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The impact of subclinical hypothyroidism on growth and development in infants and young children aged 0 to 5 years

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Abstract

Introduction: The objective was to investigate the growth and development of infants and young children with mild subclinical hypothyroidism aged 0 to 5 years, especially those aged 0 to 2 years.

Material and methods: The study was a retrospective analysis of the birth status, physical growth, and neuromotor development of patients aged 0 to 5 years, who were diagnosed with subclinical hypothyroidism during newborn screening (NBS) in Zhongshan between 2016 and 2019. Based on preliminary results, we compared 3 groups: with thyroid-stimulating factor (TSH) value of 5–10 mIU/L (442 cases), TSH value of 10–20 mIU/L (208 cases), and TSH above 20 mIU/L (77 cases). Patients with TSH value above 5 mIU/L were called back for repeat testing and were divided into 4 groups as follows: mild subclinical hypothyroidism group 1 with a TSH value of 5–10 mIU/L in both initial screening and repeat testing; mild subclinical hypothyroidism group 2 with TSH value above 10 mIU/L in initial screening; and TSH value of 5–10 mIU/L in repeat testing; the severe subclinical hypothyroidism group with TSH value of 10–20 mIU/L in both the initial screening and repeat testing and the congenital hypothyroidism group.

Results: There were no significant differences in the maternal age, type of delivery, gender, length, and weight at birth between the preliminary groups; however, the gestational age at birth was significantly different ($F = 5.268$, $p = 0.005$). The z-score for length at birth was lower in the congenital hypothyroidism group compared to the other 3 groups but showed no difference at 6 months of age. The z-score for length in mild subclinical hypothyroidism group 2 was lower compared to the other 3 groups but showed no difference at 2–5 years of age. At 2 years of age there was no significant difference in the developmental quotient (DQ) of the Gesell Developmental Scale between the groups.

Conclusion: The gestational age at birth affected the neonatal TSH level. Intrauterine growth in infants with congenital hypothyroidism was retarded compared to that of infants with subclinical hypothyroidism. Neonates with a TSH value of 10–20 mIU/L in the initial screening and a TSH value of 5–10 mIU/L in the repeat testing showed developmental delay at 18 months but caught up at age 2 years. There was no difference in neuromotor development between the groups. Levothyroxine in patients with mild subclinical hypothyroidism is not required, but we recommend that the growth and development of such infants and young children continues to be monitored.

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Key words: *infant; neuromotor development; physical growth; subclinical hypothyroidism*

Introduction

Subclinical hypothyroidism (SCH) is a disorder that presents with raised thyroid-stimulating hormone (TSH) but normal serum free thyroxine (FT4) and total thyroxine (TT4) without the clinical symptoms and signs of hypothyroidism [1]. It can be divided into mild subclinical hypothyroidism (TSH value of 5–10 mIU/L) and severe subclinical hypothyroidism (TSH above10 mIU/L), as per the TSH level [2].

Diagnosis of subclinical hypothyroidism requires 2 independent tests to indicate elevated TSH. The serum TSH values can differ based on the investigation methods, and there can be differences between laboratories. Blood collection for newborn screening (NBS) is ideally performed within 72 h–7 days after birth to avoid the impact of maternal stress etc. [3]. There can be cases of some neonates with TSH value above 10 mIU/L during the initial screening, which, due to several factors, decreases to below 10 mIU/L accompa-

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nied by normal FT4 at repeat testing. These neonates show no clinical manifestations of hypothyroidism and are diagnosed as having subclinical hypothyroidism. There have been no studies reported on the difference of physical growth and development in such neonates and those with TSH value of 5–10 mIU/L at both initial screening and repeat testing.

Hypothyroidism affects physical growth and neuromotor development to an extent related to the age at onset and the severity of thyroid function impairment. The lack of prompt treatment increases the risk of mental retardation, metabolic abnormalities, growth retardation, and impaired skeletal maturation [3]. There are mixed opinions on the impact and treatment of subclinical hypothyroidism in children. In this study, we compared the physical growth and development of patients aged 0 to 5 years with untreated mild subclinical hypothyroidism, severe subclinical hypothyroidism treated with a small dose of levothyroxine, and congenital hypothyroidism treated with levothyroxine. Furthermore, we explore the impact on physical growth and neuromotor development in patients with mild subclinical hypothyroidism who did not receive levothyroxine treatment.

