Height-for-age in Children under 5 Years Old with Down Syndrome and Hypothyroidism

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Abstract

Background: Children with Down syndrome tend to have accompanying comorbidities, such as hypothyroidism, and late detection of this ailment leads to reduced growth of the child. This study aimed to assess the growth patterns in children with Down Syndrome and hypothyroidism at diagnosis.

Methods: This cross-sectional study was conducted from September to December 2020 with 56 subjects at the Pediatric Endocrine Outpatient Clinic of Dr. Soetomo Hospital. Diagnosis of Down Syndrome was confirmed by karyotyping, while the weights and heights were assessed using a standardized curve for children with Down Syndrome and then calculated using Peditools. Fifty-six children with Down Syndrome and hypothyroidism were included, comprising 32 boys and 24 girls (mean age, 37.75 ± 34.26 months). Majority of the subjects had normal weight, height, and Body Mass Index (36/56 [mean z-score, −1.62 ± 2.36], 33/56 [mean height-z-score, −0.43 ± 2.74], and 30/56 [mean z-score, −2.00 ± 2.06], respectively). Furthermore, the mean onset of diagnosis was 17.07 ± 32.23 months, where 23 out of the 56 children had short stature and had gotten diagnosed at over 12 months of age.

Conclusion: From the results obtained, hypothyroidism can be said to be associated with reduced growth in children with DS.

Key Words: *down syndrome, growth, short stature, hypothyroidism*

Introduction

Short stature is one of the most recognized features in children with Down syndrome (DS), and in a healthy population of children with this condition, 35.7% were found to have short stature[1–3]. Consequently, several adapted growth charts are used to assess the growth of children with DS [4–7]. The prevalence of short stature is increased by 46.2% in children with DS and hypothyroidism compared to those without hypothyroidism [8]. Children with DS experience late growth until 12–15 years, when they are approximately 20 cm shorter than children at the same age but without the condition [9]. Short stature is one of many complications caused by hypothyroidism, which is, as a result, often suspected if it occurs in adolescence. It should be suspected in children with short stature, as a study conducted in India showed

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that almost 50% of these had hypothyroidism [10].

Hypothyroidism is a common comorbidity accompanying DS, and previous studies show that the incidence in people with this condition is 12 to 22 times that of individuals without[11]. Neonates suspected of having DS often demonstrate an increase in plasma thyroid-stimulating hormone (TSH), and hypothyroidism is found in 4%–8% of this population[12]. Thyroid hormone is associated with cognitive development in the central nervous system during childhood, and any abnormality in its function may interrupt brain development, and consequently, general growth and development[10,11]. Consequently, hypothyroidism is believed to impair the growth of children with DS and increase their chances of having short stature. Although the detection of congenital hypothyroidism should be performed for every baby born[13], it is different in babies with DS. A study stated that autoimmune hypothyroidism occurs at five (5) months, and many were diagnosed at eight (8) years[14]. Hence, detecting congenital hypothyroidism in babies with DS can happen after a few years[15].

Research on DS with hypothyroidism has not been widely studied in Indonesia, especially regarding the growth of children, although growth studies have been performed on subjects with Turner syndrome [16]. Therefore, this study aims to assess how hypothyroidism impacts the growth pattern of children with DS.

A greater understanding of the growth pattern of children with DS and hypothyroidism could lead to earlier diagnosis and intervention. Early intervention has proven to offer good results in preventing and treating growth disorders in patients with these conditions [17]. Indeed, current guidelines suggest evaluating thyroid function in DS just after birth and every six (6) months afterward to detect problems earlier [18]. Moreover, the high incidence of short stature in patients with hypothyroidism has been shown to improve with earlier diagnosis and appropriate therapy [17].

Materials and Methods

This study used a cross-sectional design and was performed from September to December 2020. The data were obtained from the patients' medical records, and the subjects were interviewed to collect hypothyroid history and nutritional status. This process was performed during their visit to the Pediatric Endocrine Outpatient Clinic of Dr. Soetomo Hospital.

Sample

This study involved children diagnosed with both DS and hypothyroidism and registered at the Pediatric Endocrine Outpatient Clinic of Dr. Soetomo Hospital. The inclusion criteria were patients aged 1–5 years, diagnosed with both conditions, while critically ill patients were excluded. Fifty-six (56) patients between 1 and 5 years of age (32 boys and 24 girls) were the subjects in this study. The weight-for-age, height-for-age, body mass index (BMI)-for-age, and BMI were presented.

Down syndrome

The DS diagnosis was confirmed physically by referring to the Fried *et al.* [19] criteria, which evaluated the abundant neck skin, downturned mouth corners, general hypotonia, and flat face. Other indications are dysplastic ear, epicanthic eye-fold, the gap between the first and second toes, and protruding tongue. This diagnosis was confirmed by a karyotyping test.

