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ORIGINAL ARTICLE

THE GROWTH OF CHILDREN WITH CONGENITAL HYPOTHYROIDISM: THE IMPORTANCE OF CONGENITAL HYPOTHYROIDISM SCREENING

Novina Novina[1], Yunita Puji Astuti[1], Erni Nuraeni[1], Erwin Affandi Soeriadi[2], Faisal Faisal[1].

[1]Department of Child Health, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia,

[2]Department of Nuclear Medicine, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

ABSTRACT

Background: The thyroid hormone is an important hormone that affects children's growth, especially in early life. In 2014, the Indonesia Minister of Health issued congenital hypothyroidism screening (CHS) regulations for every newborn. This screening is crucial because early detection can prevent significant negative impacts on children's growth and development. This study aimed to evaluate growth and verify the implementation of CHS in children with congenital hypothyroidism (CH).

Methods: A cross-sectional study using secondary data from medical records from January 2020 to December 2021 was conducted. Data were collected, including age, gender, CHS engagement, thyroid scintigraphy, duration of treatment, Z-scores of height for age (HAZ) and body mass index for age (BAZ), and also levels of free tetraiodothyronine (ft4) and thyroid stimulating hormone (TSH). Data were analyzed using the paired t-test and the Wilcoxon test.

Results: 25 children with CH never engaged in CHS, primarily boys (52%) aged less than three years old at the first visit (80%). After appropriate treatment during a 45-month observation period, mean HAZ and BAZ increased significantly from the first to last visit ($p<0.001$ and $p=0.037$, respectively). Also, levels of ft4 and TSH improved significantly from the first to last visit ($p=0.014$ and $p=0.001$, respectively).

Conclusion: None of the children with CH treated at RSHS ever had CHS, despite the regulations already existing. Significant improvements of growth indicators (HAZ and BAZ) and thyroid hormone levels occurred after appropriate treatment. These findings emphasize the critical need for the establishment of CHS in Indonesia.

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Introduction

Thyroid hormone is an essential hormone produced by the thyroid gland and is necessary for normal physical growth and neurological development.[1] The thyroid gland produces two primary hormones, thyroxine (T4) and triiodothyronine (T3), which are crucial in regulating the body's metabolism and the growth and development of all organs, especially the brain. Thyroid hormone is very important for infants and growing children because thyroid hormone deficiency in early life can lead to growth and developmental delays such as short stature and mental retardation.[2]

Primary CH is defined as a deficiency of thyroid hormone present from birth caused by problems in the development of the thyroid gland (dysgenesis) or disorders in the biosynthesis of thyroid hormone (dyshormonogenesis). Secondary or central CH can occur at birth due to a deficiency of thyroid-stimulating hormone (TSH) and or thyrotrophin releasing hormone (TRH), which is often associated with deficiencies in other pituitary hormones in congenital hypopituitarism. Peripheral hypothyroidism can also occur due to defects in transportation, metabolism, or the action of thyroid hormone.[3] CH can be classified as permanent or transient. Permanent CH refers to a persistent deficiency of thyroid hormone requiring lifelong treatment, while transient CH refers to a temporary deficiency of thyroid hormone that can later recover to normal. Recovery to euthyroidism usually occurs within

Address for Correspondance: Dr. Novina, Department of Child Health, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Jl. Pasteur no. 38, Bandung Indonesia.
Email: novina@unpad.ac.id

the first few months or years of life. Some forms of CH associated with defects in other organ systems are classified as syndromic hypothyroidism.[3]

In infants with primary CH, dysfunction of the thyroid gland generally leads to low levels of T4 and T3, with elevated levels of TSH and TRH due to the feedback mechanism to the hypothalamus and pituitary gland. In compensated or subclinical hypothyroidism, serum T4 levels remain normal, while TSH levels are elevated.[3]

From 2000-2013, national screening in 11 provinces in Indonesia found the ratio of CH was 1:2736. In 2014, the Indonesia Minister of Health issued CH screening (CHS) regulation, aiming to ensure that every newborn in Indonesia receives CHS services according to established standards.[2] The ideal time for blood specimen collection is when the baby is 48-72 hours old. However, in Indonesia, blood collection can still be tolerated between 24-48 hours until 14 days old. It is recommended that blood not be taken within the first 24 hours after birth, as TSH levels are still high at that time, which could result in a false positive result.

