Consanguinity and congenital heart disease in offspring

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Abstract

Background High-risk acute lymphoblastic leukemia (ALL) is one Background Congenital heart disease (CHD) is a common congenital abnormality in children. Consanguineous marriage has been identified as a risk factor of CHD. There was an autosomal recessive pattern of inheritance seen in children with some forms of congenital heart disease.

Objective To assess the possible association between consanguineous marriage and congenital heart disease incidence in the offspring.

Methods A case-control study was conducted from March to May 2016 on pediatric patients at H. Adam Malik General Hospital, Medan. Subjects were allocated into two groups, 100 children with CHD in the case group, and the rest in the control group. Data were analyzed using Chi-square and logistic regression tests. In the present study, P value less than 0.05 was considered statistically significant.

Results In the case group, 14 patients (14%) were born of consanguineous marriages. In the control group, only 5 patients (5%) were born of consanguineous marriages. There was a significant association between consanguineous marriage and CHD (OR 1.551; 95%CI 1.138 to 2.113). Based on the result of multivariate analysis, consanguineous marriage was a risk factor for CHD in offspring (Wald=4.525; P=0.033).

Conclusion Consanguineous marriage is a risk factor for CHD in offspring. [Paediatr Indones. 2018;58:75-9; doi: http://dx.doi.org/10.14238/pi58.1.2018.75-9]

Keywords: consanguineous marriage; congenital heart disease; offspring

Consanguineous marriage is a marriage between two people descended from the same ancestor, and is still common in some regions of the world. It often has genetic implications for the offspring. From the genetical point of view, marriages between couples who have a biologic relationship as second cousin or closer are considered consanguineous (originated from...
Latin consanguineus, which means having the same blood relation).\textsuperscript{13} A case-control study in Pakistan found that 49% of CHD cases were related to consanguineous marriage.\textsuperscript{14} In Lebanon, 17.9% of CHD cases were related to consanguineous marriage, particularly between close cousins.\textsuperscript{15} In Indonesia, 12 CHD cases had a family history of CHD, however, the authors did not assess the history of consanguineous marriage in the study.\textsuperscript{16} Based on prior studies, we aimed to assess for a relationship between consanguineous marriage and CHD incidence in Indonesian children.

Methods

We did an observational, analytic, case-control study to assess consanguinity as a risk factor for CHD incidence in children. It was conducted in the Cardiology Division of the Department of Child Health, H. Adam Malik Hospital, Medan between March 16 and June 16, 2016. Subjects were allocated into two groups by consecutive sampling, 100 children with CHD in the case group, and 100 children without CHD in the control group. Echocardiography was done on all patients. The inclusion criteria were 0-18 years old children, with or without CHD. Exclusion criteria were children with acquired heart disease, patients with the evaluated risk factors, i.e., family history of CHD, maternal drug use, and maternal comorbidities.

Data were analyzed to assess for the relationship between consanguineous marriage with CHD incidence using Chi-square for normally distributed data and Fischer’s exact test for abnormally distributed data. Odds ratio were obtained from 2x2 table (with 95%CI). Univariate logistic regression analysis was done for CHD types, demography characteristics, and risk factor profile, for the case and control group. Multivariate analysis was done to obtain independent predictor. A P value of $<0.05$ was considered statistically significant. We used SPSS 15 software for data analysis.

Written informed consent form was obtained from the parents of the study subjects. This study was approved by Ethical Committee of the University of Sumatera Utara Medical School.

Results

The total sample number was 200 children, with a mean age of 4.3 (SD 4.6) years. The mean birth weight and length were 3,143.5 (SD 305.8) grams and 48.1 (SD 1.2) cm, respectively. All children were delivered full term, with mean gestational age of 38.6 (SD 0.9) weeks. Demographic characteristics of children are shown in Table 1.

In the case group, 14 patients (14%) were born of consanguineous marriages. In the control group,
only 5 patients (5%) were born of consanguineous marriages. Chi-square test showed a statistically significant relationship between consanguineous marriage and CHD incidence in the offspring (OR: 1.551) (Table 2).

Logistic regression test was done to assess the effect of the risk factors of CHD, such as consanguineous marriage, family history of CHD, and maternal comorbidities. Table 3 shows consanguineous marriage as the only risk factor of CHD occurrence (Wald=4.525; P=0.033).

Discussion

Out of 100 cases of CHD and 100 controls, 19 children were offsprings of consanguineous marriages, which were 14% of cases and 5% of controls. Similar results were reported from several countries such as Iraq, Saudi Arabia, Pakistan, Iran, China, India, Lebanon, and Canada. The proportions varied among countries. We found a significant relationship between consanguninity and the risk of CHD occurrence in the offspring. The relationship of this study with the precedings is that they have similar characteristics such as demography, religion, and culture. However, we did not assess the level of relationship in the consanguineous marriages, nor the genes contributing to the risk.

Consanguninity is a significant risk factor for CHD incidence. The most common types of CHD in all population are ventricular septal defect, atrial septal defect, and tetralogy of Fallot. Our study found that the CHDs found in children from consanguineous marriage were atrial septal defect (25%), persistent ductus arteriosus (24%), ventricular septal defect (30%), hypoplastic right ventricle (2%), and transposition of the great arteries (6%). Those proportions were similar to a study in Iraq which stated that the most common CHD was of the non-cyanotic type, which was atrial septal defect (66.6%). Other cases were ventricular septal defect, persistent ductus arteriosus and transposition of the great arteries. Also, a study in United Arab Emirates found atrial septal defect (49%) as the most common type of CHD.