Instrument / Nutritional status

The nutritional status of children with DS was classified by Zemel *et al.* [2] after recalculation of the standard growth curve of children with the condition. Using the Peditools.org website, the z-score of each growth parameter was calculated. The instrument, peditools.org/downinfant/, was used for children aged 0–2 years, while peditools.org/downpedi/ was used for those older than 2 years. Then, the height-for-age was classified either as short stature or normal based on the DS curve and z-score classification by Peditools.

According to WHO child growth standards, 2006, a z-score of -3.00 is severely stunted, -3.00 to -2.01 is moderately stunted, while -2.00 to 1.01 is mild.

Evaluation of data

A descriptive test was used to analyze the data using SPSS 17.0 software (IBM SPSS), while the mean and standard deviation of each element was used for the baseline and clinical characteristics. The Kolmogorov–Smirnov test was also used to evaluate the normality of each dataset.

Ethical permission

This study received ethical approval from the Ethics Committee overseeing health research at Dr. Soetomo Hospital (Ref. No.: 1960/KEKP/IV/2020).

Results and Discussion

This cross-sectional study included 56 children with DS and hypothyroidism, comprising 32 boys and 24 girls, at 57.1% and 42.9%, respectively, with an average age of 37.75 ± 34.26 months old. The baseline characteristics and history of these patients are presented in Tables 1 and 2. Most of the subjects had normal weights, heights, and BMI (36/56 [mean z-score, −1.62 ± 2.36], 33/56 [mean height-z-score, −0.43 ± 2.74], and 30/56 [mean z-score, −2.00 ± 2.06], respectively). Based on the nutritional status, 20 of the 56 subjects, at 35.7%, were revealed to be underweight, while 23, at 41.1%, had short statures. The mean duration of hypothyroid illness was 22.97 ± 23.24 months, while the mean onset age was 21.65 ± 39.76 months. Finally, the mean z-score of all criteria was within the normal limit of $-2 < z < 2$.

Table I. Frequency of subject characteristics

Characteristic	N (%)
Sex	
- Boy	32 (57.1)
- Girl	24 (42.9)
Weight-for-age	
- Severely underweight	12 (21.4)
- Underweight	8 (14.3)
- Normal	36 (64.3)
Height-for-age	
- Short stature	23 (41.1)
- Normal	33 (58.9)
BMI-for-age	
- Severely wasted	11 (19.6)
- Wasted	15 (26.8)
- Normal	30 (53.6)

Table II. Baseline characteristics of subjects

Characteristic	Mean (SD)	Minimum	Maximum	N
Age (months)	47.75 (34.23)	2	129	56
Illness duration (months)	23.25 (23.63)	0	90	56
Onset age (months)	17.07 (32.23)	0	163	56
Weight-for-age z-score	−1.62 (2.36)	−10.13	1.66	56
Height-for-age z-score	−0.43 (2.74)	−5.66	4.88	56
BMI-for-age z-score	−2.00 (2.06)	−9.68	0.80	56

Based on the results, 23, i.e., 41.1% out of the 56 children with DS and hypothyroidism, had short statures, while the remaining 33, at 58.9%, were classified as normal. This finding is consistent with the report by Nam *et al.*, which concluded that infants with DS are likely to have short statures, especially when accompanied by comorbidities, such as a history of infectious or non-infectious diseases [20]. Adequate and complete nutrient intake is also a strong predictor of nutritional status, including height-for-age in infants [21]. Furthermore, a study by the Leung brothers had similar findings to this investigation that hypothyroidism can stunt growth and cause short stature in the absence of immediate therapy to improve the growth gap [22]. Growth failure in the thyroid may be related to the need for cartilage maturation to T3 [23]. Histologically, individuals with chronic hypothyroidism will demonstrate a delay in bone maturation and resting on the epiphysial plate [24].

As seen in Table 2, the mean age at diagnosis of hypothyroidism was 17.07 months, while some subjects were diagnosed as late as 20–23 months old. This is a cause for concern, as delayed diagnosis causes physical and intellectual disorders [13,25], and substitution therapy can improve hypothyroidism symptoms [8]. A study conducted in Turkey reported the average age of diagnosis to be 49 months [26]. Early diagnosis is crucial to prevent sequelae, as although a delay in diagnosis can lead to poor growth, it can be reversed [8], unlike intellectual delays [27].

