Research Articles

Clinical Characteristics of Down Syndrome with Congenital Heart Disease

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Abstract

Down syndrome (DS) or trisomy 21, causes overexpression of genes in most affected organs, including congenital heart disease (CHD). CHD is found in 40-60% of people with DS, with a high mortality rate in early life. Clinical signs and symptoms often found are essential indicators of early diagnosis of CHD. This study aimed to determine the clinical characteristics of DS children with and without CHD. This study was a retrospective study. The study was conducted on August until October 2019. We took data from the inpatient and outpatient medical records database for the years 2017-2019 in Dr. Kariadi Hospital, Semarang, Indonesia. Some information includes clinical signs and symptoms, nutritional status, comorbidities, and frequency of hospitalization in a month were collected. A total of 66 patients were diagnosed with DS, consisting of 44 DS patients with CHD and 22 DS patients without CHD. There were no differences in nutritional status, interrupted breastfeeding, chest retraction, respiratory rate, thyroid disorder, hearing abnormalities, acute otitis media, and obstructive sleep apnea in both groups (p> 0.05). There were significant differences in the clinical characteristics of cyanosis (p=0.005), heart murmur (p=<0.001), and frequency of acute respiratory tract infection in a year (p=<0.001), and frequency of hospitalization per month (p=0.039) in DS children with and without CHD. In conclusion, we found significant difference in clinical characteristic in DS children with and without CHD.
***Keywords**: down syndrome, trisomy 21, congenital heart disease, nutritional status, comorbidities.*

Karakteristik Klinik Sindrom Down Dengan Penyakit Jantung Bawaan

Abstrak

Sindrom Down atau trisomi tipe 21 menyebabkan overekspresi gen pada sebagian besar organ tubuh, termasuk penyakit jantung bawaan (PJB). PJB ditemukan pada 40-60% penderita Sindrom Down, dengan angka kematian yang tinggi pada awal kehidupan. Tanda dan gejala klinis yang sering ditemukan merupakan indikator penting untuk diagnosis dini PJB. Penelitian ini bertujuan untuk mengetahui karakteristik klinis anak Sindrom Down dengan dan tanpa PJB. Penelitian ini merupakan penelitian retrospektif. Penelitian dilakukan pada bulan Agustus hingga Oktober 2019. Dilakukan pengambilan data dari database rekam medis rawat inap dan rawat jalan di RS Dr. Kariadi Semarang, Indonesia. Variabel yang dikumpulkan adalah tanda dan gejala klinis, status gizi, penyakit komorbid, dan frekuensi hospitalisasi dalam sebulan. Sebanyak 66 pasien terdiagnosis DS, terdiri dari 44 pasien DS dengan PJB dan 22 pasien DS tanpa PJB. Tidak ada perbedaan status gizi, gangguan menyusui, retraksi dada, frekuensi pernapasan, gangguan tiroid, kelainan pendengaran, otitis media akut, dan obstructive sleep apnea pada kedua kelompok (p>0,05). Terdapat perbedaan yang signifikan pada karakteristik klinis sianosis (p=0,005), bising jantung (p=<0,001), frekuensi ISPA dalam setahun (p=<0,001), dan frekuensi rawat inap per bulan (p= 0,039) pada anak DS dengan dan tanpa PJB. Kami menyimpulkan bahwa terdapat perbedaan karakteristik klinis anak Sindrom Down dengan dan tanpa PJB.
***Kata kunci**: sindrom down, trisomi 21, penyakit jantung bawaan, status gizi, penyakit penyerta.*

Introduction

Down syndrome (DS) is the most common chromosomal abnormality (trisomy 21) in the world.[1] The prevalence of DS globally is 1 in 700-1000 live births and occurs around 0.45% out of every conception.[2, 3] The number of people living with DS in the world is estimated to reach as many as 8 million people, and three hundred thousand of them are in Indonesia. Based on data from Indonesia Baseline Health Study (Riskesdas), the prevalence in Indonesia in 2010 was 0.12% and increased to 0.13% in 2013.[4]

Children with DS have various physical, comorbid, and cognitive impairments caused by the overexpression of chromosome 21.[5] DS children also experience growth retardation and have lower nutritional status than healthy children, measured through head circumference, height, and body weight.[6] In addition, children with DS also have congenital anomalies and comorbid disorders that are quite complex and need to be observed and specially handled continuously. These conditions resulted in an increased number of children with DS' visitation to health services.[7]

CHD is one of the comorbidities of DS, which has a prevalence of around 40-60%. It is the most significant cause of increased morbidity and mortality in DS children's first two years of life. CHD is not always identifiable because mild defects sometimes do not manifest any apparent signs and symptoms. However, in some cases, the child experience typical signs and symptoms that can be identified through history taking and physical examination. By identifying clinical signs and symptoms, treatment can be done earlier to minimize complications and reduce mortality.

In Indonesia, only a little data regarding clinical characteristics of DS children and CHD. This study aimed to identify the differences in clinical characteristics of DS children with and without CHD.