Material and methods

Sample

In this study, we retrospectively analysed neonates until 72 h–7 days after birth in Zhongshan, from 2016 to 2019. Informed consent was obtained from their parents. Preterm infants born before 37 weeks and low birth weight infants with a birth weight below 2000 g were re-evaluated for TSH at one month after birth and when their weight reached 2500 g. Such infants were excluded from the analysis of neonates with a TSH value above 5 mIU/L but were included in the analysis of physical growth and neuromotor development within 0 to 5 years of age.

Neonate screening, re-examination, and group administration

Blood was collected from the heel of all neonates at 72 h to 7 days after birth as dried blood spots complying with the Neonatal Screening Technical Specifications (2010 edition). Samples were placed in dry plastic bags after being dried naturally at room temperature and were stored at 2–8 . The investigations were performed in the Neonatal Disease Screening Centre of Boai Hospital of Zhongshan within one week of collection. The concentration of TSH was measured using time-resolved fluoroimmunoassay (VICTOR1420 fluorescence analyser and Neonatalh TSH kit, WALLAC, Finland).

Neonates with a TSH value above 5 mIU/L in the initial screening were divided into the following 3 groups based on the TSH concentration: TSH value of 5–10 mIU/L, TSH value of 10–20 mIU/L, and TSH value above 20 mIU/L. Maternal age, type of delivery, gestational age at birth, gender, birth weight, and birth length were recorded.

Although based on the expert recommendation of the Paediatric Branch of the Chinese Medical Association, neonates with initial TSH value above 6 mIU/L should be recalled, and so those with an initial TSH value above 5 mIU/L were recalled for retesting in this study as requested by the Zhongshan Newborn Screening Centre.[3] The initial test was performed 72 h~7 days after birth, and neonates with a TSH value above 5 mIU/L were recalled for retesting within 21 days after birth. Blood TSH and FT4 levels were measured using immunochemiluminometric assays (Beckman DX1800, United States). Patients with a TSH value of 10–20 mIU/L in the initial screening and a TSH value of 5–10 mIU/L in the second testing were classified as mild subclinical hypothyroidism group 1, those with a TSH value of 5–10 mIU/L in both the initial screening and repeat testing were classified as mild subclinical hypothyroidism group 2, and those with a TSH value of 10–20 mIU/L in both the initial screening and repeat testing were classified as the severe subclinical hypothyroidism group. The congenital hypothyroidism group included patients with a TSH value above 40 mIU/L in the initial screening, patients with normal TSH but with clinical signs and symptoms of hypothyroidism, and patients with a TSH value above 10 mIU/L and FT4 less than 12 pmol/L. For neonates with normal TSH levels but signs and symptoms of hypothyroidism, we further performed FT4 testing. Neonates with reduced FT4 and normal TSH were diagnosed with central hypothyroidism and were treated with levothyroxine.

Some children were diagnosed as having subclinical hypothyroidism after the initial screening and repeat testing. Therefore, most of the children in the mild subclinical hypothyroidism group and the TSH above 5 but below 10 mIU/L group may have overlapped but not completely coincided. Similarly, patients in the severe subclinical hypothyroidism group and the TSH above 10 but below 20 mIU/L group also partially overlapped.

