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Association of Comorbid with Developmental Quotient in Down Syndrome Children

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Abstract

BACKGROUND: Down syndrome (DS) is the most common genetic disorder in children. Children with DS tend to have various comorbid due to developmental abnormalities of chromosome 21, such as congenital heart defects, hearing loss, otitis media, eye disorders, obstructive sleep apnea, thyroid hormone disorders, gastrointestinal atresia, hip joint dislocation, leukemia, and Hirschsprung's disease. Moreover, they also show cognitive impairments in concentration, communication, memory, and the ability to carry out tasks. Caput Scale/Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT-CLAMS) is one of the developmental assessment instruments to screen for cognitive disorders.

AIM: Hereby, we aimed to find the association of comorbid with developmental quotient in DS children. Data were obtained from medical record with sample age 0–18 years and suffering from DS.

METHODS: This was observational analytic study with cross-sectional approach, conducted in DS children age 0–18 years who were treated in Sanglah Hospital in 2018. Characteristic data and comorbid were obtained from medical record, meanwhile, development status was assessed using Caput Scale/CAT-CLAMS. Chi-square was applied to determine the association between comorbidities and development quotient (DQ) in DS children.

RESULTS: A total of 32 children with DS were treated in Sanglah Hospital during 2018 with median age was 2 years old and dominated by female patient (71.9%). Several comorbidities were found such as endocrine disorders in 27 children (84.3%), congenital heart disease (CHD) in 16 children (50%), and other comorbid including microcephaly, congenital cataract, palatoschizis, gastrointestinal defects, and congenital talipes equinovarus in 13 children (40.4%). The most common endocrine disorders was congenital hypothyroidism (81.25%), while the most common CHD was patent ductus arteriosus (25%). Bivariate Chi-square analysis showed significant association between comorbid and DQ (PR = 1.4 [95% CI 0.95–1.97], p = 0.03).

CONCLUSION: We found an association between comorbidities and DQ in DS children.

Introduction

Down syndrome (DS) is the most common genetic disorder found in children. Intellectual disability and other mental disorders can cause various health and developmental problems which are quite complex [1]. Management of DS in clinical practice is still limited to dealing with existing complaints. Comprehensive treatment that involves multidisciplinary science at every stage of a child's growth and development is needed to improve their quality of life in the future [1], [2], [3].

The incidence of DS in the United States is estimated 1 per 600–800 live births [3], while in Indonesia based on the results of the Basic Health Research (Riskesdas) in 2010, the cases of DS were 0.12% and increased in 2013 to 0.13%, and 2018 into 0.21% [4], [5]. This figure corresponds to the average incidence of 1 per thousand children reported in many studies. Research in America reported that the prevalence of DS increased by 31% in births of mothers aged 35 years and over [6].

Children with DS tend to have various mental disorders and malformations due to developmental abnormalities of chromosome 21 in the form of trisomy 21, translocation, or mosaicism. This chromosomal abnormality decreases the neurons in the central nervous system, delayed myelination and an irregular cell cycle which, in turn, leads to increased production of protein precursors and neurotransmitter abnormalities. The phenotype varies but generally provides sufficient constitutional features for the experienced clinician to suspect DS [7].

Comorbidities often accompany children with SD such as congenital heart defects 50%, hearing loss 75%, otitis media 50–70%, eye disorders 60% including cataracts (15%) and severe refractive errors (50%), obstructive sleep apnea 50–75%, thyroid hormone disorders 15%, gastrointestinal atresia 12%, hip joint dislocation 6%, and leukemia and Hirschsprung's disease <1% [4], [6].

Children with DS show cognitive impairments in concentration, communication, memory, and the ability to carry out tasks [7]. Comorbidities that occur

in DS children are often associated with the degree of development or growth. Research in Japan [8] showed that the speed of development of children with DS was slower than their peers who are not DS. This delay is associated with the number of comorbidities present in children with DS.