Methods

This retrospective study was conducted in Dr. Kariadi Hospital, Semarang, Central Java, Indonesia. Data were obtained from the Dr. Kariadi medical record database for the years 2017-2019. Subjects were divided into two groups, i.e., 44 children with DS and CHD but no heart surgery history, and 22 DS children without CHD aged 0-18 years. Available information includes clinical signs and symptoms, nutritional status, comorbidities, and frequency of hospitalization in a month. Symptoms and clinical signs observed and recorded were cyanosis, heart murmur, respiratory rate, and interrupted breastfeeding. Comorbidities such as respiratory tract infection in a year (RTI), thyroid disorders, otitis media, hearing loss, and obstructive sleep apnea (OSA) were also being noted. We assessed weight for age (WAZ), height for age (HAZ), weight for height (WHZ), and head circumference (HC) using the CDC Down Syndrome chart. Parents' sociodemographic data such as mother and fathers' age, education, occupation, income, and residence were also noted. The study protocol was approved by The Ethics Committee (*Komisi Etik Penelitian Kesehatan)* of the Faculty of Medicine, Diponegoro University (Number 241/EC/KEPK-RSDK/2019).

Data were analyzed using SPSS 25 application. Hypothesis testing for unpaired nominal data such as cyanosis, heart murmur, respiratory rate, interrupted breastfeeding, thyroid disorders, otitis media, hearing loss, and OSAS used the chi-square test. Hypothesis testing for unpaired numerical data such as respiratory tract infection in a year and frequency of hospitalization in a month used the Mann-Whitney test. The level of significance was set at a p-value level of <0.05.

Results

The age of patients ranged from 4 months to 6 years in both groups. The clinical characteristics of the groups are outlined in Table 1. There were no differences between the two groups on children's age, parents' age and education, residence, and income.

Table 1. Subjects Characteristic

Variable	CHD in Down Syndrome (66)		p
	With (n=44)	Without (n=22)	
Children's age			
≤2 year	28	10	0.192¥
>2 year	16	12	
Maternal age			
< 35 year	17	5	0.196¥
≥ 35 year	27	17	
Paternal age			
< 35 year	12	7	0.742¥
≥ 35 year	29	14	
Missing Data	3	1	
Father education			
Low	2	5	0.22¥
High	19	5	
Missing Data	23	12	
Mother education			
Low	3	3	0.648¥
High	19	7	
Missing Data	22	12	
Mother occupation			
Working mother	16	2	0.016¥*
Housewife	22	17	
Missing Data	6	3	
Residence			
Rural	15	11	0.239¥
Urban	28	11	
Missing Data	1		
Income			
Under regional minimum wage	7	7	0.382¥
Over regional minimum wage	13	7	
Missing Data	24	8	

* Significant ($p < 0.05$); ¥ Chi square test. Low education : elementary school- junior high school. High education: senior high school and after

Table 2 shows the differences between DS children with CHD and without CHD in clinical signs and symptoms, nutritional status, and comorbidities. In the clinical signs and symptoms item, cyanosis and heart murmur were significantly different between the two groups (p=0.005; p<0.001). However, clinical signs of respiratory rate, interrupted feeding, and retraction of the chest wall did not differ between the two groups (Chi square test, p=0.213; p=0.144: p=0.759). This study showed no differences in WAZ, HAZ, WHZ and HC of DS children with and without CHD (Chi square test, p=0.831; p=0.589; p=0.533; p=1.000)

DS patients with CHD had a higher incidence of RTI in a year than DS patients without CHD (Mann Whitney Test, p=0.00). The comorbidities such as thyroid disorders, hearing abnormalities, otitis media, and obstructive sleep apnea did not differ in the two groups (p>0.05). There was a significant difference in the frequency of hospitalization in a month between DS children with and without CHD (p=0.039)

Table 2. Signs and Symptoms, Nutritional Status, and Concomitant Disease of Down Syndrome Children with and without Congenital Heart Disease (CHD)

Variable	Down Syndrome		p
	With CHD (n=44)	Without CHD (n=22)	
Signs and Symptoms			
Cyanosis			
Yes	19	2	0.005¥**
No	25	20	
Heart murmur			
Yes	26	0	<0,001¥**
No	18	22	
Respiratory rate			
Normal	32	19	0,213¥
Takipnea	12	3	
Interrupted feeding			
Yes	18	5	0,144¥
No	26	17	
Chest retraction			
Yes	10	4	0.759¥
No	34	18	
Nutritional Status			
WHZ (n ; (%))			
Malnutrition-undernutrition	35	16	0.533¥
Good nutrition-overweight	9	6	
WAZ (n ; (%))			
Malnutrition-undernutrition	35	17	0.831¥
Good nutrition-overweight	9	5	
HAZ (n ; (%))			
Short stature	23	13	0.589¥
Normal- tall stature	19	8	
Missing Data	2	1	
HC (n ; (%))			
Microcephaly	15	7	1.000¥
Mesosephaly	3	1	
Missing Data	26	14	
Concomitant Disease			
Respiratory Tract Infection in a year (median [min-max value])	2 (1 – 6)	1 (0 – 3)	0.00022‡*
Thyroid disorder			
Present	21	9	0.600¥
No	23	13	
Acute Otitis Media			
Present	12	5	0.691¥
No	32	17	
Obstructive Sleep Apnea			
Present	3	1	1.000¥
No	41	21	
Hearing impairment			
Present	14	4	0.241¥
No	30	18	