Treatment and follow-ups

Patients in mild subclinical hypothyroidism groups 1 and 2 received no levothyroxine treatment, those in the severe subclinical hypothyroidism group received levothyroxine 5–10 μg/kg·d, and those in the congenital hypothyroidism group received levothyroxine 10–15 μg/kg·d at the time of diagnosis, and the dosage was adjusted based on TSH, FT4, and clinical manifestations. Regular follow-up was conducted. The body length at birth, 6 months, 12 months, 18 months, 2 years, and 3 years as well as the height at 4 years and 5 years were recorded. The length-for-age Z score (LAZ) calculated according to the World Health Organization (WHO) Child Growth Standards was compared between the groups. The LAZ was calculated using the WHO growth curve after adding 0.5 cm of the height values at 4 and 5 years old, to convert into body length. The presented data are the average of 3 independent measurements. The different case numbers at different ages are due to the lengthy follow-up time ranging from 0 to 5 years. We compared the physical growth in the same age group only horizontally, not longitudinally. The number of preterm infants less than 37 weeks of gestational age in each group was less than 10, all of whom were of appropriate gestational age greater than 35 weeks. All the infants had on-par growth within one year after birth. We also compared the neuromotor development at 2 years of age. We used the Gesell Infant Development Scale to analyse the adaptability, gross motor, fine motor, language, and personal social interaction levels. The results have been presented as development quotient (DQ). Persistent hypothyroidism was diagnosed using a thyroid ultrasound at the Neonatal Disease Screening Centre of Boai Hospital of Zhongshan or outside the hospital at the ages of 3 to 5 years. Due to the small number of data, they were not included in the statistical analysis.

Statistical analysis

GraphPad Prism 9.4.1 was used to analyse the data. The measurement data are expressed as $x \pm s$. One-way ANOVA was used to analyse the differences between 2 groups, followed by post hoc contrasts using the Bonferroni LSD-t test. Count data are expressed as the number of cases (%), and the chi-square test was used for comparisons between groups. $p < 0.05$ was considered statistically significant.

Results

Neonatal diseases in the different groups at initial screening

There were no significant differences in the maternal age, type of delivery, gender, length, and weight at birth among the patients in the group with TSH value 5–10 mIU/L, the group with TSH value 10–20 mIU/L, and TSH value above 20 mIU/L, as shown in Table 1. The gestational age at birth was significantly different between the 3 groups ($p = 0.005$), with gestational age at birth in children in the group with TSH value of 10–20 mIU/L being lower than in the other 2 groups.

Physical growth in patients with hypothyroidism

There were 408 neonates with a TSH value of 5–10 mIU/L in both the initial screening and repeat testing, who were classified under mild subclinical hypothyroidism group 1; 143 neonates with a TSH value of 10–20 mIU/L in the initial screening and a TSH value of 5–10 mIU/L in the repeat testing were included in mild subclinical hypothyroidism group 2; 70 neonates were in the severe subclinical hypothyroidism group, and 67 neonates were included in the congenital hypothyroidism group. There was a significant difference in LAZ among the 4 groups at birth ($p < 0.05$), and the birth length of neonates with congenital hypothyroidism was the lowest (Tab. 2). There was no significant difference in LAZ among the 4 groups at 6 months and 12 months after birth. The LAZ in mild subclinical hypothyroidism group 2 was significantly lower than that in the other 3 groups at 18 months after birth. The was no significant difference in LAZ among the groups in the 2–5 years age group.

Neuromotor development in patients with hypothyroidism

The DQ score of the Gesell scale showed no significant differences in adaptability, gross motor, fine motor, language development, and personal social interaction at the age of 2 years between mild subclinical hypothyroidism group 1 (107 cases), mild subclinical hypothyroidism group 2 (56 cases), the severe subclinical hypothyroidism group (28 cases), and the congenital hypothyroidism group (55 cases) (Tab. 3).

Table 1. *Comparison of general information in newborns with different thyroid-stimulation hormone (TSH) levels*