The degree of intellectual disability in DS children varies, ranging from mild intellectual disability (IQ: 50–70) to moderate (IQ: 35–49) and sometimes (rarely) severe intellectual disability (IQ: 20–34) [8]. Caput Scale/Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale (CAT-CLAMS) is one of the developmental assessment instruments that can be used to screen for cognitive disorders (language and visual-motor) in all children including children with DS [9]. Development quotient (DQ) is a score in the CAT-CLAMS questionnaire that will describe the proportion development in the child [9].

Many medical and psychosocial problems, both immediate and long term, cause the care of DS children become complex. An early intervention program is needed, namely, systematic program that includes therapy either surgery or correction or conservative structured by experts for comorbid, exercises, and activities designed to treat the developmental delays and minimize the negative impact of delays experienced by children with DS or other disabilities. Early intervention programs are generally multidisciplinary, consisting of speech and language therapy, physical therapy, and occupational therapy [10]. Health management, home environment, education, and vocational training greatly affect the functioning of DS children and assist their transition into adulthood. Family, friends, and community help are needed to support the mental development of DS children. Good cooperation from various parties and multidisciplinary approach is needed to achieve good health, growth and development conditions in children with DS [5], [10].

Sanglah Hospital as referral and teaching hospital needs to prepare facilities and infrastructure including sufficient human resources to provide comprehensive services to DS patients. Supporting data regarding the relationship between comorbidities and DQ in DS patients are needed as reference in planning service. These data are not yet available therefore researchers are interested in conducting this research.

Materials and Methods

This study was observational analytic study with cross-sectional approach, conducted on DS children who were treated in Sanglah Hospital in 2018. The data were obtained from medical record. The samples are those who meet the inclusion criteria and exclusion criteria. Inclusion criteria were age 0–18 years and suffering from DS. The sample will be excluded if the data are incomplete. The sample was selected by consecutive sampling, with the sample size calculated according to the estimated proportion of DS with single comorbidities of 10% [8], the difference in the expected proportions was 20%, power was 80%, and significance was 95%. Calculation of the sample size using unpaired category formula obtained minimum sample size 30 subjects.

This research has been approved by ethics committee of the Faculty of Medicine, Udayana University, with ethical clearance number 2019.02.1.0107. The data of this study include data on the characteristics and prevalence of children with DS and the analysis of the relationship between comorbidities and DQ in DS children. The basic data included age, gender, education of father and mother, income of parents, and number of siblings. Characteristics of children with DS are described based on their congenital abnormalities, nutritional status; meanwhile, child's cognitive was assessed based on CAT-CLAMS.

All data were collected and processed using computer program. Categorical variables are described in number (n) and prevalence in percentage (%). The processed data are presented in the form of tables and narratives. Bivariate analysis using Chi-square was conducted to determine the relationship between comorbidities and DQ in DS children.

Results

There were 32 children with DS who were treated at Sanglah Hospital in 2018. The median age of the subjects was 2 years (range 1–12 years). The characteristics of the research subjects were divided into gender, parental education, parental age, and nutritional status (Table 1).

Table 1: Characteristics of subjects

Characteristics	Total (%)	Single comorbid	Multiple comorbid
Age (year), median	2 (1–12)		
Gender, (n %)			
Male	9 (28.1)	4 (44.4)	5 (55.6)
Female	23 (71.9)	7 (30)	16 (70)
Father educational degree			
Elementary school	1 (3.1)	0 (0)	1 (100)
Junior high school	6 (18.8)	3 (50)	3 (50)
Senior high school	17 (53.1)	5 (29)	12 (71)
Diploma	4 (12.5)	2 (50)	2 (50)
Bachelor	4 (12.5)	1 (25)	3 (75)
Mother educational degree			
Elementary school	1 (3.1)	1 (100)	0 (0)
Junior high school	7 (21.9)	3 (43)	4 (57)
Senior high school	15 (46.9)	11 (73)	4 (27)
Diploma	2 (6.3)	2 (100)	0 (0)
Bachelor	7 (21.9)	4 (57)	3 (43)
Father's age (year), (n %)			
<35	5 (15.6)	3 (60)	2 (40)
>35	27 (84.4)	8 (29)	19 (71)
Mother's age (year), (n %)			
<35	16 (50)	8 (50)	8 (50)
>35	16 (50)	6 (37.5)	10 (62.5)
Nutritional status			
Well nourish	13 (40.6)	7 (54)	6 (46)
Malnutrition	16 (50)	3 (18)	13 (82)
Severe malnutrition	3 (9.4)	1 (50)	1 (50)