* Significant (p < 0,05); ¥ Chi square test; ‡Mann Whitney Test

Discussion

In this study, children with DS and CHD had significant differences in clinical signs of cyanosis and heart murmur. A previous study in Slovenia compared the levels of tissue oxygenation in children with and without CHD using the Near Infra-red Spectroscopy method and found that children with CHD had lower tissue oxygenation levels. Low tissue oxygen level is one of the predisposing factors for cyanosis.[8] Meanwhile, a heart murmur is the most important clinical sign in the initial step of CHD diagnosis in children under two years old. It is according to a study conducted in Spain where the subjects were children with moderate to severe CHD.[9] Another study by Mirzarahimi et al[10] in 2,928 newborns found heart murmur in 91 infants on physical examination. After being confirmed with echocardiography, 51.6% of children had a pathological heart murmur that led to the diagnosis of CHD.[10]

This study found that clinical signs such as interrupted breastfeeding, retraction of the chest wall, and increased breath rate did not differ significantly between DS children with and without CHD. However, a previous study showed that 75% of DS children with CHD had a prolonged breastfeeding duration extending to 30-60 minutes.[11] This finding also conflicted with the previous study, which showed that people with CHD (especially left-to-right shunts) experience breathing distress more often characterized by chest wall retraction and increased breathing rate than children without CHD.[12] Another study by Padedam et al[13] on children with CHD aged 0-12 years found that 57.4% of those children experienced chest retraction, which is the most often clinical sign. These differences were likely due to intermittent breastfeeding also experienced by DS children without heart abnormalities. Poor sucking and swallowing reflexes are common due to hypotonia and orofacial muscle weakness in most children with DS. Other causes were likely due to anatomical abnormalities like a large protruding tongue and poor jaw control in DS.[14]

This study showed no significant differences in the nutritional status of both groups. The results differ from the cross-sectional study in Sudan, with 109 samples of DS children with and without CHD, aged 0-12 months. Eighty-seven per cent of DS with CHD had malnutrition, and only 12.8% had normal nutritional status. Meanwhile, DS children without CHD had a better nutritional status which was 64.5%.[15] Meguid et al[16], involving children with DS aged 0-18 years in Turkey, found that children with CHD had lower body weight compared to children without CHD. However, height and head circumference showed no differences. The difference in results may be due to a higher level of selectiveness in sample selection in the previous study. Parameters such as TSH, T4, and the size of heart defects were considered, and the measurements were also made periodically.[16]

The frequency of hospitalizations in a month was significantly different in both groups, with the most common cause was bronchopneumonia. This finding is in concordance with the previous study in Florida that determines the frequency, duration, and cost of hospitalization for 2,552 DS children without, mild, and severe CHD. The frequency and duration of visits in DS children with severe and mild CHD were more frequent, more prolonged, and spent 11 times more cost than DS children without CHD.[17]

The frequency of respiratory tract infection yearly in children with DS and CHD was also higher. Research by Paula F et al[18] in Brazil on 127 children with DS found that 70% of 30 children who suffer from pneumonia have CHD. This result was also corroborated by The REGAL, a study that reviewed western journals and literature on the respiratory syncytial virus (RSV) for the past 20 years. Children with CHD, especially the hemodynamic significant CHD type, had a greater risk of severe RSV infection, especially in the first year of life, and increased risk of care in the intensive care unit compared to children without CHD.[19]

We found no significant differences in thyroid disorders, hearing abnormalities, otitis media, and obstructive sleep apnea between DS children with and without CHD. A case-control study in Iran in babies with congenital hypothyroidism and normal babies found around 22.7% cases of CHD in the case group. There were no significant differences between babies with congenital hypothyroidism and normal babies in the presence of CHD.[20] Another study in Russia involving 148 children with CHD showed that 55 children had hearing loss. But, the study did not assess the confounding variables that could affect the outcome, such as the presence or absence of DS.[21] Another study took the form of a retrospective case-note study in 46 pediatric patients with CHD. Thirty children were found suffering from a sleep-breathing disorder. However, these results did not show whether or not sleep-breathing disorder is directly related to the presence or absence of CHD.[22] Our study was

done in a tertiary hospital with more complicated diseases which may affect the result.

Conclusion

In conclusion, we found significant differences in clinical signs of cyanosis, cardiac murmur, frequency of hospitalizations in a month, and frequency of RTI yearly in DS children with and without CHD. This finding may help awareness of clinical characteristics related to CHD in DS.

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