

Congenital Heart Disease among Down Syndrome Children at Dr. Hasan Sadikin General Hospital from 2008 to 2013

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Abstract

Background: Children with Down syndrome are more prone to congenital heart disease due to the consequences of trisomy chromosomal 21 on gene expression. The aim of this study was to determine the pattern of congenital heart disease in children with Down syndrome.

Methods: This was a retrospective study of reviewed children with Down syndrome from January 2008 to January 2013 at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. This study was conducted from August until October 2014. Patients under the age of 15 years and diagnosed having congenital heart disease from 2008 to 2013 were enrolled in this study by using the total sampling method. Incomplete medical records and children who had not performed an echocardiogram were excluded. Sex, age at diagnosis for congenital heart disease, nutritional status and other comorbidities were also examined.

Results: Congenital heart disease occurred in 28 children with Down Syndrome. Patent ductus arteriosus (PDA) was the most common and found in 11 patients followed by a combination of congenital heart diseases in 5 patients. Other 3 patients had Atrioventricular septal defect (AVSD), and Tetralogy of fallot (TOF) was found in 3 patients, 2 patients had Atrial septal defect (ASD) and 1 patient had miscellaneous cardiac defect.

Conclusions: The most common CHD in Down syndrome is PDA.

Keywords: Children, congenital heart disease, Down syndrome

Introduction

The World Health Organization (WHO) confirmed that children with Down syndrome were more prone to get congenital heart disease and other diseases.¹ Incidence of congenital heart defect is higher among Down syndrome children, approximately 50% as suggested by several studies and this is associated with abnormality in genes of the children with Down syndrome.² Previous studies in the North East of England and Turkey showed that the most common single defect of congenital heart disease is an Atrioventricular septal defect.^{3,4} Several studies were also conducted to determine the pattern of congenital heart disease and they concluded that the most common types of congenital heart disease are Atrioventricular septal defect (AVSD), Ventricular septal defect (VSD), Atrial septal defect (ASD) and Tetralogy of fallot (TOF).⁵

Trisomy of Hsa21 which occurs in children with Down syndrome is associated with congenital heart defects. However, not one study has proven yet that chromosome 21 is the exact chromosome responsible for the cardiac anomaly in Down syndrome. Thus, the presence of specific gene variants such as trisomy 21 can further increase susceptibility for cardiac defects in Down syndrome.⁶

The variation in folate pathway genes plays an important role in forming the congenital heart disease in Down syndrome. In this metabolic pathway, the methylenetetrahydrofolate reductase (MTHFR) undergoes polymorphism which causes decrease in availability of 5-methylTHF for methylation, and then leads to reduction of global DNA methylation. Inhibition of DNA methylation can cause decrease in S-adenosylmethionine/S-adenosylhomocysteine ratio which results in cranial defects.⁷ The objective of this study was

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to determine the pattern of congenital heart disease in children with Down syndrome.

Methods

This study was conducted from August to October 2014 as a descriptive retrospective study, and medical records were used as the source of data. Data collection using medical records has been approved by the Health research ethics committee at Dr. Hasan Sadikin General Hospital. The target population in this study were all children with Down syndrome and the samples for this study were children with Down syndrome who were diagnosed with congenital heart disease in the Department of Child Health, Dr. Hasan Sadikin

General Hospital. The total sampling method was used in this study.

Medical records and echocardiogram reports were evaluated which included gender, height, and weight for nutritional assessment, age at diagnosis, types of congenital heart disease, and other non-cardiac diseases. Data of patients were considered eligible if the patient was under the age of 15 years and had been diagnosed with congenital heart disease from 2008 to 2013. Incomplete medical records and children who had not performed the echocardiogram were excluded.