Group TSH [mIU/L]	Case	Maternal age [yrs] X ± s	Type of delivery (n, %)		Sex (n, %)		Gestational age at birth [wk] X ± s	Birth weight [g] X ± s	Birth length [cm] X ± s
			Vaginal delivery	Caesarean delivery	Male	Female			
5.0~10.0	442	27.1 ± 4.6	280 (63.3)	162 (36.7)	276 (62.4)	166 (37.6)	39.6 ± 1.0	3211 ± 426	49.5 ± 2.5
10.1~20.0	208	27.4 ± 4.5	133 (63.9)	75 (36.1)	132 (63.5)	76 (36.5)	39.3 ± 1.1	3242 ± 420	49.5 ± 1.8
> 20.0	77	28.1 ± 5.5	47 (61.0)	30 (39.0)	39 (50.6)	38 (49.4)	39.7 ± 1.1	3225 ± 332	49.4 ± 1.4
F/χ^2		1.576[a]	0.164 [b]		4.332 [b]		5.268 [a]	0.382 [a]	0.211 [a]
p		0.208	0.922		0.115		0.005	0.683	0.810

[a]for F, [b]for χ^2

Table 2. *Comparison of the length-for-age Z score (LAZ) among children in different hypothyroidism groups ($x \pm s$)*

Group	At birth	6 months	12 months	18 months	24 months	36 months	48 months	60 months
Mild subclinical hypothyroidism group 1	0.04 ± 1.15	0.10 ± 1.02	–0.16 ± 1.01	–0.30 ± 1.00	–0.58 ± 0.94	–0.07 ± 0.98	–0.33 ± 0.99	–0.26 ± 1.02
	408[a]	246[a]	168[a]	114[a]	107[a]	76[a]	49[a]	50[a]
Mild subclinical hypothyroidism group 2	0.00 ± 1.16	–0.06 ± 0.97	–0.22 ± 1.08	–0.61 ± 0.81	–0.38 ± 0.94	–0.22 ± 1.22	–0.31 ± 1.21	–0.05 ± 0.63
	143[a]	111[a]	82[a]	88[a]	56[a]	35[a]	31[a]	24[a]
Severe subclinical hypothyroidism	0.41 ± 1.09	0.27 ± 1.03	–0.01 ± 1.10	–0.19 ± 0.89	–0.18 ± 1.24	–0.56 ± 1.25	–0.20 ± 0.92	0.12 ± 0.90
	70[a]	37[a]	45[a]	34[a]	28[a]	25[a]	18[a]	14[a]
Congenital hypothyroidism	–0.10 ± 1.16	0.22 ± 1.21	0.20 ± 0.96	–0.15 ± 1.24	–0.46 ± 1.13	–0.04 ± 0.78	–0.36 ± 0.80	0.08 ± 1.34
	67[a]	47[a]	67[a]	66[a]	55[a]	33[a]	26[a]	24[a]
F	2.708	1.396	2.601	3.341	1.307	1.596	0.095	0.894
p	0.044	0.243	0.052	0.020	0.273	0.192	0.963	0.447

Note: [a]for follow-up cases

Table 3. *Comparison of development quotient (DQ) among 2-year-old children in different hypothyroidism groups ($x \pm s$)*

Item	Case	Adaptability	Gross Motor	Fine Motor	Language	Personal social interaction
Mild subclinical hypothyroidism group 1	107	99.56 ± 10.96	102.70 ± 11.61	93.74 ± 9.52	101.3 ± 14.91	101.1 ± 16.23
Mild subclinical hypothyroidism group 2	56	100.1 ± 11.97	106.60 ± 13.71	94.61 ± 11.12	99.00 ± 12.88	99.07 ± 11.68
Severe subclinical hypothyroidism group	28	97.07 ± 9.165	101.80 ± 13.70	96.32 ± 13.57	100.6 ± 16.60	99.25 ± 15.05
Congenital hypothyroidism	55	97.16 ± 14.35	104.10 ± 12.38	95.73 ± 11.13	99.05 ± 12.78	99.18 ± 12.91
F		0.931	1.441	0.664	0.463	0.355
p		0.427	0.232	0.575	0.708	0.79