The blood collection technique used is through a 'heel prick' on the lateral side of the baby's left or right heel. This technique is highly recommended and is the most commonly performed method worldwide. The first drop of blood is wiped away with sterile gauze; then, a gentle massage is applied to form a sufficiently large drop of blood. The blood is then dropped onto special filter paper until the circles on the paper are completely filled with blood. Once dry, the paper is sent to the laboratory for testing.[4] More than 95% of infants with CH did not show typical symptoms at birth. Children with CH tend to be short in stature, intellectually disabled, and have poor nutritional status due to a lack of thyroid hormone, which has an important role in body metabolism.[3]

Current management in CH recommends giving levothyroxine immediately after diagnosis to prevent or correct stunted growth and development in children. This study aimed to evaluate the growth of children and verify the implementation of CHS in children with congenital hypothyroidism treated at Hasan Sadikin General Hospital, Bandung.

Methods

This was a cross-sectional study conducted at Hasan Sadikin General Hospital. The data were taken from secondary data obtained from the medical records of the outpatient pediatric endocrinology clinics from January 2020 to December 2021. The inclusion criteria for this study were children with primary congenital hypothyroidism and the exclusion criteria were patients with Down syndrome and skeletal abnormalities. Data of Age, gender, CHS engagement, thyroid scintigraphy, and duration of treatment were recorded. Data were collected during the first and last visits after a 45-month period, which included anthropometric measurement of weight, height, z-scores of height for age (HAZ), body mass index for age (BAZ), and thyroid hormone levels. Length/height and weight measurements were performed according to a standard procedure. The weight was measured to 100 grams using a weighing scale. The length of children ≤2 years old was measured using an infantometer in a supine position. In children >2 years old, height was measured using a stadiometer to the nearest 0.1 centimeter.5 Infantometer, stadiometer, and weighing scale manufactured by SECA.

The thyroid function test was assessed based on free tetraiodothyronine (fT4) levels in ng/dL and thyroid stimulating hormone (TSH) in mIU/mL. Thyroid function tests and thyroid scintigraphy were executed in Nuclear Medicine Department of Dr. Hasan Sadikin General Hospital. Radioimmunoassay (RIA) and Immunoradiometric Assays (IRMA) methods were used to measure thyroid hormones (T3 and fT4) and TSHs.6 Thyroid scintigraphy is a nuclear medicine modality to detect the thyroid gland using Iodine 123 (I-123) and Technetium-99m Pertechnetate (Tc-99m) scans are preferred in the detection of primary hypothyroidism in infants and children. At RSHS, thyroid scintigraphy is performed using Tc-99m. The disadvantage of the I-123 is the availability is limited and costly due to production by a cyclotron; in the contrary, Tc-99m is widely used and cheaper than I-123. Tc-99m scan is one of the most accurate tests in determining the etiology of congenital hypothyroidism.7 Thyroid scintigraphy is not performed on children under the age of 3 years because it requires a 4 to 6-week period of treatment interruption, which poses significant risk to neurocognitive condition.3

This study was approved by the Ethics Committee of Dr. Hasan Sadikin General Hospital, Ethical Approval No. LB.02.01/X.2.2.1/25310/2022 and conformed to the ethical guidelines of the Declaration of Helsinki.

All data collected were analyzed statistically. The essential characteristics are described in numbers and percentages for categorical data. In contrast, numerical data with a normal distribution will be expressed in terms of the average and standard deviation. If the data were not normally distributed, it would be expressed as a median with a range. Comparative analysis was conducted to determine whether there were differences between the variables measured using the paired t-test when the data distribution was normal. A comparison test was carried out with the Wilcoxon test for data with an abnormal distribution. Data processing used the Statistical Package for the Social Sciences (SPSS) 26.0 program with statistical test criteria. The significance level (α value) was set as 0.05.

Results

In total, 25 children visited the outpatient clinic of pediatric endocrinology from January 2020 to December 2021; most of the patients (64%) were less than three years old at the first visit, consisting of boys (52%) and girls (48%). There's no child engaging in CHS at birth (0%). The most common etiology of CH in this study was thyroid agenesis (44%). A total of 5 children (20%) had no thyroid scintigraphy/scan due to the child's age at the first visit to the was 15 months. Children with congenital hypothyroidism received levothyroxine therapy with a mean duration of 45 months during the study period (Table 1).

Children's height at the first visit was significantly shorter than at the last visit ($P<0.01$). Comparing between the first and last visit, both HAZ and BAZ showed significant improvement ($P<0.01$ and $P=0.037$, respectively) (Table 2). Thyroid hormone levels improved significantly, with median fT4 increasing and

Table 1. Subject Characteristics.

