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Health comorbidities in children with down syndrome (DS) at Dr. Sardjito General Hospital, Yogyakarta

Suryono Yudha Patria, Agung Triono*

Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia

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ABSTRACT

Down syndrome (DS) is a disease caused by trisomy of chromosome 21. The phenotype in DS leads to manifestations in several organ systems. This study aimed to identify the pattern of comorbidities in DS patients. It was a single-center, cross-sectional study at Dr. Sardjito General Hospital, Yogyakarta. Medical records of pediatric patients with DS from a period of January 2022 to May 2023 were included. Descriptive analysis was performed to demonstrate demographic and clinical characteristics. A total of 355 pediatric patients with DS were found at Dr. Sardjito General Hospital and the majority were male (196 children or 55.2%). As much as 339 children (95.49%) had comorbidities. The highest comorbidity was congenital heart disease (230 patients or 67.84%) in specifics were atrial septal defect (41 patients or 12.39%), atrioventricular septal defect (29 patients or 8.17%), and patent ductus arteriosus (28 patients or 7.88%). The second highest comorbidity was endocrine system disorders (102 patients or 30.09%), with 100 patients (28.16%) children suffering hypothyroidism. The number of children who had one comorbidity was 248 patients (69.86%), 74 patients (20.48%) had two comorbidities, and 17 patients (4.79%) had three or more comorbidities. The highest co-prevalence of the two comorbidities was congenital heart disease and endocrine system disorders (36 patients or 10.14%). The highest co-prevalence of 3 or more comorbidities was a combination of congenital heart disease, visual impairment, and hearing impairment (6 patients or 1.69%). In conclusion, 95.49% of children with DS have comorbidities. The most common comorbidity was heart defects. About 25.63% of patients had more than one comorbidity. Children with DS who have comorbidities require more attention to prevent complications and to reduce morbidity.

ABSTRAK

Sindrom Down (SD) merupakan penyakit yang disebabkan oleh trisomi kromosom 21. Fenotipe dari SD menimbulkan manifestasi pada beberapa sistem organ. Penelitian ini bertujuan untuk mengidentifikasi pola penyebaran komorbid pada pasien SD. Penelitian pada satu senter, studi potong lintang di RSUP Dr. Sardjito, Yogyakarta. Rekam medis pasien anak dengan SD periode Januari 2022 sampai Mei 2023 diikutkan dalam penelitian. Analisis deskriptif dilakukan untuk menunjukkan demografis dan karakteristik klinis pasien SD. Total 355 pasien anak dengan SD di RSUP Dr. Sardjito pada kurun waktu penelitian dan mayoritas laki-laki yaitu sebanyak 196 pasien (55,2%). Sebanyak 339 pasien (95,49%) dengan komorbid. Komorbid tertinggi adalah penyakit jantung bawaan (230 pasien atau 67,84%) dengan perincian kasus *atrial septal defect* (41 pasien atau 12.39%), *atrioventricular septal defect* (29 pasien atau 8,17%), dan *patent ductus arteriosus* (28 pasien atau 7.88%). Komorbid tertinggi kedua adalah kelainan sistem endokrin (102 pasien atau 30,09%) dengan 100 pasien (28.16%) yang menderita hipotiroid. Jumlah yang memiliki satu komorbid sebanyak 248 pasien (69,86%), 74 pasien (20,48%) memiliki dua komorbid dan 17 pasien (4,79%) memiliki tiga komorbid atau lebih. Ko-prevalensi dua komorbid tertinggi adalah penyakit jantung bawaan dan kelainan sistem endokrin (36 pasien atau 10,14%). Ko-prevalensi tiga atau lebih komorbid tertinggi adalah kombinasi dari penyakit jantung bawaan, gangguan penglihatan, dan gangguan pendengaran (6 pasien atau 1,69%). Simpulan, anak dengan SD yang memiliki komorbid sebesar 95,49%. Komorbid terbanyak adalah kelainan jantung. Sebanyak 25,63% pasien memiliki komorbid lebih dari satu. Anak SD yang memiliki komorbid memerlukan perhatian lebih untuk mencegah komplikasi dan mengurangi morbiditas.