Discussion

Congenital hypothyroidism can lead to mental and physical retardation in children if it is not diagnosed and treated in time. It has been included in the NBS in China since 1981. Early diagnosis and timely levothyroxine therapy can prevent impairment of the nervous system and physical development [3]. Subclinical hypothyroidism is defined as increased TSH, with normal thyroxine levels such as FT4 without corresponding clinical symptoms and signs of hypothyroidism [2]. Subclinical hypothyroidism is common in adults with Hashimoto's thyroiditis. Most of the subclinical hypothyroidism in neonates is reversible. Few cases are caused by gene mutations such as DUOX2 etc. [4]. Subclinical hypothyroidism is divided into mild subclinical hypothyroidism (TSH value of 5–10 mIU/L) and severe subclinical hypothyroidism (TSH value of 10–20 mIU/L), according to the TSH level. While there is consensus that low-dose levothyroxine therapy is essential in neonates with severe subclinical hypothyroidism, opinion is divided on whether the levothyroxine therapy is vital in neonates with mild subclinical hypothyroidism [3, 5, 6]. In this paper, we mainly compared the physical growth and neuromotor development of children in the following types of neonatal hypothyroidism: mild subclinical hypothyroidism, severe subclinical hypothyroidism, and congenital hypothyroidism.

NBS was performed from 72 h to 7 days after birth to avoid the impact of birth stress on the TSH value. The TSH value of neonates with TSH value above 5 mIU/L may be affected by premature and low birth weight [7]. Re-evaluation of TSH is therefore needed after the corrected gestational age and standard weight is reached. There is no consensus in different studies on whether other maternal and infant factors, in addition to preterm birth and low birth weight, have an impact on TSH value [8]. Zung *et al.* found that the birth weight and gestational age at birth were lower in neonates with hyperthyrotropinaemia than those with congenital hypothyroidism [9]. Aguilar *et al.* reported that male neonates and caesarean delivery had higher TSH levels [10]. The results of our study revealed that the gestational age at birth of neonates with a TSH value of 10–20 mIU/L was significantly lower than that of neonates with TSH value of 5–10 mIU/L and TSH value above 20 mIU/L, after excluding the impact of preterm birth and low birth weight. This suggests that gestational age at birth may affect the TSH value during NBS. Birth weight, birth length, type of delivery, and maternal age were less likely to affect the TSH value during NBS because there was no significant difference in these among the 3 groups mentioned. Moreover, in the interpretation of TSH results during NBS, it is necessary to consider the possible interference of gestational age at birth.

It is accepted globally that low-dose levothyroxine therapy is essential for severe subclinical hypothyroidism [1, 3], while the necessity of levothyroxine therapy in mild subclinical hypothyroidism depends on whether it affects the growth and development of children [11–13]. The 2021 Consensus of the European Society for Paediatric Endocrinology (ESPE) [14] recommends levothyroxine treatment in the case of TSH value of 6–20 mIU/L. The decision to continue treatment is based on FT4 and TSH results after 21 days of postnatal review. The impact on the physical growth and neurological development of infants with a TSH value of 5–10 mIU/L who are untreated remains inconclusive [15, 16]. Some neonates with mild subclinical hypothyroidism can normalize their thyroid function on their own in the first few years of life, and those with a TSH value above 10 mIU/L are less common [16]. The treatment of infants with a TSH value of 5–10 mIU/L remains controversial. All cases with the TSH value of 5–10mIU/L in this study were neonates from 2016 to 2019, and they were not treated.

Earlier research on the monitoring and follow-up of physical growth and neuromotor development in congenital hypothyroidism after treatment have been reported in Zhongshan [17]. However, there are few reports on the impact of subclinical hypothyroidism on growth and development, especially mild subclinical hypothyroidism in neonates. Most studies focused on reporting the growth and development of subclinical hypothyroidism in adolescents [18, 19]. Our study compared and analysed the changes in physical growth and neuromotor development indexes in patients with different degrees of subclinical hypothyroidism and congenital hypothyroidism.