Characteristics (n=25)	Frequency
Age, mean (months) Age when diagnosed, n (%) <12 months 12-36 months >36 months	31 18 (72) 2 (8) 5 (20)
Gender, n (%)	
Boys	13 (52)
Girls	12 (48)
CHS engaging, n (%)	0 (0)
Thyroid scintigraphy, n (%)	
Thyroid Agenesis	11 (44)
Thyroid Hypoplasia	2 (8)
Thyroid Ectopic	1 (4)
Dyshormonogenesis	6 (24)
NA	5 (20)
Duration of monitoring treatment, mean (months)	45

Note: CHS= Congenital hypothyroidism screening, NA= Not available

Table 2. Anthropometry Measurement on First and Last Visit During 45-month Observation Period with Levothyroxine Treatment.

Variable	First visit	Last visit	P-Value
Z scores Height-for-Age (mean)	-4.465	-2.43	<0.001*
Z scores Body Mass Index-for-Age (mean)	-1.30	0.07	0.037*
Body length/height (median) cm	65	98	<0.001**

Note: *Paired t-test, **Wilcoxon test

Table 3. Thyroid Hormone Function on First and Last Visit During 45-month Observation Period with Levothyroxine Treatment.

Variable	First visit	Last visit	P-Value
FT4 (median) ng/dL	0.90	1.50	0.014*
TSH (median) mIU/mL	21.6	2.2	0.001*

Note: *Wilcoxon test, FT4 and TSH were measured using RIA and IRMA

TSH decreasing from the first to the last visit (P=0.014 and P=0.001, respectively) (Table 3).

Discussion

Congenital hypothyroidism (CH) is a condition where there is a deficiency of thyroid hormones present since birth, typically caused by problems in thyroid gland development (dysgenesis) or disorders in thyroid hormone biosynthesis (dyshormonogenesis).[8] Congenital hypothyroidism can be divided into two types: Permanent CH refers to a persistent deficiency of thyroid hormone requiring lifelong treatment with thyroid hormones, and transient CH refers to a temporary deficiency of thyroid hormone detected at birth which later recovers to normal thyroid hormone production.[8] Permanent CH can be further classified into permanent primary CH and secondary (or central) CH. Abnormalities in the thyroid gland itself cause primary hypothyroidism, while secondary hypothyroidism is caused by thyroid hormone deficiency due to disorders affecting the pituitary or hypothalamus.[9]

Most newborns with CH do not have a prominent clinical manifestation of hypothyroidism; this is because most infants have some residual thyroid function, and signs of hypothyroidism are relatively nonspecific. In developed countries with newborn screening programs, all infants with CH are diagnosed after detection by the newborn screening test. If hypothyroidism is left untreated or treated insufficiently, newborns with CH become symptomatic, including hoarse cry, macroglossia, large

fontanels, facial puffiness, lethargy, hypothermia, bradycardia, umbilical hernia, protuberant abdomen, feeding difficulties, hypotonia, constipation, and prolonged jaundice. Other clinical indicators include widespread myxoedema, limited growth, delayed deep tendon reflexes, and developmental delay. If not treated or inadequately treated, this can lead to intellectual disability.[9]

Over twenty years ago, a preliminary study of CHS in Indonesia was held in Indonesia with the assistance of the International Atomic Energy Agency (IAEA) in two laboratories in Hasan Sadikin General Hospital and Cipto Mangunkusumo Hospital. Indonesia's Minister of Health issued CH screening (CHS) regulation on every newborn with TSH testing in 2014.[2] However, the implementation since 2014 still needs to be nationally completed. The Ministry of Health has relaunched the Congenital Hypothyroidism Screening (CHS) program for newborn babies in all healthcare facilities across Indonesia. The inauguration occurred at the Batujajar Community Health Center in West Bandung Regency, West Java, on Wednesday, August 31st, 2022. This is the implementation of the transformation of primary care that emphasizes preventive and promotive efforts, considering that most cases of congenital hypothyroidism do not show symptoms, so parents are not aware of it. Typical new symptoms appear as the child gets older.[10] A multicenter cross-sectional study was conducted in hospitals in Denpasar, Banten, Jakarta, Semarang, and Yogyakarta from October 2015 to January 2016 screening 1,226 babies for CH using TSH testing. The result showed high recall rates of 1:1,226 and was found to be the actual positive case by a confirmatory test with TSH and FT4.[11] One study found that only 2% of newborn screening coverage in Indonesia.[12] Therefore, government support, good partnerships with health services, and increased societal awareness are importance.

