



Growth, Development, and Quality of Life in Children with Congenital Heart Disease

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Abstract

BACKGROUND: Despite the advances in medical and surgical care have improved the survival rates of children with congenital heart disease (CHD), they still remain risky for nutritional, cognitive problems, and quality of life. Those impacts vary according to the severity of heart lesions and still manifested years after surgery.

AIM: The objective of this study was to compare growth, development, and quality of life between cyanotic and acyanotic CHD.

METHODS: The study was performed on 52 patients aged 24–69 months old from June to January 2018 in Sanglah Pediatric Cardiology clinic used WHO Anthro software, The Mullen Scales of Early Learning and PedsQL Cardiac module.

RESULTS: We found significant different proportion of underweight 11.5% in acyanotic children, 42.3% in cyanotic by weight/age z-score <-2SD (p = 0.033). Height/ age z-score <-3SD 38.5% in cyanotic versus 11.5% in acyanotic (p = 0.025). The cyanotic showed a significant difference in cognitive function, presented by early learning composite score (p = 0.044) particularly in gross motor (p = 0.034) and receptive language (0.047). Quality of life differs significantly between both groups in heart problem and therapy (p = 0.042), treatment anxiety (p = 0.016), cognitive problems (p = 0.038), and communication (p = 0.022).

CONCLUSION: Development, growth problems, and lower quality of life are common in cyanotic children, thus highlight the need for longitudinal surveillance.

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Introduction

Congenital heart disease (CHD), the most common cause of major congenital anomalies, representing global health problems in pediatric patients [1], [2], [3], [4] with estimated prevalence is 8 per 1000 live births [1]. Despite the advances of medical and surgical care, the increase in survival rates of children with heart disease into adulthood increase [2], several investigators have demonstrated children with CHD remain at risk for nutritional [1] and cognitive problems [5], [6], [7], [8], [9] which rely on the complexity of the heart lesion. The cognitive disorders include areas of intelligence, academic achievements, languages, visual construction perceptions, attention, executive functioning, fine motor skills, gross motor skills, and psychosocial maladjustment [6], [7]. The impacts of cognitive outcomes for these children vary widely, according to the severity of heart lesions [5] and still being observed many years after successful surgery, manifested as learning or behavioral difficulties, which implies that they are not transient in nature [6].

Despite most of the CHD children have normal birth weight, they tend to develop malnutrition within the first months of life [10], [11]. Decreased energy intake,

tissue hypoxia, cardiac acidosis, peripheral acidosis, intestinal malabsorption, increased energy requirement, and attribute infection increase metabolism rate, which ends to growth impairment [1], [3], [10], [12]. Cyanotic heart defect children commonly demonstrate markedly poor growth compared with acyanotic defect children [10], [13]. As these children reach adulthood those morbidities can limit educational achievements, employability, insurability, and can particularly affect the child's overall health-related quality of life [7]. As shown by several studies children with cyanotic heart defect have a lower score in quality of life compared with healthy peers in the same age group [14]. In effort to improve the outcome, we aimed to study the nutritional status, cognitive function, and quality of life in children with cyanotic and acyanotic CHD.

Materials and Methods

This cross-sectional study was conducted from June 2017 to January 2018, Bali, after obtaining clearance from the institutional ethics committees of Udayana university with protocol study number 2017.02.1.0542.

This study consecutively recruited congenital heart defect children aged 24–69 months old (cyanotic and acyanotic) in Pediatric Cardiology outpatient clinic, with consideration of the instrument we use and cooperation from the child. As we know, 24 months is the starting age to assess the quality of life using PedsQL Cardiac module. Meanwhile, for neurocognitive evaluation using The Mullen Scales of Early Learning (AGS edition) were limited from birth to 69 months old. The required sample size was calculated based on the study by Nasiruzzaman *et al.* [3] and Rachmawati *et al.* [4] using power 95%, alpha 5% (two-tail), estimated proportion difference (P_1-P_2) 40%, and gross motor as the most frequent cognitive problem (which affected 60% of their sample; 15 from 28 cyanotic; and 15 from 22 acyanotic) [3]; we got 26 children per group from unpaired categorized analytic formula. Meanwhile, the proportion of malnutrition based on the WHO criteria was 19 from in 28 cyanotic [9], with P_2 0.67, we got 13 subjects per group.