The consensus is that once the condition is diagnosed, levothyroxine therapy must be started immediately. Low-dose levothyroxine therapy is used in severe subclinical hypothyroidism. For further study, we followed up children with mild subclinical hypothyroidism who did not receive levothyroxine therapy. Diagnosis of subclinical hypothyroidism requires 2 independent evaluations considering the influences of gestational age at birth and differences in laboratory testing in the TSH value during NBS. The diagnosis of congenital hypothyroidism was based on expert consensus in this study [3], and the diagnosis of severe subclinical hypothyroidism was made with the TSH value of 10–20 mIU/L in both the initial screening and repeat testing. Retrospective analysis revealed that some neonates had a TSH value of 10–20 mIU/L at initial check-up, but this decreased to 5–10 mIU/L in the repeat testing, and they were thus classified as having mild subclinical hypothyroidism if TSH remained within the range 5–10 mIU/L at the second re-evaluation. There are no reports on whether differences exist in the physical growth and neuromotor development between children with mild subclinical hypothyroidism whose TSH differed in the initial screening and repeat testing, and children with TSH value of 5–10 mIU/L.

The results of our study revealed that there were statistically significant differences in birth length of neonates between the mild subclinical hypothyroidism, severe subclinical hypothyroidism, and congenital hypothyroidism groups. The birth length was highest in patients with severe subclinical hypothyroidism and lowest in patients with congenital hypothyroidism, suggesting that the lower thyroxine level may affect intrauterine growth.

There was no significant difference in the length at 6 months and 12 months after birth, suggesting that children with congenital hypothyroidism achieved on-par growth at the age of one year after birth following the early diagnosis during NBS and timely treatment. At 18 months after birth, there was no significant difference in body length among children aged 0–5 years with mild subclinical hypothyroidism (TSH value of 5–10 mIU/L at initial screening and repeat testing) without euthyroidism treatment, compared with children treated with severe subclinical hypothyroidism and congenital hypothyroidism. However, the body length in children with mild subclinical hypothyroidism group 2 without levothyroxine therapy at 18 months after birth was significantly delayed when compared with the other groups. On-par growth was achieved after 2 years of age, and there was no difference in body length between the 4 groups between 2 and 5 years of age. Children with mild subclinical hypothyroidism who had not received levothyroxine showed growth delay for a period after birth but were able to catch up.

In addition to physical growth, hypothyroidism also affects the development of the nervous system in children [20]. It is not clear whether neuromotor development is affected in subclinical hypothyroidism without levothyroxine therapy. Lain et al. found a worse neurocognitive outcome in children of school age with neonatal screening TSH concentrations between the 75th and 99.9th percentiles [21]. In a Belgian cohort of children, there was no relationship between mild neonatal TSH elevation and neurodevelopment at the preschool age [22–23]. Compared with healthy children, attentional sensitivity decreased in Wechsler Intelligence Scale scores in children with subclinical hypothyroidism, but no other significant differences were found [15, 17]. There are a few reports on the effects of neuromotor development in the early postnatal period of neonates. We used the Gesell scale at the age of 2 years to compare mild subclinical hypothyroidism without treatment, severe subclinical hypothyroidism with low-dose levothyroxine therapy, and congenital hypothyroidism with levothyroxine therapy. The results showed no significant differences in adaptability, gross motor, fine motor, language development, and personal social interaction.

Conclusion

We retrospectively analysed TSH data during NBS in Zhongshan from 2016 to 2019 and found that physical growth was temporarily delayed in infants and young children with untreated mild subclinical hypothyroidism in the age group of 0–5 years, and especially in those aged 0–2 years. However, compared with infants and young children with severe subclinical hypothyroidism and congenital hypothyroidism treated with levothyroxine therapy, they achieved on-par growth. We did not find any significant change in neuromotor development. We recommend that growth and development indicators should be monitored in infants and young children with untreated mild subclinical hy-

pothyroidism. Levothyroxine therapy is essential when development delay is detected.

There are some limitations to this study, such as the small sample size due to drop out in the follow-up of patients in the age group 4 to 5 years. Moreover, we only assessed neuromotor development at the age of 2 years. A larger sample size and more test items are required to obtain more effective data.

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Ethical approval and consent to participate

This study was conducted with approval from the Ethics Committee of Boai Hospital of Zhongshan Affiliated to Southern Medical University (2017-ky-001). This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participant parents.

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