

Research Article

The Relationship Between the Onset of Levothyroxine Therapy in Congenital Hypothyroidism and Children's Language and Cognitive Development

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Abstract

Thyroid hormones play an important role in the formation and maturation of the central nervous system. Congenital hypothyroid very rarely shows clinical symptoms in early life so that cases of delayed treatment increase. Babies with untreated congenital hypothyroidism can develop into individuals with intellectual disabilities and be accompanied by motor deficits, such as impaired gross and fine motor function and balance coordination. This study aims to proving that there is a relationship between the onset of therapy in congenital hypothyroid patients and the child's language and cognitive development. The study was conducted using a cross sectional design. This research was conducted at the Children's Polyclinic at Ngoerah Hospital and Wangaya Hospital Denpasar from Desember 2022 until August 2023, using the consecutive sampling method. Based on the sample size formula of 2 unpaired proportions, the minimum number of samples is 96. Inclusion criteria are congenital hyothyroid patients were diagnosed based on TSH levels >10 uIU/mL, currently undergoing therapy and carrying out control to monitor the success of therapy for a minimum of 6 months with age ≤ 3 years and obtain written consent from parents by signing an informed consent form. Exclusion criteria included incomplete data and clinically down syndrome. This study involved 107 subjects, with 45 subjects had been therapy under 3 months old and 62 subjects had been therapy more than 3 months old. Initial characteristics of the study showed that the mean age was 13.3 (± 3.64) in therapy under 3 months old compare with 16.5 (± 6.32) in therapy more than 3 months old. Bivariate analysis, we found significant relationship between levothyroxine therapy on language and cognitive function ($p = 0.032$, PR 1.74, CI=1.156-5.594). Multivariate analysis, therapy ≤ 3 months had a significant relationship with language and cognitive development in hypothyroid children with an adjusted OR of 3.404 (95% CI 1.330 – 8.710, P value 0.011). There is a relationship between the onset of therapy in congenital hypothyroid patients and children's language development and cognition.

Keywords

Congenital Hypothyroid, Levothyroxine, Children, Language and Cognitive Development

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1. Introduction

Congenital hypothyroid (CH) screening has been designed by the government and is included in the Regulation of the Minister of Health of the Republic of Indonesia Number 78 of 2014 and CHS (Congenital Hypothyroid Screening), but the overall achievement of this screening is still below 2%. The latest data until the end of 2023, as many as 1.2 million babies have been screened for congenital hypothyroidism in Indonesia with coverage of up to 28%. Congenital hypothyroid screening has also been carried out in Bali Province and has started to increase since 2022 with coverage of up to 45%. Congenital hypothyroid screening data has also been reported by Prof Ngoerah Hospital with coverage of up to 60% [1].

Thyroid hormones play an important role in the formation and maturation of the central nervous system. Babies with untreated congenital hypothyroidism can develop into individuals with intellectual disabilities and be accompanied by motor deficits, such as impaired gross and fine motor function and balance coordination [2].

Disturbed child development in congenital hypothyroid patients who are late in receiving treatment is closely related to the child's brain development. Children's brain development from the age of 0 to the first 3 years is a crucial time so it is important to maximize children's potential up to the age of 3 years. The human brain develops about 80 percent in this period. Disorders that occur during this period can cause permanent damage to the brain. At the age of 3-10 months, the growth and development of the brain occurs very quickly, one of which is the process of synaptogenesis, so this period is very important to ensure that there are no disturbances [3] So this research wants to know the relationship between levothyroxine therapy and language and cognitive development.

2. Materials and Methods

This research uses a cross-sectional design. Research subjects during their journey will be divided into starting therapy at the age of < 3 months and over 3 months who are given therapy for a minimum of 6 months and their progress is evaluated. This research was conducted at the Children's Polyclinic at Ngoerah Hospital and Wangaya Hospital Denpasar from Desember 2022 until August 2023, using the consecutive sampling method.

The subjects of this research were all children with congenital hypothyroidism who received therapy at the Children's Polyclinic at Ngoerah Hospital and Children's Polyclinic at Wangaya Denpasar Hospital who met the inclusion and exclusion criteria with a minimum sample size of 100. Inclusion criteria are congenital hyothyroid patients were diagnosed based on TSH levels >10 uIU/mL, currently undergoing therapy and carrying out control to monitor the success of

therapy for a minimum of 6 months with age < 3 years and obtain written consent from parents by signing an informed consent form. Exclusion criteria included incomplete data and clinically down syndrome. All children who meet the inclusion and exclusion criteria must sign an informed consent, collect initial data such as weight, height and developmental examination using the CAT/CLAMS sheet.