The comparison quality of life from 17 cyanotic children with 37 acyanotic children showed that quality of life-based on parental report was significant lower in cyanotic group in the following segments including heart problem and therapy (53.3 ± 9.26 vs. 71.4 ± 7.75 ; $p = 0.007$), physical appearance (67.5 ± 20.57 vs. 90.2 ± 4.89 ; $p = 0.033$), treatment anxiety (57.3 ± 11.34 vs. 83.6 ± 14.28 ; $p = 0.001$), and cognitive problem (53.3 ± 5.16 vs. 78.3 ± 4.85 ; $p = 0.001$) [14]. Based on that, the composite of standard deviation using the formula for unpaired analytic categories and numeric we got the biggest sample size was 21 children per group. From the above calculation, we concluded 26 children per group as the biggest sample size for each group.

Children were eligible for inclusion if they presented with symptoms and signs suggestive of CHD, which had been confirmed by echocardiographic examination, parents both mentally and educationally capable of answering the questionnaire and agree to participate by signing the informed consent after been explained the purpose of the study. Patient was excluded from the study if they have clinically genetic syndrome or disorders (Turner, Down, VACTERL association, microcephaly, deafness, blindness), neurologic disorder (cerebral palsy, epilepsy), hematologic or oncology problem (ITP, thalassemia, retinoblastoma, and leukemia), or history of psychiatric problem. Psychiatric problem was assessed if the patient had medical history of being consulted to the psychiatric department or consuming psychiatric medication. Full medical history as well as complete cardiac examination, including the result of echocardiography, catheterization (if one had been done), was documented for all children.

Variables definition

Cyanotic heart disease was defined as type of CHD that occurs due to structural defect of the heart (right to left shunting, and malposition of great artery)

or any condition which increases pulmonary vascular resistance that causes mixture of oxygenated and unoxygenated blood entering the systemic circulation with oxygen saturation $<85\%$, for example, tetralogy of Fallot, hypoplastic left heart syndrome, transposition of great artery, tricuspid atresia, pulmonary atresia, and atrioventricular septal defect.

Acyanotic heart disease was defined as type of CHD that occurs due to structural defect of the heart that causes left to right shunting, with normal level of oxyhemoglobin saturation in systemic circulation, for example, ventricular septal defect, atrial septal defect, and patent ductus arteriosus.

Economy class was defined from monthly family income such as money received periodically from commerce, employment, and investments based on Bali Governor decrets no 67/2016 with minimum wages in Denpasar was Rp.2.173.000/month. Anthropometric measurements included weight (kilogram) and height (centimeter) were performed according to standard WHO procedures. Nutritional status was interpreted from Waterlow, the percentage ratio of observed weight, and expected weight from observed height.

In the purpose of assessing child's development status in cognitive and motor ability, we used The Mullen scales of early learning (AGS edition), which consisted of gross motor, visual reception, fine motor, expressive language, and receptive language from birth to 68 months with completion time: 15 min (1 year); 25–35 min (3 years); and 40–60 min (5 years).

The children's quality of life were assessed using the PedsQL Cardiac module, which was specific to toddlers (2–4 years of age) and young child (5–7 years of age) with heart disease by parents' response. The higher the score, the better the child's quality of life.

Those data, including anthropometric, development, and quality of life, were compared between cyanotic and acyanotic children. Quantitative data were presented in frequency and percentage. The Shapiro–Wilk test was used to analyze the data distribution if $p > 0.05$, then its normally distributed and presented as mean and standard deviation (weight in cyanotic, height cyanotic, and acyanotic group). Data with normal distribution were presented as median and percentile, such as age in cyanotic and acyanotic, and weight in acyanotic group. Categorical data including nutritional status, body mass index/age, gross motor, fine motor, receptive language, and early learning composite were analyzed using Chi-square (weight/age z-score [WAZ], and height/age z-score [HAZ]) or Mann–Whitney. Unpaired t-test was used to compare continuous variable with a normal distribution (cognitive problems) and Mann–Whitney for abnormal distributed data (heart problem and therapy, treatment, perceived physical appearance, treatment anxiety, and communication). The significance level was set at $p < 0.05$.

Results

Demographic and anthropometric characteristics of the samples are shown in Table 1. The median age was 34.0 months for cyanotic CHD children and 28.5 months for acyanotic CHD children, most of them were dominated by male patients. The majority of patients (both cyanotic and acyanotic) were from middle economic class with monthly income around Rp.2.173.000–6.519.000, and their healthcare were covered by government health insurance. No significant difference in baseline characteristics was seen in both groups.