Keywords:
children;
comorbidities;
down syndrome;
prevalence;
manifestation

*corresponding author: agungtrionodr@yahoo.com

INTRODUCTION

Down syndrome (DS) is one of the chromosomal disorders with the highest prevalence in humans, caused by the trisomy of chromosome 21.[1,2] The phenotype in DS encompasses various clinical manifestations that can affect several organ systems, particularly the nervous, musculoskeletal, and cardiovascular systems.[1] Clinical features include intellectual disabilities, short stature, a flat facial profile, prominent epicanthal folds, upward slanting fissures of the eyelids, and a protruding tongue.[2]

According to WHO's data from 2018, the prevalence of DS is approximately one in every 1,000 births.[2] It is also found that the prevalence of DS has significantly increased as the global population grows. In the United States, the population prevalence of DS increased from around 50,000 in 1950 (3.3 per 10,000 individuals) to about 212,000 in 2013 (6.7 per 10,000 individuals).[1] Currently, in the United States, around 500 live births with DS occur each year, and over 200,000 individuals live with this disorder.[3]

Based on data from the Indonesian Ministry of Health of Republic of Indoensia (*Pusdatin Kemenkes* RI), the incidence of DS cases in Indonesia has risen over the years. In the Basic Health Research (*Riskesdas*) results of 2010, DS cases in children aged 24 to 59 mo were recorded at 0.12%, increasing to 0.13% in the 2013 *Riskesdas*, and further rising to 0.21% in the 2018 *Riskesdas*.[4] According to the Hospital Information System (SIRS), among 2,488 hospitals, 1,657 cases of DS were reported in 2015. In 2016, data from 2,598 hospitals indicated 4,449 cases of DS, while in 2017, 2,776 hospitals reported 4,130 cases of DS.[4]

Down syndrome exhibits diverse clinical phenotypes that affect various organ systems. Over time, a study in England and Wales in 2020 reported that patterns and prevalence of comorbidities in DS may change due to improvements in care and treatment. Therefore, up-to-date information on DS and its comorbidities is essential for clinical practitioners, individuals, families, and caregivers.[5]

Another study in the United Kingdom in 2023 reported multiple morbidities were found in DS patients that show distinct patterns of age-related incidence trajectories and clustering that differ from those found in the general population and in people with other intellectual disabilities. The multiple morbidities have implications for provision and timing of health-care screening, prevention, and treatment for people with DS.[6]

We also found no studies in Indonesia, especially in Yogyakarta Special Region, that show and elaborate different cases of morbidities in DS patients. Therefore, increasing trend of DS cases in Indonesia each year and the need for current information on the pattern of comorbidities in DS cases in Indonesia serve as the fundamentals of this study. This study is expected to contribute valuable information on the patterns of comorbidities in DS cases in Indonesia, particularly in Yogyakarta Special Region.

This study is essential as identifying patterns of common comorbidities, especially in Indonesia, can benefit healthcare services in Indonesia to foresee common comorbidities in DS patients and can benefit DS patients with early intervention and enhance the quality of healthcare.

MATERIAL AND METHODS

Design and subjects

It was a cross-sectional study conducted at Dr. Sardjito General Hospital, Yogyakarta using data of the medical records of pediatric patients who confirmed with a diagnosis of DS in a period of January 2022 to May 2023. The diagnosis of DS was established by a pediatric specialist and consultant endocrinologist based on clinical criteria as documented in the medical records.

Procedure

The data collected for this study include age, gender, and the comorbidity profile of patients with DS. Patients with confirmed diagnoses of DS were included in this study, and patients with incomplete data were excluded from this study. Comorbidities were established by a pediatric specialist based on clinical criteria as documented in the medical records. This study followed the criteria of medical ethics and was accepted by the Institutional Review Board of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta (KE/FK/0666/EC/2023).