In descriptive analysis, data is presented in the form of tables and graphs. Categorical data is presented in percentage form. Before analysis, the numerical data was first tested for normality using the Shapiro Wilk test. The data obtained has a non-normal distribution and is presented in the form of median and interquartile range. The bivariate test between the independent variable on a categorical scale and the dependent variable on a categorical scale used Chi-Square and Fisher's test because the distribution was not normal. Multivariate analysis using logistic regression was carried out to control confounding variables if these variables were significantly related to the dependent variable. The significance level (α) of this research was set at a probability value (p) of less than 0.05.

This study received ethical clearance from the Research and Development Unit (Litbang) of the Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G. Ngoerah General Hospital, No: 2289/UN14.2.2.VII.14/LT/2022. It also received approval from the Ministry of Health of the Republic of Indonesia, Directorate General of Health Services, Prof. Dr. I.G.N.G. Ngoerah General Hospital, No: LB.02.01/XIV.2.2.2/57717/2022. The study was conducted with principles of anonymity and confidentiality.

3. Results

The research was conducted at the Children's Polyclinic at RSUP Prof. Dr. I.G.N.G. Ngoerah and Wangaya Regional Hospital, Denpasar through medical records by taking subjects who met the inclusion and exclusion criteria. The research sample used consecutive sampling to meet the minimum sample criteria. There were 113 children with hypothyroidism who underwent examination at the polyclinic. Of the total hypothyroid patients, there were subjects who met the exclusion criteria, namely 6 patients with clinical Down syndrome. There were 45 subjects get therapy at the age of < 3 months and 62 therapy subjects at the age of > 3 months.

The initial characteristics of the sample consisted of age, gender, nutritional status, history of LBW, history of prematurity, history of asphyxia, history of sepsis, family income, length of screen time exposure and primary caregiver can be seen in Table 1.

Table 1. General characteristics.

characteristics	Neonates born to mothers infected with COVID-19 (N=67 (%))	Neonate born to a mother who is not infected with COVID-19 (N=100 (%))
Age (month)	13.3 ($\pm$ 3.64)	16.5 ($\pm$ 6.32)
Gender, n (%)		
Male	27 (48.2)	29 (51.8)
Female	18 (35.3)	33 (64.7)
Nutritional status, n (%)		
Well nourish	32 (49.2)	33 (50.8)
Malnutrition	13 (39.7)	29 (60.3)
History of low birth weight (LBW), n (%)		
History LBW	22 (44.9)	27 (55.1)
No history of LBW	23 (39.7)	35 (60.3)
History of prematurity, n (%)		
History of prematurity	22 (45.8)	26 (54.2)
No history of prematurity	23 (38.9)	36 (61.1)
History of Asphyxia, n (%)		
History of asphyxia	10 (35.7)	18 (64.3)
No history of asphyxia	35 (44.3)	44 (55.7)
History of sepsis, n (%)		
History of sepsis	14 (48.3)	15 (51.7)
No history of sepsis	31 (39.7)	47 (60.3)
Family income		
<3 million idr	6 (25)	18 (75)
>3 million idr	39 (46.9)	44 (53.1)
Length of screen time exposure, n (%)		
< 1 hour	9 (52.9)	8 (47.1)
>1 hours	36 (40)	54 (60)
Primary caregiver		
Biological parent	44 (45.4)	53 (54.6)
Not biological parents	1 (10)	9 (90)

Table 2. Characteristics of subjects by developmental level using CAT/CLAMS.

	CAT.CLAMS Result			
	Normal	suspect	Communication disorders	Mental retarded
Therapy at age $\leq$ 3 months	27	47	10	5
Therapy at age > 3 months	23	87	8	20

Table 3. Relationship of levothyroxine therapy to language and cognitive function.