Table 1: Demographic and anthropometric characteristic

| Demographic characteristic | Cyanotic CHD (n=26) | Acyanotic CHD (n=26) |
|--|---------------------|----------------------|
| Age, months, median (p10–90) | 34/24–65.6* | 26/24–48* |
| Gender (males/females) | 12/14 | 7/19 |
| Family income, n (%) | | |
| Lower class | 5 (19.2%) | 3 (11.5%) |
| Middle class | 17 (65.3%) | 22 (84.6%) |
| Upper class | 4 (15.3%) | 1 (3.8%) |
| Anthropometric characteristic, mean (SD) | | |
| Weight, kg | 11.75 (2.92)** | 11 (8–15.3)* |
| Height, cm | 89.76 (11.98)** | 87.26 (9.55)** |

CHD: Congenital heart disease.

The cyanotic group was dominated by Tetralogy of Fallot; meanwhile, the acyanotic group was dominated by ventricle septal defect, as shown in Table 2.

Table 2: Distribution of heart disease among the patients

| Congenital heart disease | Frequency n (%) |
|--------------------------|-----------------|
| Acyanotic | |
| PDA | 6 (23) |
| ASD | 3 (11.5) |
| VSD | 13 (50) |
| COA + PDA | 1 (3.8) |
| PS + ASD-II | 3 (11.5) |
| Cyanotic | |
| TOF | 13 (50) |
| TA | 1 (3.8) |
| DORV | 4 (15.4) |
| ECD | 3 (11.4) |
| RV hypoplasia | 1 (3.8) |
| Pulmonary atresia | 1 (3.8) |
| PTA | 3 (11.5) |

ASD: Atrial septal defect, ECD: Endocardial cushion defect, COA: Coarctation of the aorta, DORV: Double outlet right ventricle, PDA: Patent ductus arteriosus, PS: Pulmonary stenosis, TOF: Tetralogy of Fallot, PTA: Persistent truncus arteriosus, RV: Right ventricle, VSD: Ventricle septal defect, SADC: Sub arterial double committed, TA: Tricuspid atresia, TR: Tricuspid regurgitation, PR: Pulmonary regurgitation.

In Table 3, we found a significant difference in proportion of underweight in CHD children ($p = 0.008$). In cyanotic, the proportion of underweight (WAZ $< -2SD$) was 43.3%, which was higher than acyanotic that only 10%. A significant difference was also found in the height/age ($p = 0.024$) in which the cyanotic group showed normal height only in 23.3%, compared with acyanotic, which showed 56.7%. Meanwhile, the proportion of severely stunted was higher in cyanotic (23.3%) rather than acyanotic (13.3%).

The cognitive scores profile of cyanotic and acyanotic CHD children are shown in Table 4. The

Table 3: Comparison of anthropometric profile

| Anthropometric variables | Cyanotic CHD (n=26) | Acyanotic CHD (n=26) | p |
|--------------------------|---------------------|----------------------|-------|
| Nutritional status* | | | |
| Overweight | 3 (11.5) | 5 (19.2) | 0.149 |
| Normal | 3 (11.5) | 7 (26.9) | |
| Mild malnutrition | 12 (46.2) | 9 (34.6) | |
| Moderate malnutrition | 7 (26.9) | 3 (11.5) | |
| Severe malnutrition | 1 (3.8) | 2 (7.7) | |
| WAZ | | | |
| Normal | 8 (30.8) | 17 (65.4) | 0.033 |
| Underweight | 11 (42.3) | 3 (11.5) | |
| Severe underweight | 7 (26.9) | 6 (23.1) | |
| HAZ | | | |
| Normal | 5 (19.2) | 13 (50.0) | 0.025 |
| Stunted | 11 (42.3) | 10 (38.5) | |
| Severe stunted | 10 (38.5) | 3 (11.5) | |
| BMI/age* | | | |
| Obese | 3 (11.5) | 2 (7.7) | 0.149 |
| Risky for overweight | 0 (0.0) | 2 (7.7) | |
| Normal weight | 17 (65.4) | 13 (50.0) | |
| Wasted | 4 (15.4) | 5 (19.2) | |
| Severe wasted | 2 (7.7) | 4 (15.4) | |

*Mann-Whitney, WAZ: Weight for age z-score, HAZ: Height for age z-score, BMI: Body mass index, CHD: Congenital heart disease.

cyanotic CHD children significantly showed lower scored than acyanotic children in gross motor ($p = 0.034$) and in receptive language ($p = 0.048$) which had effect on early learning composite score ($p = 0.014$).