In this study, the children's standard age was under the age of 15 years, and age was recorded in months and years. Age at diagnosis was calculated by deducting the age of children when first diagnosed having a congenital

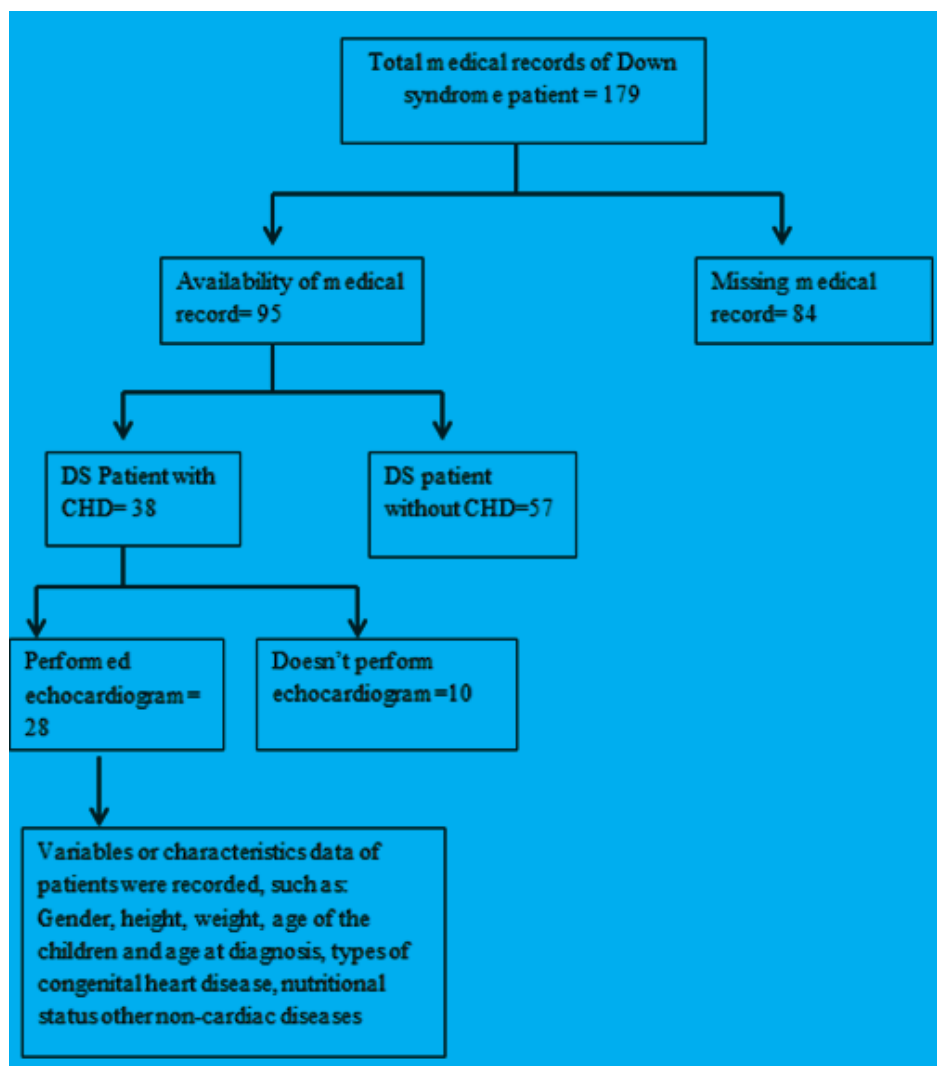


Figure 1 Flow chart of data collection

heart disease with date of birth of that child. Moreover, age group were classified according to Nelson's paediatric age classification which was neonates (less than 1 month), infant (1 month to 2 years), pre-school children (2 to 5 years), middle childhood (6 to 11 years) and early to middle adolescents (12 to 14 years).⁸

Types of congenital heart disease were diagnosed using the echocardiogram and it was classified according to ICD-10. The nutritional status was measured according to WHO child growth assessment. Children under the age of 6 years were measured for their weight for length or weight for age. The nutritional status in children more than 6 years old was calculated by BMI. This was done to determine the height and weight appropriate to children's age. For the interpretation, Z-score classification system is used. Children are considered obese if the Z-score is above 3, overweight if the Z-score is above 2, possible risk of overweight if the children have a Z-score above 1. Z-score 0 to -1 are considered normal weight and Z-score below -2 indicates that the children are wasted and Z-score -3 means the children are severely wasted.⁹

Results of the study were arranged in frequency tables and graphics charts to evaluate the pattern of congenital heart disease

in Down syndrome children according to sex, age when diagnosed having congenital heart disease, types of congenital heart disease and other comorbidities. The results were then analysed and explained descriptively by using the Microsoft Office Excel 2011®.

