different groups of CHD patients. Among patients with consanguineous parents, single disorders such as Ebstein's anomaly and Eisenmenger syndrome were not observed (P= 0.03).

Discussion

Despite the many investigations that have been conducted on the relationship between consanguinity and CHD, the precise nature and significance of the association remains unclear (29, 30). Third-degree consanguineous marriages are common in India. According to the study in 2010, parental inbreeding is considered as a risk factor for CHD (31). In 2001, a study conducted in Saudi Arabia reported a significant association between first cousin consanguinity and defects such as atrial septum defects, ventricular septal defects, atrioventricular septal defect, pulmonary stenosis, and pulmonary atresia which suggests a recessive component contributing to the multifactorial inheritance (11, 32). In another study among British Asian Muslims, it was found that marriages with a higher degree of inbreeding are common and congenital heart anomalies in this particular population is higher than the general population (33). In 2003, Nabulsi et al. carried out a study at the University of Beirut among 759 Lebanese patients with congenital heart malformations and showed that all cardiac abnormalities other than coronary artery disease and large artery, were significantly associated with parental consanguinity (12). Many of the more common CHDs appear to be genetically heterogeneous. This group of congenital defects may occur by a single gene mutation, chromosomal rearrangement or by contact with teratogenic infections like rubella or maternal diabetes (29, 34-36). In the majority of cases, the cause is unknown and the diseases are often regarded as multifactorial (9). In the multifactorial threshold model, the risk for first degree relatives is equal to the square root of the incidence of the corresponding trait in the general population, which is different from single gene traits where the risk for siblings is completely independent from the population incidence. Our data on incidence of common types of heart defect, and in comparison to the recurrence risk of those defects in siblings, are in favour of a multifactorial origin of CHDs. These values can be used to estimate the recurrence risk in first degree relatives, while for second and third degree relatives the risk would be lower, but not

Table 2. Distribution of consanguineous marriages in Khorasan province between 1380-1384 years

Consanguineous marriages (%)			
Total	**More than third-degree**	**Third-degree**	
33	13	20	Khorasan province-1380
33	13	20	Khorasan province-1381
34	14	20	Khorasan province-1382
33	14	19	Khorasan province-1383
32	13	19	Khorasan province-1384
33.2	13.6	19.6	Average of these years
46	13	33	Patients in this study

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much higher than the risk for the population. Finally, consanguinity increases the overall risk of heart diseases in the population.

Major categories of CHD affect many children every year, imposing heavy costs and emotional effects to families and society, highlighting the importance of disease prevention. This study investigated the role of consanguinity in CHD occurrence in Khorasan province of Iran and the findings can be useful in genetic counseling, newborn screening programming or prenatal diagnosis.

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Conflict of interest

The authors declared no conflict of interests.

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