Prevalence of Congenital Heart Disease: A Single Center Experience in Southwestern of Iran

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Abstract
Background: Congenital heart disease (CHD) refers to complex abnormalities that affect the structure or function of the heart due to embryonic defects. There is little accurate statistical data about prevalence, incidence and frequency in many developing countries such as Iran. The aim of this study was to evaluate the frequency of CHD in patients who were referred to the Department of Pediatric Cardiology in a large single-center in Southwestern of Iran.

Methods: This is a retrospective, cross-sectional study. Patients with various cardiac malformations were each investigated separately. A check list was used to collect information. It was comprised of three parts; demographic characteristics, Patient’s birth details and maternal data.

Results: The frequency of ventricular septal defect (VSD), atrial septal defect (ASD) and tetralogy of fallot (TOF) were 125 (28.47%), 48 (10.93%) and 41(9.3%) respectively. Family history was reported in 26(11.1%) cases. Down syndrome, skeletal anomaly and hematological anomaly were the most common co-anomalies. Parental consanguinity was 48.7%.

Conclusions: Present study showed that VSD was the most common CHD subtype followed by family history, familial marriage, extra cardiac anomalies (ECAs), birth weight, and maternal concomitant disease. But there was a controversial relationship between birth order and drug history in CHD.

Keywords: congenital heart disease, prevalence, risk factors, ventricular septal defect, atrial septal defect, Iran

1. Introduction
Congenital heart disease (CHD) refers to complex abnormalities that affect structure or function of the heart due to embryonic defects. CHD is the most common of all birth defects that occurs about 4/1,000 to 50/1,000 in live births annually (van der Linde et al., 2011). The onset of CHD varies in different countries. Unfortunately, there is little accurate statistical data on prevalence, incidence and frequency in many developing countries such as Iran (Fixler et al., 1990; Amel-Shahbaz et al., 2014; Amaral et al., 2015).

Although many studies have been conducted on the etiologies of CHD, they are yet to be discovered. Nevertheless it seems that CHD is a multi-factorial and polygenic disease caused by environmental factors and genetic background (Vecoli et al., 2014). Some environmental factors that play a probable role in its etiologies include history of maternal illness during pregnancy, positive familial history, number of pregnancies, maternal hypertension, maternal medications and exposure to medications during pregnancy (Ogeng’o et al., 2013). Different studies have shown that risk factors such as gender, familial marriage, maternal age, medication during pregnancy, number of pregnancies and birth weight are indeterminate. Almost 15% of the CHD etiologies can be related to a specific cause (Nielsen et al., 2005; Sadowski, 2009; Almawazini & Al-Ghamdi, 2011; van der Bom et al., 2011; Zhang et al., 2012; Naghavi-Behzad et al., 2013; Simeone et al., 2015; Su et al., 2015).
The aim of this study was to investigate the frequency of CHD in 234 patients. Unlike most studies, patients with multiple cardiac malformations (complex CHD) were evaluated individually. Except for known complex CHDs such as TOF. Then investigated each one of their malformations singly.

2. Method

The present investigation was a retrospective, cross-sectional study performed in the Department of Pediatric Cardiology in Golestan Hospital- a large single-center in Southwest of Iran (located in Ahvaz)-during 2009 to 2010. Inclusion criteria were as follows: all patients aged 0-18 years whom echocardiographic, computed tomography angiography or angiographic examination had confirmed their disease. Patients with insufficient information were excluded. We separated patients who had multiple cardiac malformations (complex CHD), then investigated each one of their malformations singly. The total number of abnormalities was 439. Medical records of the patients were collected by three medical students and were confirmed by a pediatric cardiologist. Data were entered into a CHD check list.

The check list was divided to three parts:

1) Demographic characteristics included name of the child, gender and date of birth.
2) Patient’s birth details included gestational age (preterm, term or post-term), birth weight, associated anomalies, family history and CHD type.
3) Maternal data included history of illness and drug consumption during pregnancy, number of pregnancies and familial marriage.

A written informed consent was taken from the patients or their family members. Collected data were analyzed using statistical package for social sciences (SPSS) software version 15. Chi-square test was used to reveal the correlation between CHD and other variables. P<0.05 was considered significant.

3. Result

A total of 234 CHD cases were evaluated. Out of which 106 (45.3%) were female and 128(54.7%) were male. The age range was 0 to 18 years with mean age of 3.3 years. Birth weight data was available for 190 cases, from which the minimum weight 1.3kg and the maximum weight 5kg was obtained (mean birth weight, 3.07±0.646kg). There were 14.7% CHD cases with birth weight <2.5kg. According to Figure 1, the most common CHD subtypes were ventricular septal defect (VSD) (28.47%), atrial septal defect (ASD) (10.93%), tetralogy of fallot (TOF) (9.3%), and pulmonary stenosis (PS) (9.1%). Other types of CHD are shown in Figure 2.