Results

Furthermore, a total of 179 cases of congenital heart disease among children with Down syndrome was reported from January 2008 to January 2013. However, about 84 medical records were lost, and out of the remaining 95 medical records, 57 patients did not have a congenital heart disease, 10 patients did not perform the echocardiogram, so 28 samples (33%) were selected according to the inclusion criteria.

Moreover, the highest number of cases were reported in 2013 which were 11 cases among 28 cases. Overall, it showed the distribution of patients increased about 32.8% from 2008 to 2013, as 2 cases were reported in 2008 and another 2 cases were reported in 2009. In 2010, 5 Down syndrome patients were reported having a congenital heart disease and 4 people came in 2011 and 2012.

The number of female patient was 18 patients

Table 1 Characteristics of Down Syndrome Patient with Congenital Heart Disease

| Data Characteristics | Frequency (n=28) |
|-----------------------------|------------------|
| Sex | |
| Male | 8 |
| Female | 15 |
| Age group | |
| ≤ 1 month | 1 |
| 1 month – 2 years | 22 |
| 2 – 5 years | 4 |
| 6 – 11 years | 0 |
| 12 – 14 years | 1 |
| Nutritional status | |
| Obese | 0 |
| Overweight | 1 |
| Possible risk of overweight | 0 |
| Normal | 13 |
| Wasted | 8 |
| Severely wasted | 6 |

Table 2 Type of Congenital Heart Disease among Children with Down Syndrome

| Type of congenital heart disease | Frequency (n=28) |
|----------------------------------|------------------|
| ASD | 2 |
| VSD | 3 |
| AVSD | 3 |
| PDA | 11 |
| TOF | 3 |
| Combined | 5 |
| Unspecific | 1 |

Notes: ASD=Atrial Septal Defect; VSD= Ventricular Septal Defect; AVSD= Atrio Ventricular Septal Defect; PDA= Patent Ductus Arteriosus; TOF= Tetralogy of Fallot

Table 3 Other Non-cardiac Diseases in Down Syndrome Patient with Congenital Heart Disease

| Other defects | Frequency |
|------------------------|-----------|
| Total | 28 |
| Congenital hypothyroid | 10 |
| Bronchopneumonia | 8 |
| Pulmonary hypertension | 3 |
| Sepsis | 3 |
| Failure to thrive | 2 |
| Respiratory failure | 2 |

while male patients were 10. Consequently, the dominated gender among the patients was female. The samples for the study were divided into five categories according to their age. The majority of patients were one month until 2 years old. Whereas 13 patients were found to be in the normal category but about 50% of patients were in the abnormal category where 8 patients were wasted, and 6 patients were severely wasted. These provided indications of malnutrition occurrences in half of the patients.

The most common type of congenital heart disease among Down syndrome patients was PDA which accounted for 11 patients, followed by multiple type of congenital heart disease with 5 patients. Among the 5 patients who had multiple type of congenital heart disease, 4 patients were diagnosed with PDA+ASD while the remaining 1 patient had AVSD+TOF. Moreover, PDA associated lesions were the most common in combined lesions. The unspecific lesion or miscellaneous cardiac defect was found in 1 patient where the diagnosis was stated as ICD q 24.9.

Furthermore, congenital hypothyroid was the highest defect in Down syndrome patients with congenital heart disease followed by bronchopneumonia.

Discussion

A number of researchers from previous studies stated that half of the children with Down syndrome had a congenital heart disease. In this study, the total frequency of Down syndrome children with a congenital heart disease was 33.3% which was less than previously estimated. Many factors might affect the results, firstly, it could be due to health care systems aspects. A huge number of medical records were missing which could cause big changes in the data. The use of echocardiogram and routine screening for congenital heart disease was not really practiced to all the children. Approximately 15 samples were excluded due to this factor. Secondly, the lower frequency in samples could be due to ethnic or race factors. Previous studies proved that less Asian people with Down syndrome had

a congenital heart disease. A study that was carried out by the Atlanta Down Syndrome Project, showed that only 13 Asian people with Down syndrome had cardiac defect among 243 people.² Another study also stated that among 487 patients with Down syndrome only 20 Asian people had congenital heart disease. Thus, this could be the corresponding reason for the lower frequency number in the present study.¹⁰

According to this study, the common type of congenital heart disease in children with Down syndrome was PDA. From previous studies, PDA is one of the common congenital heart disease in Down syndrome. However, many studies indicated the AVSD and VSD as the common type of congenital heart disease among children with Down syndrome. Several studies suggested that factors like ethnic and geographic differences such as high altitude with lower partial pressures of oxygen may contribute to a higher frequency of PDA. At a high altitude, arterial oxygen desaturation can occur. The usual left-to-right shunting of blood reverses will cause right-sided pressures to increase.¹¹ However, these hypotheses need to be tested by further large-scale multinational collaborative studies.

