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Original Article

Familial congenital heart disease in Bandung, Indonesia

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Abstract

Background Congenital heart disease (CHD) may occur in several members of a family. Studies have shown that familial genetic factor play a role in CHD.

Objective To identify familial recurrences of CHD in families with at least one member treated for CHD in Dr. Hasan Sadikin Hospital, Bandung Indonesia.

Methods In this descriptive study, subjects were CHD patients hospitalized or treated from January 2005 to December 2011. We constructed family pedigrees for five families.

Results During the study period, there were 1,779 patients with CHD. We found 5 families with 12 familial CHD cases, consisting of 8 boys and 4 girls. Defects observed in these 12 patients were tetralogy of Fallot, transposition of the great arteries, persistent ductus arteriosus, ventricular septal defect, tricuspid atresia, pulmonary stenosis, and dilated cardiomyopathy. Persistent ductus arteriosus was the most frequently observed defect (4 out of 12 subjects). None of the families had a history of consanguinity. The recurrence risk of CHD among siblings was calculated to be 0.67%, and the recurrence risk of CHD among cousins was 0.16%. ***Conclusion*** Familial CHD may indicate the need for genetic counseling and further pedigree analysis. **[Paediatr Indones. 2013;53:173-6.]**

Keywords: *Familial genetic, congenital heart disease, Indonesia*

One of the most frequently found congenital anomalies is congenital heart disease (CHD). Congenital heart disease incidence has been reported to be 8-10 of 1,000 births in nearly all countries.[1] In Indonesia, the birth rate is 4 million per year,[2] so the incidence of CHD has been estimated to be 32-40 thousand per year.

To date, it is unknown why CHD occurs. Past studies reported that familial or genetic factors play a role, since CHD may occur repeatedly in families.[3-5] Furthermore, consanguinity may also increase the risk of CHD.[6] Familial factors may be due to chromosomal anomalies or gene mutations.[5] In addition to genetic factors, maternal factors such as infection, metabolic anomalies, immune disorders, obesity,[7] consuming drugs during pregnancy,[3] ethnicity, and advance age at pregnancy have been correlated with CHD.[8,9] Other factors such as engaging in sex, consuming alcohol or smoking during pregnancy, climate, and environment (urban, suburban, or rural) [9, 10] have not been shown to correlate to CHD.[11] Therefore, CHD has been associated with genetic and non-genetic factors, or interactions between the two.[11]

The aim of this study was to identify the familial recurrences of CHD in families that had a member with CHD hospitalized in Dr. Hasan Sadikin Hospital, Bandung, Indonesia.

Methods

We retrieved data from patients' medical records

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hospitalized in Dr. Hasan Sadikin Hospital, Bandung, Indonesia from January 2005 to December 2011. Diagnosis of congenital heart disease was based on echocardiographic examination performed by pediatric cardiology consultants using a General Electric Type Logic 700 or General Electric Type Vivid 3 machines. Based on this data, three-generation family pedigrees were generated for each affected family.

Results

During a 7 year-study period, there were 1,779 patients with CHD in our hospital. Five families had a total of 12 familial CHD members, consisting of 8 boys and 4 girls. Defects observed in these subjects were tetralogy of Fallot (TOF), transposition of the great arteries (TGA), persistent ductus arteriosus (PDA), ventricular septal defect (VSD), tricuspid atresia, pulmonary stenosis, and dilated cardiomyopathy. Persistent ductus arteriosus was the most common defect in the subjects. No history of consanguinity was found. A medical pedigree was used to describe the families. The symbols used were defined as follows: squares represent boys; circles represent girls; solid black indicates CHD or suspected CHD; hatch lines indicate individuals with other congenital malformations.

Figure 1 shows three individuals with CHD and one with suspected CHD in Family 1. Defects found in these individuals were as follows: TOF+PDA (II.9), VSD+PDA (III.14), TGA (III.15, died at age 2 months), and suspected CHD (III.16, died at age 2 months due to respiratory failure and cyanosis). Two individuals, II.9 and III.14, underwent corrective procedures. One individual had labiopalatoschisis (III.13).

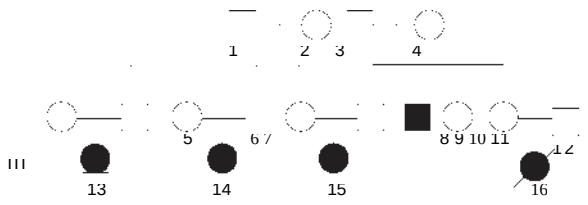

Figure 1. Family 1 pedigree

Family 2 was a mixed marriage between an Indonesian mother and a Korean father with 2 affected children (**Figure 2**). Child II.3 had TGA and was diagnosed based on echocardiography at the age of 4 years, while child II.5 was diagnosed with VSD. One child with VSD underwent a closure at 5 months of age. The other child's with TGA defect was inoperable due to pulmonary vascular disease, and he is now 16 years old. Hypospadias was a congenital malformation found in individual II.6.