Zemel *et al.* conducted an epidemiological study on nutritional status and DS in the United States [2]. It showed that the mean z-scores of height-for-age (−1.7 ± 1.2), weight-for-age (−0.8 ± 1.2), Head Circumference (HC)-for-age (−1.6 ± 1.0), and BMI-for-age (0.9 ± 1.0) were accompanied by a BMI value of 21.1 ± 5.8. These values are similar to our study, although only individuals with DS and hypothyroidism were included. However, several studies reported no decrease in the z-score of the nutritional status as a result of hypothyroidism [28]. The hypothyroid condition is a hypometabolic state in which the basal metabolic rate (BMR) decreases [29,30], hence, some individuals with hypothyroidism experience excess nutrients rather than a lack [31]. Also, the BMR in healthy individuals and those with DS devoid of other comorbidities are similar, meaning that DS does not affect BMR[32].

Concerning the nutritional status of the patients in this study, 35.7% were underweight and severely underweight, compared with the research by Al-Fahham *et al.*, where the prevalence in the DS group was only 14.3%[3]. However, this previous research also found congenital heart disease (CHD) in DS patients, a common comorbidity in this condition, similar to

this study, where 25% of the sample also had CHD[15]. Conversely, Al-Fahham found that the incidence of underweight subjects in the CHD group at 34.2%, which was greater than that observed in this study. Hypothyroidism is a chronic disease that can affect an individual's nutritional status, especially during growth and development[8]. A study from Al-Aaraj *et al.* showed an improvement in the nutritional status of individuals with DS undergoing hypothyroidism therapy at height-for-age and BMI-for-age[8].

The main limitations of the current study were that it was single-centered and included only a small proportion of children with DS and hypothyroidism that had short stature, meaning more research of similar samples is required to confirm this this relationship. Also, it did not compare a population of children with DS without hypothyroidism. This should be considered in prospective studies, as it would assist in drawing conclusions about the association between both conditions. Also, it will be important in future studies to perform early screening of hypothyroidism when examining the incidence of short stature in a similar population of children. If possible, the Indonesian multi-center epidemiological research will be performed to obtain more representative results on these conditions.

Conclusion and Acknowledgement

Hypothyroidism, as a comorbidity, has been shown to be associated with reduced growth of subjects with DS. Although late diagnosis is common, earlier detection could prevent these issues before they worsen, making the evaluation of the thyroid hormone status of patients born with suspected DS important. Finally, adolescents with short stature should undergo testing for hypothyroidism, and education should be provided to the community to create awareness of these associations and their consequences if left undiagnosed.

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References

1. Aburawi EH, Nagelkerke N, Deeb A, Abdulla S, Abdulrazzaq YM. National growth charts for United Arab Emirates children with Down syndrome from birth to 15 years of age. J Epidemiol. 2015;25(1):20–9.
2. Zemel BS, Pipan M, Stallings VA, Hall W, Schadt K, Freedman DS, et al. Growth charts for children with down syndrome in the United States. Pediatrics. 2015;136(5):e1204–11.
3. Al-Fahham M, Kotby A, Elabd H, Tawfik A, Ali H. Nutritional assessment of children with down syndrome with and without associated congenital heart defects. J Pediatr Gastroenterol Nutr. 2018;66:980.
4. Cronk C, Crocker AC, Pueschel SM, Shea AM, Zackai E, Pickens G, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. Pediatrics. 1988;81(1):102–10.
5. van Gameren-Oosterom HBM, van Dommelen P, Oudesluys-Murphy AM, Buitendijk SE, van Buuren S, van Wouwe JP. Healthy growth in children with down syndrome. PLoS One. 2012;7(2):1–8.
6. Piro E, Pennino C, Cammarata M, Corsello G, Grenci A, Giudice CL, et al. Growth charts of Down syndrome in Sicily: Evaluation of 382 children 0-14 years of age. Am J Med Genet. 1990;70(SUPPL. 7):66–70.
7. Fernandes A, Mourato AP, Xavier MJ, Andrade D, Fernandes C, Palha M. Characterisation of the somatic evolution of Portuguese children with Trisomy 21--preliminary results. Downs Syndr Res Pract. 2001;6(3):134–8.
8. AlAaraj N, Soliman AT, Itani M, Khalil A, De Sanctis V. Prevalence of thyroid dysfunctions in

infants and children with Down Syndrome (DS) and the effect of thyroxine treatment on linear growth and weight gain in treated subjects versus DS subjects with normal thyroid function: a controlled study. Acta Biomed. 2019;90(8S):36–42.