Children with CH that have been confirmed by TSH and fT4 serum levels, need to receive immediate therapy by giving levothyroxine (LT4).[13] With adequate doses, it is estimated that children with non-syndromic congenital hypothyroidism will have normal growth.[14] The phenomenon of 'catch-up growth' in CH is influenced by various factors, such as age at symptom onset, the severity and duration of hypothyroidism, the age at diagnosis, and the genetic target height.15 In this study, monitoring for 45 months with LT4 showed good growth improvement, as indicated by a significant increase of HAZ and BAZ at the first visit compared to the last visit. These results are in line with the findings in India that catch-up can be achieved with adequate thyroxine therapy in the first few years of therapy.[16] In study of a 5-year follow-up, the growth pattern of children with CH showed a positive effect after treatment. The Z score for body mass index for age also improved after receiving levothyroxine therapy.[17] Earlier treatment and appropriate LT4 might cause a more optimal outcome in children's growth development, including height, weight, and head circumference.[18] Children with CH who are diagnosed and begin therapy later are more likely to experience developmental disorders.[19] Another study shows a partial improvement in the height standard deviation score deficit in children with CH congenital hypothyroidism who have received a few years of treatment.[20]

Thyroid hormone affects growth by increasing the effectiveness of insulin growth factor-1 (IGF-1) on cartilage and increasing the bioactivity of growth hormone binding protein, IGF-1, IGF-2, and IGF-binding protein (IGF-BP). In children with CH, deficiency of thyroid hormone may also affect and insulin- like growth factor levels. Thyroid hormones act on the growth plates, bones, and GH-IGF-1 axis to modulate growth.[21] To support growth function, children receiving levothyroxine therapy are targeted to maintain TSH serum levels <5 mIU/mL, and fT4 levels are still below the upper limit of the normal range of 0.8-2.3 ng/dL in the first two years of life. This study shows median fT4 and TSH levels after treatment were within the target levels; this indicates that the patient's thyroid hormone levels have reached the recommended target. Regular examination of fT4 and TSH levels is very important for dose adjustment to guarantee adequate thyroid hormone levels. It is important to consider several factors that can affect treatment outcomes in children taking levothyroxine, such as medication adherence and comorbidities.

Scintigraphy or thyroid scan is the most accurate diagnostic support to determine the etiology of congenital hypothyroidism. Thyroid dysgenesis (thyroid agenesis, thyroid ectopic, and thyroid dysplasia) was the most common cause of congenital hypothyroidism (85%), according to the results of this study, which showed that most (56%) cases were caused by thyroid dysgenesis.[22] Consistent with this study, thyroid agenesis was the most common etiology (44%). However, another study revealed, ectopy thyroid was the most common cause of children with congenital hypothyroidism.[23]

When etiologic studies are not performed at birth, scintigraphy should be done after the age of 3 years when treatment interruption no longer poses a risk (the critical period of neurocognitive development has passed).[24,25] Scintigraphy examinations are still limited and only available at a few health centers. Hormonal treatment in the first three years leads to excellent neurocognitive and developmental outcomes in CH patients.

The limitation of this study is that only physical growth was assessed, without examining cognitive intelligence before and after therapy. Future research should include comprehensive evaluations of the effects of treatment on cognitive function and intelligence in children with congenital hypothyroidism (CH). This would provide a more complete understanding of the impact of treatment on overall development and help to establish best practices for managing the condition.

Conclusion

In conclusion, none of the children with CH treated in Hasan Sadikin Hospital from January 2020 to December 2021 ever had CHS, despite the existing regulations that have existed since 2014. After appropriate treatment during 45-month observation period, there was a significant increase in HAZ and BAZ, as well as an improvement in thyroid hormone FT4 and TSH levels in children with CH. This significant increase in height shows a marked catch-up compared to age-matched normal growth standards. Appropriate treatment in

children with CH can significantly improve growth and thyroid hormone levels. These findings highlight the importance of screening and appropriate treatment of CH to prevent serious complications such as growth and developmental disorders, including mental retardation. It is important to ensure that government policies, in this case, those of the Ministry of Health of the Republic of Indonesia, are effectively implemented across all healthcare facilities in Indonesia and to evaluate the effectiveness of therapy in children with CH, especially in terms of long–term management and monitoring of their growth and neurocognitive development.

Compliance with Ethical Standards
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Conflict of Interest None

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