The congenital heart disease was higher in female compared to male and this result corresponds with previous studies. According to a study carried out by the National Down Syndrome Project (NDSP), it was proven that the incidence of Atrioventricular Septal Defect (AVSD) in Down syndrome are about two times greater in female than male.² In this study, the age group of 1 month until 2 years showed the highest frequency of congenital heart disease among Down syndrome children. This might be due to the improved medical facilities and interventions in early detection of congenital heart disease. Based on a study, it stated that early diagnosis of heart disease in Down's syndrome is important in order to initiate a timely referral to the concerned specialties and to educate the parents regarding the early and late complications of Down syndrome.¹²

The researcher also studied the nutritional status of children with Down syndrome with congenital heart disease. Although characteristics of Down syndrome patients with congenital heart disease showed the highest frequency in normal nutritional status however 50% of children were wasted and severely wasted (Table 1). Many studies looked for the relationship of congenital heart disease with nutritional status; the researchers found out that it is common for children with

congenital heart disease to have malnutrition due to multifactorial issues which include inadequate nutritional intake due to difficulties in feeding, malabsorption, and increased energy requirements caused by increased metabolism.¹³ Inadequate feeding capabilities in neonates with congenital heart disease are usually due to respiratory compromise or vocal cord paralysis or because of underlying neurological consequences which lead to growth failure if untreated.¹⁴ However, one patient was overweight in this study. The American Heart Association guidelines indicate that children with CHD are less likely to meet physical activity recommendations due to self-esteem and physical self-concept which may lead to overweight or obesity.¹⁵

Moreover, other defects were evaluated in this study. The congenital hypothyroid showed the highest frequency which was 35.7% compared to other defects such as bronchopneumonia, pulmonary hypertension, sepsis, failure to thrive and respiratory failure. Based on a previous study, the abnormalities in thyroid are due to slow maturation of negative feedback control systems in the hypothalamo-pituitary axis in Down syndrome which lead to the production of a less active form of TSH, or TSH insensitivity in the thyroid gland.¹⁶

In a study, it was stated that the thyroid hormone deficiency may cause abnormalities in the cardiovascular function such as an impaired cardiac contractility and diastolic function, increased systemic vascular resistance, decreased endothelial derived relaxation factor, increased serum cholesterol, increased C-reactive protein, and increased homocysteine where this conditions will enhance the severity of the heart disease.¹⁷ Additionally, Murine Nkx-2.5, is a gene which is expressed in the early embryogenesis of thyroid and myocardium, thus patients with congenital hypothyroid are associated with cardiac defects.¹⁸ Pulmonary hypertension which showed remarkable occurrences in previous studies was less in the present study because it is more associated with the AVSD type of congenital heart disease. This is due to the uncorrected left-to-right shunt increases the pulmonary pressure that eventually leads to vascular remodelling and dysfunction. Thus, the progressive rise in pulmonary vascular resistance and increased pressures in the right heart occurred as a result.¹⁹

There were certain limitations in this study. Firstly, it was due to the loss of some medical records. This factor could influence the results of the study due to the small sample size. If

there was a more systematic way and the number of medical records were complete, the results would be more accurate. Besides, many patients did not perform the echocardiogram test. This could be due to several factors. First, many children were not followed up until the echocardiogram results or the patients wanted to be referred to another hospital which was nearer. Not many Down syndrome patients visited or were being referred here. It was either they did not visit the primary care physician or the parents' socioeconomic status did not allow them to visit the general hospital in Bandung from their remote hometown or they died prior to the diagnosis, since the survival rate of Down syndrome with congenital heart disease is usually low.

In conclusion, the most common congenital heart disease in children with Down syndrome is PDA.

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