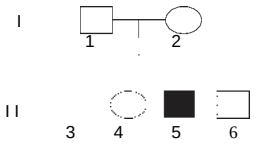

Figure 2. Family 2 pedigree

In family 3 there were 2 siblings with PDA, II.3 and II.5, and 1 sibling with mental retardation, II.6 (**Figure 3**).

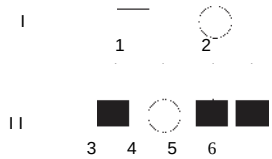

Figure 3. Family 3 pedigree

Figure 4 shows an affected child (II.3) with familial dilated cardiomyopathy, who is now 5 years old. Her father (I.1) died at 30 years of age.

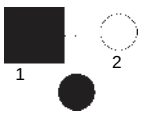

Figure 4. Family 4 pedigree

Figure 5 shows two affected children in family 5, one with tricuspid atresia + VSD (II.3) and the other with pulmonary valve stenosis (II.5).

The recurrence risk of CHD among siblings was calculated to be CHD/siblings = 0.67%. The recurrence risk of CHD among cousins was CHD/ cousins = 0.16%. None of the families had a history of consanguinity.

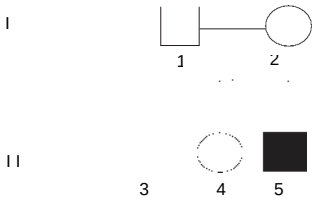

Figure 5. Family 5 pedigree

Discussion

Congenital heart disease is a common occurrence, but its etiology is poorly understood. Genetic factors have been correlated with CHD in studies carried out on the role of gene mutations in CHD.[4] The aim of this study was to identify familial recurrences of CHD to be used as a framework for further genetic studies. We found that the recurrence risk for CHD was 0.67%. Previous studies found familial recurrence

Table 1. Types of congenital heart disease in the five families

Type of CHD	Total
Tetralogy of Fallot	1
Transposition of great arteries	2
Persistent ductus arteriosus	4
Ventricular septal defect	3
Tricuspid atresia	1
Pulmonary stenosis	1
Dilated cardiomyopathy	2

Table 2. Extracardiac anomalies accompanying congenital heart disease

Extracardial anomaly	Relationship	n
Labiopalatoschisis	Cousin	1
Mental retardation	Elder brother	1
Hypospadia	Younger brother	1

risks of CHD of 1-3%.[12] The highest recurrence risk is reportedly among siblings.[12]

Tetralogy of Fallot and TGA are conotruncal defects of CHD. In TGA, embryological anomaly may occur on the conotruncal or ventricular outflow tract, i.e., transposition of both great arteries, so that the aorta moves out from the right ventricle and the pulmonary artery from the left ventricle. Such anomalies were found in about 5% of all CHD patients, characterized by parallel unrelated systemic and pulmonary circulations. The survival of a neonate who was born with such an anomaly depends mostly on good mixture of systemic venous return and pulmonary venous return through the atrial septal defect (ASD), VSD, or PDA.[13,14]

Recurrence of TGA is rarely found because it generally occurs sporadically.[14] We found that different defects occurred in a single family, as seen in Family 1 in which the first child had TGA and the third child had a VSD. Ventricular septal defect accounts for about 20% of CHD defects, but in our study we found only one patient with VSD. A previous study suggested that familial VSD is due to genetic factors.[15]

Tetralogy of Fallot is a cyanotic type of CHD. Its prevalence is about 5—10% of all CHD cases. Tetralogy of Fallot was first described by Arthur Louis Etienne Fallot, who performed an autopsy on a patient with cyanosis, known as "la maladie bleu."[16] Tetralogy of Fallot consists of VSD, pulmonary arterial stenosis, overriding aorta and right ventricular dilatation. Currently this combination of the four anomalies is referred to as TOF. The main cause of the four anomalies is antero-cephalad deviation of the muscular outlet septum insertion relative to the limbs of the septomarginal trabeculation, coupled with an arrangement of the septoparietal trabeculations which produces a squeeze at the mouth of the infundibulum.[16,17] Previous studies revealed the recurrence risk of TOF to be 2.5—3%.[18] Tetralogy of Fallot was also a recurrent defect in this study.

In our study, the most frequently recurring familial defect was PDA. In contrast, previous studies showed that PDA had a low risk for familial recurrence, at only 3%, because it is generally of a polygenic etiology.[19] Previous studies stated that ASD was the CHD with the highest rate of recurrence, at 40-100%. However, no familial ASD was found in our subjects. In Indonesia, a study on the GATA4 gene mutation in ASD found that spontaneous mutation had no correlation with familial ASD.[20]

In conclusion, familial CHD may indicate the need for genetic counseling and further pedigree analysis. The result of this study may be used as a framework for identifying gene mutations affecting CHD.

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