	CAT/CLAMS result		P	PR	CI 95%
	Normal	Abnormal			
Therapy at age $\leq$ 3 months	27 (60%)	18 (40%)	0.032	1.74	1.156-5.594
Therapy at age $>$ 3 months	23 (37%)	39 (63%)			

Table 3 shows that 60% of the therapy group at age $<$ 3 months experienced normal language and cognitive development, while in the therapy group at age $>$ 3 months only 37%. The difference is statistically significant ($P < 0.05$) with

a prevalence ratio of 1.74. This means that children who receive levothyroxine therapy at age $<$ 3 months have a 1.74 times risk of experiencing normal CAT/CLAMS results compared to therapy at age $>$ 3 months.

Table 4. Multivariate analysis of factors influencing preterm birth.

Research variables	Adjusted OR (exp B)	P	95% CI	
			minimum	maximum
Therapy at age $\leq$ 3 months old	3.404	0.011	1.330	8.710
Gender	0.786	0.602	0.318	1.944
Nutritional status	0.684	0.446	0.257	1.820
History of LBW	0.533	0.165	0.219	1.296
History of asphyxia	0.429	0.122	0.147	1.252
History of sepsis	2.186	0.127	0.800	5.972
Family income	0.933	0.901	0.313	2.782
Length of screen time exposure	4.557	0.023	1.229	16.904
Primary caregiver	0.933	0.105	0.056	1.314

4. Discussion

Children with thyroid hormone deficiency can affect brain growth and development. The effects of thyroid hormone during fetal development are in terms of tissue differentiation and development. Babies may have a higher risk of developing hypothyroidism under certain conditions. These conditions include a history of low birth weight, a history of birth less than 37 weeks' gestation, respiratory problems at birth (asphyxia) and infection (sepsis) which can increase the baby's risk of congenital hypothyroidism.

Congenital hypothyroidism is reported to occur more often in baby girls than in baby boys. Studies suggest a female-to-male ratio of approximately 2:1, although variations may occur across populations. Estrogen can influence gene expression and thyroid development during fetal life, ex-

plaining women's predisposition to this disorder [4] The initial characteristics of this research sample were that there were more men than women. The results of this study are different from research by Chen CY et al in 2013, where it was found that men suffered less from congenital hypothyroidism than women [5] The same results by Jo HY in 2023 showed that only 40% of men suffered from hypothyroidism compared to women [6] In a meta-analysis by Rezaeian S et al in 2017, it was stated that women have a 0.26 times higher risk of suffering from congenital hypothyroidism compared to men, but it is still not known for certain whether this is a direct risk factor or not and it is estimated that there are confounding factors that could influence the results of this study [7].

Hypothyroid patients have a role in changing nutritional status. Hypothyroidism causes a decrease in basal metabolic rate and can cause linear growth disorders so that body weight can appear larger than body height. On the other hand, chil-

dren with hypothyroidism often experience fatigue and decreased appetite, which can affect food intake. Levothyroxine therapy helps restore metabolic function to normal levels. With corrected thyroid hormone levels, children can catch up with delayed linear growth, resulting in a better height to weight ratio [8].

Literature supports that poor nutritional status can worsen hypothyroidism through micronutrient deficiencies such as iodine, selenium, and iron. That study reported that iodine deficiency worsens the effects of hypothyroidism on neurological development. In subjects with poor nutritional status, levothyroxine therapy may not be enough to offset the impact of poor nutrition on development [9] This study showed that nutritional status was not significantly associated with language development and cognitive function ($p = 0.684$) after multivariate analysis. The finding that nutritional status did not significantly affect language and cognitive development does not mean that nutrition is not important, but suggests that there are other factors that may be more dominant in this study population.

Hypothyroidism in children, both congenital and acquired, is an endocrine disorder that can affect growth and development. Prenatal and perinatal factors, such as low birth weight (LBW), asphyxia, prematurity, and neonatal sepsis, have been identified as important risk factors for the occurrence of hypothyroidism, both transient and permanent. During the prenatal period, fetal thyroid function is highly dependent on the transfer of thyroid hormones from the mother, especially in the early to middle trimester of pregnancy. Impaired thyroid hormone transfer or damage to the hypothalamic-pituitary-thyroid axis during this critical period may increase the risk of hypothyroidism. In addition, perinatal complications such as asphyxia or sepsis can worsen the thyroid condition through inflammatory mechanisms or metabolic stress. Several studies show that premature or LBW babies are more susceptible to transient hypothyroidism, due to immature thyroid function. Additionally, conditions such as perinatal asphyxia can cause hypoperfusion or destruction of thyroid tissue, contributing to thyroid dysfunction. In this study, subjects with a history of LBW and prematurity were quite high. The results of this study have the same results as research by Zhou J et al in 2020. In this study, there was a 0.506 times increased risk of suffering from congenital hypothyroidism in patients with premature birth [10].