![Frequency of Birth Weights](image-url)

Figure 1.
Figure 2.

According to the evaluations; ASD, tricuspid regurgitation (TR), pulmonary stenosis (PS), transposition of the great arteries (TGA), VSD and TOF were the most common lesions in males and patent ductus arteriosus (PDA) was the most common anomaly in females. According to the gestational age; 211 (90.17%), 15(6.41%), 8 (3.41%) were term, pre-term and post term, respectively. CHD recurrence was assessed via family pedigrees in all subjects. A total of 222 cases were analyzed for family history. 26(11.1%) of cases were found to have family history of CHD. VSD was strikingly associated with a positive family history.

In the current study parental consanguinity was 48.7%. The most common CHD subtypes in familial marriage were VSD (68, 59.6%), ASD (28, 24.6%) and PS (15, 13.2%). Moreover, Down syndrome and skeletal anomaly had superlative association with familial marriage.

According to Figure 3, the percentage of cases with 1st, 2nd and more birth order were 41.5%, 25.5%, and 32.9%, respectively.

Figure 3.
Of all cases, 49(21.2%) of children had associated anomalies. As shown in Figure 4, Down syndrome, skeletal and hematological anomalies were the most common anomalies. According to our study, 12(5.1%) cases of 216 had positive history of maternal medication exposure during pregnancy. Approximately 37 (16.3%) mothers had concomitant disease during pregnancy. Data showed that gestational hypertension (GHTN) and gestational diabetes mellitus (GDM) were the most common diseases with frequencies of 27% and 24.5%, respectively.

Figure 4.

The most frequent malformations were evaluated in order to find out their association with each other. There was no significant association between the factors of gender, age, birth weight, associated anomalies, type of extra cardiac anomalies (ECAs), history of maternal illness and medications during pregnancy, gestational age, number of pregnancies and positive family history of consanguinity with CHD (P > 0.05).

4. Discussion

In our investigation, we evaluated the frequency of all CHD subtypes separately, except for known complex CHD such as TOF. Finally, 439 types of CHD subtypes were found. The most common subtypes comprised VSD (28.47%), ASD (10.93%) and TOF (9.3%). We performed a similar method to our study with other studies; i.e. the frequency of all CHD subtypes in the following studies was calculated singly. This was done in order to compare the results with other studies. In our study, the most frequent CHD belonged to VSD. This finding was confirmed by Yang et al. and Fixler et al. studies (Table 1) (Fixler et al., 1990; Yang et al., 2009). But, ASD was the most frequent subtype in Kapoor et al. and Nikyar et al. studies (Kapoor & Gupta, 2008; Nikyar et al., 2011). Also, ASD frequency came second. This result was similar to the study of Yang et al., whereas Nikyar et al. and Kapoor et al. introduced VSD as the second prevalent CHD subtype (Kapoor & Gupta, 2008; Yang et al., 2009; Nikyar et al., 2011).

Table 1. Comparison of the frequency of congenital heart disease in different studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Years</th>
<th>VSD</th>
<th>ASD</th>
<th>TOF</th>
<th>PS</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallas (USA)</td>
<td>1971-1984</td>
<td>42.8%</td>
<td>7%</td>
<td>8.9%</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>2002-2007</td>
<td>22.8%</td>
<td>23.5%</td>
<td>4.6%</td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>2007</td>
<td>34%</td>
<td>10.8%</td>
<td>4.7%</td>
<td>9.2%</td>
<td></td>
</tr>
<tr>
<td>Gorgan (Iran)</td>
<td>2007-2008</td>
<td>17.52%</td>
<td>38.14%</td>
<td>2.06%</td>
<td>7.21%</td>
<td></td>
</tr>
<tr>
<td>Ahvaz (Iran)</td>
<td>2009-2010</td>
<td>27.14%</td>
<td>11%</td>
<td>9.3%</td>
<td>5.73%</td>
<td></td>
</tr>
</tbody>
</table>
The investigation by Yang et al. had similar findings for frequency of VSD and ASD with 34% and 10.8%, respectively (Yang et al., 2009). But Tandon et al., Rahim et al. and Nikyar et al. introduced ASD as the most prevalent CHD subtypes with the frequency of 44.54%, 19.54% and 38.14%, respectively (Nikyar et al., 2011; Amel-Shahbaz et al., 2014). Unlike our study, Nikyar et al. and Tandon et al. (2010) introduced VSD as the second prevalent CHD subtype with the frequency of 22.72% and 17.52%, respectively (Nikyar et al., 2011). In the present study, TOF was the third frequent CHD, while PS was the third common CHD in the studies of Kapoor et al., Yang et al. and Nikyar et al. In our study and Fixler et al.’s study, PS had the fourth frequency and in contrast with other studies where it belonged to TOF (Fixler et al., 1990).