Based on the type of comorbidity that children with DS have, 27 children (84.3%) with endocrine disorders, 16 children (50%) with congenital heart disease (CHD), 13 children (40.4%) with other comorbid such as microcephaly, congenital cataract, palatoschizis, gastrointestinal defects, and congenital talipes equinovarus (CTEV). The most common endocrine disorders was congenital hypothyroidism (81.25%), while the most common CHD was patent ductus arteriosus (PDA) (25%) (Table 2).

Table 2: Types of comorbidities in DS children

Variables	n=32
Microcephaly, n, %	2 (6.25)
Congenital cataract, n, %	2 (6.25)
Palatoschizis, n, %	1 (3.1)
Gastrointestinal, defect n, %	3 (9.3)
Atresia ani	1 (3.1)
Hirschsprung	1 (3.1)
Hernia umbilicalis	1 (3.1)
CHD, n,%	16 (50)
Complete atrioventricular septal defect (CAVSD)	2 (6.25)
PDA	8 (25)
Atrial septal defect (ASD)	2 (6.25)
Ventricular septal defect (VSD)	4 (12.5)
Endocrine disorders, n,%	27 (84.37)
Congenital hypothyroidism	26 (81.25)
Micropenis	1 (3.1)
CTEV, n, %	2 (6.25)

CTEV: Congenital talipes equinovarus, PDA: Patent ductus arteriosus, CHD: Congenital heart disease.

Screening for the possibility of developmental delays in children with DS can be carried out with several tools, including Denver II and CAT-CLAMS. In this study, we used CAT-CLAMS and the result was dominated by “suspect” category.

Table 3: CAT-CLAMS scores of children with DS

Variables	n=32
Suspect, n,%	21 (65.6)
Mental retardation, n,%	6 (18.8)
Communication disorder, n,%	5 (15.6)

CAT-CLAMS: Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale, DS: Down syndrome.

The description of DQ score category for children with DS is shown in Table 3. There were 21 children (65.6%) with suspected, 6 children (18.8%) with mental retardation, and 5 children (15.6%).

Table 4: The association of comorbid with DQ in DS children

Variables	Category DQ		PR	CI 95%	p-value
	Disorder	Suspect			
Comorbidity, n %					
Multiple	21 (65.6)	0 (0)	1.4	0.95–1.97	0.033
Single	8 (25)	3 (9.4)			

Bivariate Chi-square analysis of the association between comorbid and DQ is shown in Table 4. Multiple comorbidities were associated with DQ scores of children with DS. The relationship was statistically significant (PR=1.4 [95% CI 0.95–1.97], p=0.03).

Discussion

This study showed that most of the DS subjects were female, from parents graduated from senior high school. Many theories suggest that possible identified risk factor for the birth of baby with DS is parenteral age as the most common. Older maternal age plays an important role in DS births. Approximately 2% of recognized pregnancies in women under 25 years of age was trisomy, which increase to 10% in women above 36 years and to 33% in age 42 [11], [12].

This result is similar with Podder *et al*. [13] who stated that several studies have reported positive relationship between parity and DS but their results found that the probability of having baby with DS is more influenced by genetic age. The increase in age of all groups showed telomere loss, but the loss was greatest in the group of mothers in meiosis II and the smallest in the group of euploid mothers and the mother group of meiosis I in the middle. In addition, Sotonica *et al*. [14] found that 44 cases (34.6% of DS children) had younger mothers, who were <30 years of age. The possible explanation of younger mothers who have children with DS is the consumption of alcohol, tobacco, environmental toxins, and drugs which cause chromosomes without disjunction. Young mothers tend to be sleep deprived, have unbalanced diet so as not to gain weight and accidental pregnancies which all lead to bad pregnancy habits. Our study found that the frequency of maternal age was balanced at age <35 years and >35 years.