Table 4: Comparison of cognitive function by Mullen

| Cognitive function | Cyanotic CHD (n=26) | Acyanotic CHD (n=26) | p |
|---------------------------|---------------------|----------------------|-------|
| Gross motor* | | | |
| NA | 15 (57.7) | 9 (34.6) | 0.034 |
| Very low | 8 (30.8) | 8 (30.8) | |
| Below average | 2 (7.7) | 2 (7.7) | |
| Average | 1 (3.8) | 7 (26.9) | |
| Visual reception | | | |
| Very low | 12 (46.2) | 10 (38.5) | 0.627 |
| Below average | 9 (34.6) | 8 (30.8) | |
| Average | 5 (19.2) | 8 (30.8) | |
| Fine motor* | | | |
| Very low | 13 (50.0) | 14 (53.8) | 0.833 |
| Below average | 9 (34.6) | 5 (19.2) | |
| Average | 4 (15.4) | 6 (23.1) | |
| Very high | 0 (0.0) | 1 (3.8) | |
| Receptive language* | | | |
| Very low | 10 (38.5) | 6 (23.1) | 0.047 |
| Below average | 9 (34.6) | 4 (15.4) | |
| Average | 6 (23.1) | 16 (61.5) | |
| Above average | 1 (3.8) | 0 (0) | |
| Expressive language | | | |
| Very low | 13 (50.0) | 7 (26.9) | 0.231 |
| Below average | 6 (23.1) | 9 (34.6) | |
| Average | 7 (26.9) | 10 (38.5) | |
| Early learning composite* | | | |
| Very low | 16 (61.5) | 9 (34.6) | 0.044 |
| Below average | 3 (11.5) | 5 (19.2) | |
| Average | 7 (26.9) | 9 (34.6) | |
| Above average | 0 (0.0) | 3 (11.5) | |

*Mann-Whitney, CHD: Congenital heart disease

The quality of life assessment from parent's report in cyanotic and acyanotic CHD children is shown in Table 5. In general, the cyanotic children showed lower scores in all the trajectories than children with congenital acyanotic heart disease. Significant differences were found in heart problem and therapy ($p = 0.042$), treatment anxiety ($p = 0.016$), cognitive problems ($p = 0.038$), and communication ($p = 0.022$).

Table 5: Quality of life comparison

| Variables | Cyanotic CHD (n=26) | Acyanotic CHD (n=26) | p |
|-------------------------------|---------------------|----------------------|-------|
| Heart problem and therapy | 48.46 (17.55)** | 62.49 (31.09–92.85)* | 0.042 |
| Treatment | 100 (25–100)* | 100 (44.99–100)* | 1.000 |
| Perceived physical appearance | 100 (89.16–100)* | 100 (78.32–100)* | 0.708 |
| Treatment anxiety | 31.25 (25–81.25)* | 75 (25–100)* | 0.016 |
| Cognitive problems | 46.40 (21.31)** | 60.76 (26.63)** | 0.038 |
| Communication | 75 (25–100)* | 100 (42.5–100)* | 0.022 |

* median, p10–90 (data not distributed normally), **mean, SD (data distributed normally), CHD: Congenital heart disease.

Discussion

Consistent with the previous study on the developmental outcome of children with CHD, our study also found that nutritional problem [3], [10], [15], cognitive delay [3], [5], [9], and lower quality of life [8], [14] are common problems in CHD children [10]. In nutritional assessment, both groups showed the same proportion of severely underweight 50.0%. The cyanotic group was dominated significantly by underweight (WAZ < -2) 42.3%, which differ from the acyanotic group; the proportion of underweight was 15.4%, while it was more dominated by normal weight (65.4%). Severe stunted proportion was higher in cyanotic group 38.5% compared with acyanotic only 11.5%. Most of the acyanotic group was found had normal height (50%) based on HAZ, in comparison to cyanotic group, which was dominated by stunted children (42.3%). Cyanotic patients were affected in growth, depending on the severity of tissue hypoxemia and the degree of physiological adaptation. Acyanotic lesions, affect weight more than height. In other words, cyanotic lesions were related to chronic malnutrition, whereas acyanotic lesions were related to acute malnutrition [15].

Our study is in accordance with study in India, which showed the majority of the CHD children were malnourished, and weight was found to be more affected than height in both cyanotic and acyanotic groups. Both height and weight were affected much more in the cyanotic group when compared to acyanotic group, despite not significant statistically by height category [12]. It also appropriates with a study in Cairo which found that malnutrition, stunting, and wasting proportion were significantly higher among cyanotics (62.8%, 74.4%, and 25.6%) compared with acyanotics (49.5%, 63.3%, and 18.3%) [12]. In addition, cyanotic heart defect was known to have a correlation with the decrement of insulin growth factor-1 level ($r = 0.402$, $p < 0.05$) [14], which is in agreement with Eren *et al.* who stated chronic hypoxia had a negative effect on nutrition and growth hormone, by decreasing insulin growth factor-1 (somatomedin) level that is produced in the liver and regulated by the binding of growth hormone to growth hormone receptors. These findings indicated that chronic hypoxemia might serve as the underlying cause by decreasing the production of insulin growth factor-1 which induced growth failure in patients with cyanotic CHD [11], [16], [17].