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A South Indian study found that the most commonly found CHDs were atrial septal defect and persistent ductus arteriosus. However, our study contrasted from these studies that we did not assess the level of relationship in the consanguineous marriages, e.g., first cousins, while this was assessed in the previous studies in Iraq, Saudi Arabia, and South India.

In contrast, a Pakistani study reported that the CHD cases had the following types: ventricular septal defect (97 cases), persistent ductus arteriosus, atrial septal defect, pulmonary stenosis, tetralogy of Fallot, transposition of great arteries, and hypoplastic right ventricle. A similarity in our study was that non-cyanotic CHDs were more commonly found than cyanotic CHDs, with transposition of the great arteries as the most common cyanotic CHD found in both studies. An Egyptian study reported CHD cases with ventricular septal defect and atrial septal defect, accompanied by dysmorphic features from chromosome disorders trisomy 21 and trisomy 14. In our study, no dysmorphic features were found in the study subjects. A Lebanese study had CHD cases of tetralogy of Fallot, valvar aortic stenosis, and atrial septal defect.

In this study, there was a slightly higher incidence of CHD in males. This finding is consistent with several studies, such as in Iraq, Saudi Arabia, Pakistan, and Lebanon. In contrast, a study in China reported that CHD was more prevalent in males.

Table 2. Relationship between consanguineous marriages and CHD incidence

<table>
<thead>
<tr>
<th>Congenital heart disease</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>14 (14)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>No</td>
<td>86 (86)</td>
<td>95 (95)</td>
</tr>
</tbody>
</table>

Table 3. Risk factors of CHD

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Constant</th>
<th>Wald</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consanguineous marriage</td>
<td>1.154</td>
<td>4.525</td>
<td>0.033</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>1.214</td>
<td>1.085</td>
<td>0.298</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>-0.169</td>
<td>0.072</td>
<td>0.789</td>
</tr>
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*logistic regression test
Overall, there was no significant difference in the occurrence of CHD between the two sexes.

In this study, the majority of CHD cases were found in Muslims. This might be due to the fact that the majority of Indonesia’s population is Muslim. Furthermore, the reason for consanguineous marriage is to tighten the relationships and kinships between relatives. As a result, the practice of matchmaking between family relatives persists. Ethnic relations and cultural practices influence the occurrence of consanguineous marriage. Most patients who visited the Cardiology Department of Haji Adam Malik Hospital came from the province of Aceh and North Sumatra, where customs, regulations, and culture strongly influence the society. However, the ethnic group that dominates visits to the Cardiology Department is Bataknese, from both the father and the mother. The occurrence of consanguineous marriage is higher in the Batak population due to cultural influences such as marga (clan), pariban, and impal. However, consanguineous marriage is more likely to occur in rural areas compared to urban areas, where people have more opportunity for education and wider options for finding a spouse. Lack of knowledge and education about the risk factors of CHD are obstacles that increase the risk of CHD occurrence. Thus, genetic counseling in rural areas is needed to decrease the morbidity and mortality of CHD cases. Our study is consistent with studies in Saudi Arabia, Iran, Pakistan, and Lebanon, with majority Muslim populations. However, in India and South India the majority of people are Hindu. A study in Canada showed that CHD was mostly found in migrants from the Middle East.

According to studies in Pakistan and South India, not all consanguineous marriages put offspring at risk for CHD. This finding is consistent with our results, in which there were five (2.5%) children from consanguineous relationships who did not develop CHD. In this study, other risk factors for CHD were evaluated. There were three CHD cases with a family history of CHD, without consanguineous marriages. This finding is consistent with a study in Indonesia which reported persistent ductus arteriosus to be the most prevalent, and without consanguineous marriage. It is also found in other studies, such as in Pakistan (14%), China (4.6%), Canada (19%), and Egypt (13%). In this study, comorbid risk factors of the occurrence of CHD were found in 2.5% of cases, i.e., hypertension during pregnancy, but it was not statistically significant. This finding is consistent with research in Pakistan where 14% of CHD cases were associated with maternal hypertension and diabetes during pregnancy. In our study, we found no significant relationship between maternal use of drugs and the risk of CHD in children. The Pakistani study found maternal use of drugs in 2% of cases.

Genetic mutations associated with CHD can now be detected. It should be noted that a wide variety of genes are involved in the process of cardiogenesis. With the rapid development of science, the types of genes in each individual can be detected by single nucleotide polymorphisms (SNPs). An Egyptian study proposed an autosomal recessive role as a cause of CHD in children associated with consanguineous marriage, with the exception of patent ductus arteriosus. We used echocardiography for the diagnosis of CHD and conducted interviews to find a history of consanguineous marriage. However, evaluation of the genetic abnormalities from the SNPs in the 19 cases of CHD and consanguinity was not feasible due to the lack of available equipment. The role of autosomal recessive inheritance on the occurrence of CHD in children in this study cannot be ruled out. Therefore, further research is needed.

Limitations of this study were the small sample size and lack of genetic evaluation in the form of SNPs. In conclusion, consanguineous marriage is a risk factor for congenital heart disease in the offsprings.

**Conflict of interest**

None declared.

**References**

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