Data analysis

Data were presented as frequency and percentage. Descriptive analysis was employed to present the demographic and clinical characteristics of the patients.

RESULTS

A total of 355 children with DS were involved in this study. The characteristics of patients are presented in TABLE 1. More male patients were found in this study with the average age was 3.88 ± 3.73 yr.

Among 355 pediatric patients with DS, most the patients (339 children or 95.49%) had comorbidities (FIGURE 1). The highest comorbidity was congenital heart disease (230 children or 67.84%).

The most common comorbidity found was congenital heart disease (230 or 67.84%) in specifics were atrial septal defect (41 patients or 12.39%), atrioventricular septal defect (29 patients or 8.17%), and patent ductus arteriosus (28 patients or 7.88%). The second highest comorbidity was endocrine system disorders (102 patients or 30.09%), with 100 patients (28.16%) children suffering hypothyroidism (TABLE 2).

This study found that some patients has a combination of 2 comorbidities (74 patients or 20.48%). Congenital heart disease and endocrine system disorders are the most common combinations (36 patients or 10.14%). The most minor combination found was visual impairments along with hearing impairments (9 patients or 2.53%) (TABLE 3).

This study also found that some children were diagnosed with 3 combinations of comorbidities (TABLE 4). The highest combination of comorbidities found was congenital heart disease with visual impairments and hearing impairments (6 patients or 1.69%).

TABLE 1. Characteristics of pediatric patients with DS (n=355) at Dr. Sardjito General Hospital, Yogyakarta

Characteristics	Number
Age (mean ±SD yr)	3.88 ± 3.73
Gender [n (%)]	
• Male	196 (55.2)
• Female	159 (44.8)

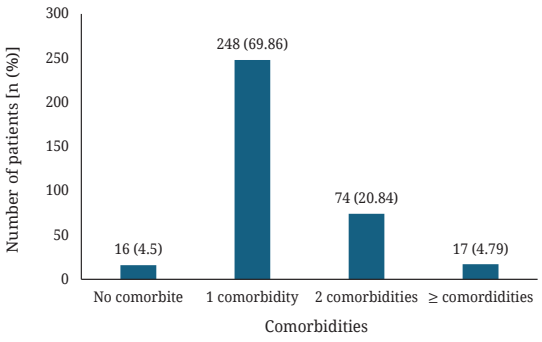

FIGURE 1. Number of comorbidities of pediatric patients with DS (n=339) at Dr. Sardjito General Hospital, Yogyakarta

TABLE 2. Detailed comorbidities profile of pediatric patients with DS at Dr. Sardjito General Hospital

Comorbidities	Number [n (%)]
Central nervous system disorders	21
• Global developmental delay	12 (3.38)
• Epilepsy	7 (1.97)
• Sleep apnea	2 (0.56)
Congenital heart disease	230
• Atrial septal defect	41 (12.39)
• Atrioventricular septal defect	29 (8.17)
• Patent ductus arteriosus	28 (7.88)
• Ventricular septal defect	16 (4.60)
• Tricuspid insufficiency	10 (2.81)
• Tetralogy of fallot	4 (1.12)
• Mitral insufficiency	3 (0.84)
• Atresia of pulmonary artery	3 (0.84)
• Pulmonary valve insufficiency	3 (0.84)
• Pulmonary valve stenosis	1 (0.28)
• Persistent foramen ovale	1 (0.28
• Tricuspid stenosis	1 (0.28)
• Ebstein anomaly	1 (0.28)
• Dextrocardia	1 (0.28)
Endocrine system disorders	102
• Hypothyroidism	100 (28.16)
• Growth and skeletal anomalies	3 (0.84)
• Congenital foot deformities	3 (0.84)
• Thyrotoxicosis	1 (0.28)
• Diabetes mellitus	1 (0.28)
Genitourinary system disorders	10
• Cryptorchidism	10 (2.81)
Gastrointestinal system disorders	28
• Biliary obstruction	9 (2.53)
• Hirschsprung's disease	9 (2.53)
• Duodenal atresia and/or stenosis	6 (1.69)
• Anal atresia and/or stenosis	4 (1.12)
Visual impairments	27
• Refractive errors	13 (3.66)
• Cataracts	6 (1.69)
• Strabismus	4 (1.12)
• Nystagmus	4 (1.12)
Hearing impairments	31
• Sensori-neural hearing loss	29 (8.16)
• Auditory perception disorders	2 (0.56)
Total	339 (95.49)