Normal fetal brain growth and development rely on adequate delivery of oxygen and substrate, which is influenced by the anatomic structure of the heart and myocardial function [9]. CHD fetal has delayed brain growth since the third trimester, characterized by a decrement of N-acetylaspartate/Choline ratio (Naa/Cho) and Choline/Creatinine ratio (Cho/Cr), and increment of Myoinositol/Choline (Ino/Cho) and lactate [18]. Thus underlies the worse neurocognitive outcomes

[9] in children with cyanotic heart defects due to less mature macro and micro structural brain development with lower total brain volume as proven by Rollins *et al.*, that CHD children have reduction of total brain volume at 1 year of age driven by differences in cerebral white matter which correlates with language impairment [18]. In our study, receptive language impairment was more significant in cyanotic group compared with acyanotic, which can be caused by the reduction of total brain volume ($p = 0.047$).

In addition, the prolonged period of hypoxics cerebral vascular tone in CHD tends to normalize, with downregulation of neuronal and glial metabolism that results in reduced cerebral VO₂ leads to periventricular leukomalacia, characterized by focal necrosis in the periventricular white matter [19], [20], [21]. Those alterations of white matter will disturb volumetric growth, gyrfication of the cortical gray matter, and impair myelination which linked to worse cognition, motor and behavioral functioning, as well [22], [23].

Recently, a systematic review stated that brain metabolism and microstructural development also played role in delayed cerebral development, which was significantly lower than neonates without congenital heart defect and corresponded to a delay of 4 weeks in structural brain sulcation [23]s.

Our study showed the proportion of underweight was significantly higher in cyanotic group, which would increase morbidity and mortality, as indicated by frequent hospitalization, poor surgical outcomes, persistent impairment of somatic growth, and increased death. The underweight can be caused by feeding problems such as inadequate nutritional intake or absorption, feeding difficulty, excessive energy expenditure, frequent respiratory infections, limitation of growth potential, and genetic syndromes [15]. The feeding difficulty in CHD infants can be linked to oropharyngeal dysphagia [24]. Moreover, these feeding and language problems also can be linked to the immaturity of brain development proven by the incomplete closure of the cerebral opercula, which is the sensory-motor cortical representation of buccal, glottis, and esophageal structures, as well as receptive and expressive language [20].

Besides nutrition, in cognitive trajectory evaluated by Mullen showed that cyanotic group had significant impairment in gross motor and receptive language than acyanotic group. It showed agreement with a study in Bangladesh in which about 32% had cognitive impairment, 44% children had speech delay, with gross motor and fine motor delay as the main developmental problems [25]. Besides brain impairment, the development of motor skills in children (infants until school-age) also takes place as a resultant of activity and interaction between person and environment. Children influence their environment in an active way and adapt their behavior to the environment. Movement serves as a catalyst

in a child's development. In this way, high level of movement ensures the advancement of the child's physical development, especially the locomotor system, which, through movement, gains the impulses needed for normal development [26]. Interestingly, we also found parents focused on the treatment and tend to restrict their child physical activity. We assumed it was caused by lack of adequate information to caregiver or parents, who limit the child's motoric stimulation that possibly causes development delay by restriction of physical activity and sheltered upbringing by main caregivers, who are generally more protective. Majority of parents who have children with CHD were reported to have a higher stress level compared with the normal population that makes them difficult to set limit and control for their children. They tend to assimilate their parenting style in accordance with the child's need that leads to overprotective behavior. Finally, it will limit the children interaction with their peers, not least regarding physical activity, which might influence the child's social competence and motor development [26].

Despite the measures taken to treat, these children may experience maladjustment in physical activities, social relationships, academic performances, and emotional, which decrease the quality of life in CHD patients. The quality of life assessment from parent's reports in cyanotic significantly lower than acyanotic in the following aspect such as heart problems and therapy, treatment anxiety, cognitive problems, and communication. In our study, the cyanotic showed the poor quality of life than acyanotic heart disease children; it supposed to be related to the difference in cognitive and nutritional status. Therefore, a multidisciplinary approach should be applied for early identification of those impairments to offer the best opportunity for treatment that may allow the child to reach the fullest potential in adulthood and minimize the negative impact on the quality of life and parents should be more aware and responsive to the development and nutrition aspect of their child [27].

Conclusion

Cognitive delay, nutritional problems, and quality of life are common in cyanotic CHD children.

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