Thyroid hormones have an immunomodulating effect. In hypothyroidism, the systemic inflammatory response to sepsis may be less effective or even excessive, increasing the risk of organ dysfunction. Sepsis triggers a systemic inflammatory response with the release of proinflammatory cytokines such as IL-6, IL-1 β , and TNF- α , which can cause brain damage through oxidative stress and disruption of the blood-brain barrier. Severe sepsis can cause hypotension and hypoperfusion, which reduces blood flow to the brain and increases the risk of septic encephalopathy with long-term effects of neurocognitive deficits, including impaired attention, memory,

and executive function.

In this study, it was found that sepsis was not significantly related to the developmental and cognitive outcomes of subjects with hypothyroidism, so this is different from theory. This result could be caused by the absence of data on the severity of sepsis and the duration of the subject suffering from sepsis. No other research has specifically discussed the relationship between sepsis and hypothyroidism. Letarte et al developed a scoring system to clinically diagnose patients with congenital hypothyroidism based on 14 signs and symptoms. In developing countries, such as Indonesia, where newborn screening rates are low, a scoring system to diagnose congenital hypothyroidism clinically may be useful although further confirmatory testing is needed. This is based on the large number of late diagnoses resulting in late therapy [11].

Thyroid hormone deficiency in children can cause speech delays, memory loss, and difficulty controlling emotions. Early intervention with levothyroxine is critical to ensure the brain receives adequate levels of thyroid hormone during critical periods of brain development. Research from Susan et al in 2022 said that babies with congenital hypothyroidism who started therapy in the first 2-4 weeks had better cognitive development compared to babies who started therapy later [12] In this study, it was found that there was a significant relationship regarding the relationship between providing early therapy on the cognition of patients with hypothyroidism. This research also found that the prevalence outcome in the levothyroxine therapy group < 3 months of age was 1.7 times greater than the > 3 months therapy group for improving cognitive function. Similar results were also obtained in another study by Pulungan AB in 2019. This research shows the importance of early diagnosis and early therapy in congenital hypothyroid patients, especially in Indonesia [13].

The effect of levothyroxine dose on children with congenital hypothyroidism (CH) is very significant on their cognitive and physical development. This study used levothyroxine dose recommendations based on the diagnosis and management of congenital hypothyroidism by IDAI in 2017. Studies have shown that the use of higher initial doses of levothyroxine can provide better psychomotor development index outcomes compared to standard doses. In a case study in Bali, 12 children with congenital hypothyroid (CH) were analyzed, and the results showed that those who received high initial doses had better psychomotor development [14] Other studies have shown that administration of high initial doses of levothyroxine (12–17 $\mu\text{g/kg/day}$) can increase T4 and FT4 levels to target within 3 days and TSH levels return to normal within 2 weeks after initial therapy. Optimal therapy started before 3 weeks of age with an initial dose above 9.5 $\mu\text{g/kg/day}$ can achieve FT4 levels within the upper limit of normal in the first year, so that congenital hypothyroid patients can achieve normal mental development at the age of 10–30 months [15].

The timing of initiation of levothyroxine therapy also plays an important role in the outcome of hypothyroid patients. Administration of levothyroxine therapy in the first 2 weeks

of life showed very significant results in neurological development and in achieving intellectual outcomes in children with CH. A systematic review in 2016 concluded that initiation therapy in the 2nd to 3rd week of life was associated with better outcomes than not receiving initiation therapy. The outcomes in question included intellectual development and physical growth. The Intelligence Quotient of congenital hypothyroid patients who received initiation therapy was higher than those who were not given or were given it late. Cases of delays in hypothyroid therapy were found in areas that did not conduct hypothyroid screening, resulting in delays in diagnosing hypothyroidism and administering therapy [3].

This study used the levothyroxine initiation therapy benchmark with a cut off of 3 months. The difference between therapy initiation before 3 months and systematic results before 2 weeks shows that although therapy started before 3 months still provides good results, earlier initiation, ideally within the first 2 weeks of life, can provide greater benefits. Delaying therapy until close to 3 months risks reducing effectiveness in preventing developmental disorders. Therefore, early detection and intervention are highly recommended to maximize the developmental potential of children with CH.