9. Bertapelli F, Agiovlasitis S, Machado MR, Roso R do V, Guerra-Junior G. Growth charts for Brazilian children with Down syndrome: Birth to 20 years of age. J Epidemiol [Internet]. 2017;27(6):265–73. Available from: http://dx.doi.org/10.1016/j.je.2016.06.009
10. Virmani A, Menon PSN, Karmarkar MG, Kochupillai N, Seth V, Ghai OP, et al. Evaluation of thyroid function in children with undiagnosed short stature in north India. Ann Trop Paediatr. 1987;7(3):205–9.
11. Uppal H, Chandran S, Potluri R. Risk factors for mortality in Down syndrome. J Intellect Disabil Res. 2015;59(9):873–81.
12. Bull MJ, Saal HM, Braddock SR, Enns GM, Gruen JR, Perrin JM, et al. Clinical report - Health supervision for children with Down syndrome. Pediatrics. 2011;128(2):393–406.
13. Seth A, Aggarwal V, Maheshwari A. Hypothyroidism in children beyond 5 y of age: Delayed diagnosis of congenital hypothyroidism. Indian J Pediatr. 2012;79(7):891–5.
14. Shalitin S, Phillip M. Autoimmune thyroiditis in infants with Down's syndrome. J Pediatr Endocrinol Metab. 2002;15(5):649–52.
15. Graber E, Chacko E, Regelmann MO, Costin G, Rapaport R. Down Syndrome and Thyroid Function. Endocrinol Metab Clin North Am [Internet]. 2012;41(4):735–45. Available from: http://dx.doi.org/10.1016/j.ecl.2012.08.008
16. Novina N, Gunardi H, Pulungan AB. Height and Upper/Lower Body Ratio in Turner Syndrome Adolescents in Indonesia; Is There any Significant Difference Based on Karyotype? In: 58th Annual ESPE meeting. Vienna, Austria: European Society for Paediatric Endocrinology; 2019.
17. Ranke MB, Schwarze CP, Mohnike K, Von Mühlendahl KE, Keller E, Willgerodt H, et al. Catch-up growth after childhood-onset substitution in primary hypothyroidism: Is it a guide towards optimal growth hormone treatment in idiopathic growth hormone deficiency? Horm Res. 1998;50(5):264–70.
18. Hardy O, Worley G, Lee MM, Chaing S, Mackey J, Crissman B, et al. Hypothyroidism in Down syndrome: Screening guidelines and testing methodology. Am J Med Genet. 2004;124A(4):436–7.
19. FRIED K. a Score Based on Eight Signs in the Diagnosis of Down Syndrome in the Newborn. J Intellect Disabil Res. 1980;24(3):181–5.
20. Nam JY, Choi Y, Jung MK, Shin J, Cho KH, Kim W, et al. The effect of neonatal hypothyroidism and low family income on intellectual disability: A population-based cohort study. PLoS One. 2018;13(11):1–13.
21. Lutter CK, Rivera JA. Nutritional status of infants and young children and characteristics of their diets. In: Journal of Nutrition. 2003.
22. Leung AKC, Leung AAC. Evaluation and management of the child with hypothyroidism. World J Pediatr [Internet]. 2019;15(2):124–34. Available from: https://doi.org/10.1007/s12519-019-00230-w
23. Williams GR. Thyroid Hormone Actions in Cartilage and Bone. Eur Thyroid J. 2012;3–13.
24. Boersma B, Otten BJ, Stoelinga GBA, Wit JM. Catch-up growth after prolonged hypothyroidism. Eur J Pediatr. 1996;155(5):362–7.
25. Pulungan AB, Oldenkamp ME, van Trotsenburg ASP, Windarti W, Gunardi H. Effect of delayed diagnosis and treatment of congenital hypothyroidism on intelligence and quality of life: An observational study. Med J Indones. 2019;28(4):396–401.

26. Tarim OF, Yordam N. Congenital hypothyroidism in Turkey: a retrospective evaluation of 1000 cases. Turk J Pediatr. 1992;34(4):197–202.
27. Seo MK, Yoon JS, So CH, Lee HS, Hwang JS. Intellectual development in preschool children with early treated congenital hypothyroidism. Ann Pediatr Endocrinol Metab. 2017;22(2):102.
28. Zafar Y, Suddaby SR, Shafiq M. Hypothyroidism Manifesting as a Combination of Ascites and Malnutrition Requiring Total Parenteral Nutrition: A Unique Presentation. Cureus. 2019;11(8):5338.
29. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014;94(2):355–82.
30. Johansen K, Hansen JM, Skovsted L. The Preferential Role of Triiodothyronine in the Regulation of Basal Metabolic Rate in Hyper- and Hypothyroidism. Acta Med Scand. 1978;204(1–6):357–9.
31. Ghizlane EM, Bouznad N, El AN. Effects of hypothyroidism on nutritional status: which impact? Endocr Abstr. 2017;
32. SCHAPIRO MB, RAPOPORT SI. Basal metabolic rate in healthy Down's syndrome adults. J Intellect Disabil Res. 1989;33(3):211–9.