TABLE 3. Co-prevalence of 2 comorbidities of pediatric patients with DS at Dr. Sardjito General Hospital, Yogyakarta

Co-prevalence comorbidities of patients with DS	Number [n (%)]
Congenital heart disease + endocrine system disorders	36 (10.1)
Congenital heart disease + hearing impairments	14 (3.94)
Congenital heart disease + visual impairments	12 (3.38)
Visual impairments + hearing impairments	9 (2.53)
Total	71 (19.95)

TABLE 4. Co-prevalence of 3 comorbidities of pediatric patients with DS at Dr. Sardjito General Hospital, Yogyakarta

Co-prevalence comorbidities of patients with DS	Number [n (%)]
Congenital heart disease + visual impairments + hearing impairments	6 (1.69)
Congenital heart disease + endocrine system disorders + hearing impairments	2 (0.56)
Congenital heart disease + gastrointestinal system disorders + visual Impairments	1 (0.28)
Congenital heart disease + endocrine system disorders + genitourinary system disorders	1 (0.28)
Visual impairments + growth and skeletal anomalies + hearing impairments	1 (0.28)
Endocrine system disorders + growth and skeletal anomalies + gastrointestinal system disorders	1 (0.28)

DISCUSSION

In this study, it was observed that children with DS were predominantly male, consistent with findings from other studies indicating a higher prevalence of males among individuals with DS.[5,7]

Based on other studies, children with DS are known to have a higher risk of congenital anomalies such as heart and abdominal wall disorders. Additionally, they are more susceptible to vision and hearing impairments, sleep apnea, as well as growth and skeletal disorders. Individuals with DS also exhibit vulnerabilities to immune and endocrine system disorders.[8] Our study indicates that patients with DS may have multiple comorbidities, potentially more than one concurrent condition.

In this study, several children with DS were found to have comorbid epilepsy, aligning with a study by Altuna *et al.*,[9] which revealed a vulnerability to epilepsy in individuals with DS. This susceptibility may be attributed to various mechanisms, including frontal and temporal lobe hypoplasia, dendritic dyskinesia, abnormal neuronal lamination, reduced neuron density, disruptions in inhibitory GABAergic interneuron function, changes in membrane ion channel activities, and other metabolic abnormalities.[9]

Patients with DS in this study were also identified with global developmental delay. This aligns with the findings of Ferreira-Vaques and Lamonica, indicating that individuals with DS perform lower, especially in language and fine motor domains.[10] According to other studies, individuals with DS are more vulnerable to brain function disorders due to several factors, including morphological disorders of pyramidal neurons or excessive changes in inhibitory function.[11] Other studies have proposed hypotheses causing developmental delays, especially in motor skills. These include 1) Changes in the shape and size of neurons and the cerebrum; 2) Maturity disorders of the central nervous system; 3) Pathophysiological processes such as degeneration of the nervous system, disorders in the regulation of neuron apoptosis, excessive gene expression, and decreased neurotransmitter release.[12]

The majority of patients with DS in this study were found to have congenital heart disease. This aligns with several studies that found congenital heart disease to be the most frequently encountered anomaly in individuals with DS.[7,8] In this study, atrial septal defect was the most prevalent congenital heart disease, although other studies have reported atrioventricular septal defect as the most common.[8,13] However, geographical variations may lead to differences in the types of congenital heart diseases in individuals with DS.[13]

According to other studies, individuals with DS are prone to congenital heart disease due to two hypotheses. The first is the gene dosage amplification theory, stating that an increased genetic dosage from chromosome 21 (Hsa 21) in DS can enhance genetic expression leading to congenital heart disease. The second theory, the gene mutation theory, suggests that mutations on the trisomy 21 locus can increase the occurrence of congenital heart disease.[14]