A significant finding in our study was the higher frequency of CHD among family pedigrees (11.1%). However, in Oyen et al. and Fung et al. study, the prevalence of CHD in first degree relatives was reported as 3.1% and 9% respectively (Oyen et al., 2009; Fung et al., 2013). Some studies have shown CHD recurrence between 2.7% and 4.1% (27). The prevalence of CHD seems to be higher than expectation levels probably due to some undiagnosed CHD cases. Thus, screening family members, who have had procedures such as echocardiography or genetic evaluation, may be helpful. The higher recurrence rate of family pedigrees in our study may have come from differences in environmental and ethnic factors. Parental consanguinity existence in our study was 48.7% versus Tandon et al.’s study where it was 26.36% (Tandon et al., 2010).

In the present study, ECAs rate was 21.2% with the highest rate belonging to Down syndrome (7.26%). Skeletal and hematological anomalies were 4.27% and 3%, respectively. In a cohort study, Fung et al. (2013) demonstrated that the number of ECAs in CHD cases had a higher frequency in comparison with the control group (27.3% vs. 9.0%) (Fung et al., 2013). According to our investigation, Down syndrome was the most prevalent ECAs (4.14%). It should be noted that this rate was slightly lower than Fung et al.’s study (Fung et al., 2013) but, musculoskeletal anomalies had the same frequency (4.0%) in both studies. Due to our limitations, particularly in genetic evaluation, we were unable to compare other ECAs with Fung et al.’s study (Fung et al., 2013). Using genetic evaluation for screening and diagnosis of ECAs are likely to reduce adverse complications by early intervention. In order to achieve this goal, we need to develop high-resolution genomic arrays (Greenway et al., 2009; Stevens et al., 2010; Arrington et al., 2013). We reckoned that infants’ birth order might be one of the effective causes of CHD occurrences. On the contrary to this assumption, our evaluations showed a negligible relation between more than one birth order and CHD which was not significant. some studies have reported that birth order of infants with more than one is another important risk factor, but several investigators indicated that birth order with more than second, increases the risk of (23,24). We suspected that the occurrence of CHD was affected by birth weight. The question was; whether individuals with lower birth weight (<2,500 g) were at a higher risk for the CHD than those with birth weight (>2,500 g). We could not find a clear and absolute response to this in our assessments. However, there is some evidence that CHD is associated with low birth weight (Tandon et al., 2010).

Maternal disease during pregnancy acted as an important agent in CHD occurrence. Zhieva et al. and Nielsen et al. studies demonstrated that GDM was an evidence for this assertion. Additionally, our results showed that 16.3% of mothers had positive history (Nielsen et al., 2005; Zhang et al., 2012). Our study also displayed that 12 (5.1%) cases of 216 had positive history for maternal medication exposure during pregnancy. Another important environmental agent generating a major challenge is maternal medication exposure during pregnancy. This does not include only teratogen drugs, but safe medications as well. Fung et al. have expressed doubt regarding the existence of a relationship between positive history of drug use during pregnancy and CHD (Fung et al., 2013). 5% of mothers had a positive drug history during pregnancy, although this result is biased due to the vast missing data.

The main limitation of our study was the absence of a control group. Another limitation was the lack of hospital-based genetic screening for all CHD families which could have resulted in an underestimation of ECAs recurrence. On the other hand, gene-environment interactions contribute to complex multi-factorial disorders like CHD. It is probable that some death in children with CHD remains undetected because of the co-disorders and undiagnosed CHD. We should consider other possible factors like infections, occupational history, dust affection and other habits (smoking, alcohol, etc.) before and during pregnancy. Conducting a retrospective study, data related to the mothers during pregnancy was biased. Thus, the findings need to be interpreted carefully and others associated factors should not be dropped out. Our study showed VSD, ASD, TOF and PS were the most common CHD subtypes, respectively. We concluded that family history, familial marriage, ECAs, birth weight, maternal concomitant disease had a high rate in CHD cases, although, there was a controversial relationship between birth order and drug history in CHD.
Author’s suggestions:
1) Regular and standardized marriage consultations especially for family marriage in ethnicities with high prevalent rates of CHD or those with positive first degree relation family history.
2) Population-based CHD registration should be launched, particularly in developing countries.
3) Patients with high frequency of ECAs especially down syndrome should be examined for CHD.
4) More studies should be done about other risk factors such as alcohol consumption based on its different impacts on different ethnicities.
5) Emphasizing on more investigations in paternal roles which unfortunately is being neglected at the majority of studies.

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Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

References


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