Another study also discussed the role of paternal age in the birth of babies with DS. Research from Sotonica *et al*. [14] showed that paternal age also makes a difference when calculating the probability of genetic disorders. The highest percentage of DS children was in the group of fathers aged 30 and over and older than 40 (44.9% and 32.3%), respectively. Younger fathers (22.8% of cases) having children with DS may have the same reasons when talking about young mothers, and are more likely that younger men whom have older partner may also contribute to the high prevalence of DS. Older men produce more sperm with aneuploidy. Our study found that 84.3% (27 of 32 subjects) had a paternal age of >35 years.

DS is a combination of dysmorphic facial features (which facilitates the diagnosis) and several associated visceral anomalies [15], [16]. Poaty *et al*. [17] found that mortality in DS remained high and was frequently associated with visceral malformations. Research by Unachak *et al*. [18] showed that 37.9% of DS patients suffered hypothyroidism, thus hypothyroidism is the most common thyroid disorder in DS. King *et al*. [19] also conducted study on the thyroid in 148 patients with DS and the results showed that 53% had hypothyroidism and stated that children with DS had higher risk of thyroid dysfunction than normal children. This study found that endocrine disorders were the most common comorbidities especially congenital hypothyroidism.

CHD is considered to be the most important clinical phenomenon of DS that contributes to morbidity and mortality in affected infants [20], [21]. The risk of CHD in DS is well known, but the type and frequency

of the various categories of CHD are debated and are expected to cooccur with other congenital anomalies among children with DS [22]. The study in Atlanta by Forsey *et al*. [23] found that the most common CHD in DS was PDA. This study suggests that several factors such as ethnicity and geographic differences contribute to increase the frequency of PDA as they are associated with lower oxygen partial pressures [23], [24]. In this study, PDA was found as the most common type of CHD in DS.

Global developmental delay is predicted occur in children with DS, which affects motor, cognitive, language, and personal skills [25], [26]. This is in accordance with research in Aoki *et al*. [26] which showed that the speed of development of children with DS was found to be slower than that of children with DS. This delay is associated with the large number of comorbidities present in children with DS [26]. Vadakedom *et al*. [25] in their study found that most of the samples were globally delayed with hypotonic conditions. Delays in motor area in children with DS are predictable related to hypotonia conditions that occur in children with DS, including primitive reflexes and joint hypermobility that affect the ability to control posture so that they play role in movement and motor coordination.

Caput Scale/CAT-CLAMS as screening instrument for developmental disorders can be used to assess the level of cognitive development of children through the DQ score which will describe the proportion of development in the child. Global developmental delays are predicted occur in children with DS, which affect motor, cognitive, language, and personal skills. This delay is often associated with comorbidities found in DS children. This study proves that there is a comorbid relationship with DQ in DS children. Chi-squared analysis showed significant association between multiple comorbidities and DQ in children with DS. The results of this study are in accordance with the results of research in Japan by Aoki *et al*. [26] which showed that the speed of development of children with DS was slower than their peers who were not primary school. This delay is associated with the large number of comorbidities that exist in children with DS [27], [28]. The results of this study are also reinforced by Kim *et al*. [27], 2016, who said that children with DS have several comorbidities and require surgical intervention as early as possible which is needed to reduce the negative effects on motor development and cognitive development [27]. The limitation of this study is that the investigators did not evaluate the process of administering developmental stimulation to patients with DS.

Conclusion

This study proved that there is an association between comorbidities and DQ in DS children. However, this study lacks of data specifications and completeness because it was highly dependent on retrospective medical record data. Further prospective studies are needed to obtain better results.

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