Child development is a complex process influenced by various factors, both internal factors such as genetics and physical health, as well as external factors such as the social environment and interactions with primary caregivers. One factor that has received increasing attention in recent decades is the influence of screen time or time spent in front of digital devices on child development, especially in terms of language, cognitive, social, and emotional development. Various studies have shown that excessive exposure to digital media can affect children's language skills, social skills, and motor skills.

Screen time, or the time children spend in front of a screen (TV, smartphone, tablet, computer), has a significant impact on the brain development of children under 3 years, especially because at this age brain development occurs very rapidly. The influence of screen time in early childhood is very dependent on the duration, type of content, and parental involvement in screen use. Several scientific studies have examined in depth the impact of screen time on the brain development of children under 3 years of age. The study results confirm that excessive screen exposure can have various negative consequences on children's cognitive, language, social-emotional and physical aspects. Neuropsychological studies show that the use of screen time in early childhood results in reduced white matter, cortical thickness, and sulcus depth. This indicates that excessive screen time can affect the integrity of brain structures which are important for cognitive and language functions [15].

Parenting styles have a crucial role in children's language and cognitive development. Various studies have examined how interactions and parenting methods can influence important aspects of a child's growth. A study by Hanum and Khomsan (2016) shows that toddlers with normal nutritional

status have higher language and cognitive development achievements than stunted toddlers. Although there were no significant differences in parenting patterns between the two groups, the scores for maternal eating patterns of normal toddlers were higher, indicating the important role of parenting patterns in children's language development [16, 17].

Other research by Joni (2015) revealed that authoritarian or coercive parenting can have a negative impact on children's language acquisition. Children whose interactions with the outside environment are limited tend to have less significant language development due to limited vocabulary acquired only from the family environment. On the other hand, children who are given the opportunity to socialize have a richer vocabulary and better adaptability [18].

Parental parenting styles also have a significant influence on children's cognitive development. Research conducted by Kadrianti and Pajeriati (2019) shows that there is a relationship between parenting styles and the cognitive development of grade 1 children in elementary school. A democratic parenting style, where parents provide a balance of support and freedom, contributes positively to children's cognitive development [19].

The role of primary caregivers in parenting, especially parents, has a significant influence on children's language and motor development. Consistent interaction and appropriate stimulation from primary caregivers can support optimal child development in both aspects. Primary caregivers from biological parents tend to have a stronger emotional bond with their children, which provides a higher sense of security and stability for the child. Parental caregivers often know their children's emotional and physical needs more deeply, so they can provide faster and more appropriate responses. This interaction also allows parents to provide direct feedback that supports the improvement of children's motor skills. The results of this study indicate that primary caregivers do not have a significant effect on children's language and cognitive development, even though 90% of the primary caregivers involved in the study were biological parents. This finding is interesting because in general, there is a lot of literature showing that interactions with primary caregivers, especially biological parents, have a significant impact on children's language and cognitive development. However, the results of this study provide deeper insight into other factors that may play a role in child development, which do not only depend on the presence of biological parents as primary caregivers.

5. Study Limitations

This study has several weaknesses, namely the presence of recall bias which can affect the results of the study. In this study, the etiology of hypothyroidism in the subjects was also unknown because there was no scintigraphy tool.

6. Conclusions

There is a relationship between the onset of therapy in congenital hypothyroid patients and children's development and cognition. Therefore, the earlier hypothyroid patients are diagnosed and given therapy, the better their language and cognitive development will be.

Abbreviations

TSH	Thyroid Stimulating Hormone
CH	Congenital Hypothyroid
CHS	Congenital Hypothyroid Screening
COVID-19	Corona Virus Disease
CAT/CLAMS	Cognitive Adaptive Test/CLAMS (Clinical Linguistic & Auditory Milestone Scale
IL	Interleukine
TNF	Tumor Necrosis Factor
T4	Tiroksin
µg	Microgram
TV	Television
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus 2
TORCH	Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes Simplex
IUGR	Intrauterine Growth Restriction
CMV	Cytomegalovirus
PCR	Polymerase Chain Reaction Test
LBW	Low Birth Weight
PPROM	Preterm Premature Rupture of Membranes

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Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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