Most patients with DS in this study, with comorbid endocrine system disorders, suffered from hypothyroidism. This aligns with other studies reporting that individuals with DS are significantly more vulnerable to hypothyroidism compared to normal children, up to 25-38 times higher.[8,15-17] Theoretically, this vulnerability can occur due to several hypotheses, including 1) Excessive TRH stimulation, causing delayed maturation of the hypothalamus-pituitary-thyroid axis, leading to high TSH levels with normal fT4 and fT3 and negative anti-thyroid antibodies at three years of age; 2) Peripheral resistance to thyroid hormones, causing reduced TRH secretion; 3) Lack of TSH release due to central disorders or disruption of dopaminergic control; 4) TSH insensitivity; and 5) Reduced TSH bioactivity.[15]

Patients with DS in this study were also found to have growth and skeletal anomalies. This finding aligns with other studies suggesting that individuals with DS may experience arthropathy, joint weakness, hypermobility, foot deformities, scoliosis, and hip instability.[9] This aligns with the study by Foley and Killeen, which found that the majority of patients with DS suffer from Pes Planus.[18]

The study also identified patients with DS who had genitourinary system disorders, all presenting with cryptorchidism. Another study found that individuals with DS may

experience disorders in the genitourinary system, such as posterior urethral valves, pyelectasis, megaureter, kidney malformations (renal hypoplasia, horseshoe kidney, renal ectopia), hypospadias, cryptorchidism, and small penis.[8]

In this study, comorbid gastrointestinal system disorders were also found, consistent with other studies that reported congenital anomalies in the gastrointestinal system in individuals with DS, such as duodenal atresia, anal atresia/stenosis, esophageal atresia, and esophageal fistula. Hirschsprung's disease, constipation, celiac disease, and biliary obstruction were also identified.[8,19]

Patients with DS in this study were also found to have visual impairments. Visual impairment findings in this study align with other studies indicating an increased incidence of refractive disorders due to the failure of emmetropization processes. Additionally, oblique astigmatism, cataracts, blepharitis, and nystagmus were found in patients with DS.[8,20]

The study also identified patients with DS with comorbid hearing impairments, especially sensorineural hearing loss. Another study found that 38%-78% of individuals with DS experience hearing impairments, most commonly caused by otitis media effusion and sensorineural hearing loss.[8] Another study found that the likelihood of sensorineural hearing loss is due to cochlear nerve deficiency, genetic factors, or excessive noise exposure.[21]

In this study, several patients with DS were diagnosed with multiple comorbidities. The most prevalent combination of comorbidities in this study was congenital heart disease and endocrine system disorders. This aligns with the study conducted by Mulu and Fantahun, which found a significant association between hypothyroidism and congenital heart disease in patients with DS.[13] Yaqoob *et al.*[22] also found a high number of individuals with DS having thyroid function disorders and congenital heart diseases. According to Lerner *et al.*,[23] patients with congenital heart disease have a high prevalence of thyroid dysfunction, both genetically and embryonically determined.

This study provides new insights into characteristics and patterns of comorbidities in children with DS in Indonesia, especially in Yogyakarta. These new insights can benefit healthcare services, especially in Indonesia, to foresee common comorbidities in children with DS and benefit patients with early diagnosis, early intervention, and enhanced healthcare quality.

On the downside, this study can only provide a descriptive analysis. However, this study is a cornerstone for future studies, especially in Indonesia, to better understand comorbidities and DS in children, especially in Indonesia, with more complete data and analysis in the future. Future studies to include nutritional data and analysis on comorbid outcomes of DS patients are recommended.

CONCLUSION

This study finds that most children with DS in Dr. Sardjito General Hospital, Yogyakarta suffer at least one comorbid. The most common comorbid found was congenital heart disease. Future studies are needed to enhance health care, especially for DS patients in Indonesia.

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