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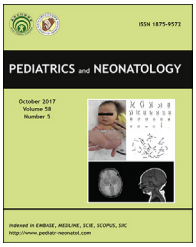

Original Article

Three-year follow-up of children with abnormal newborn screening results for congenital hypothyroidism

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Key Words
congenital hypothyroidism;
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transient

Background: To analyze predictive factors suggesting transient congenital hypothyroidism (TCH) compared to permanent congenital hypothyroidism (PCH) or transient thyroid function test (TFT) abnormalities among children who had positive screening results at our centers over the past decade.
Methods: A retrospective chart review of 105 subjects who presented elevated TSH levels on a newborn screening test (NST) was done. TCH was defined when a trial-off therapy was successful, and PCH was defined when a trial failed or when the subject was kept on medication beyond 3 years of age. A transient TFT abnormality was defined when follow-up TFTs were normalized without levothyroxine (LT4) therapy.
Results: Congenital hypothyroidism (CH) was diagnosed in 75.2% (TCH 35.2% and PCH 40.0%) of all subjects; the others (24.8%) showed transient TFT abnormalities. Initial NST-TSH levels (optimal cutoff point, 31.0 μIU/mL), the LT4 dose at 2 years of age (4.1 μg/kg/day), and the maximal LT4 dose (50 μg/day) merged as significant predictive factors discriminating between TCH and PCH. The initial serum level of free T4 (1.06 ng/dL) and not TSH (27.2 μIU/mL) was the only discriminating factor between transient TFT abnormalities and TCH.
Conclusion: Earlier re-evaluation might be possible when a patient's initial NST-TSH levels and maximal or 2-year LT4 doses are low, as both are important predictors of successful trial-off therapy in CH patients. When the initial serum level of free T4 is above the average value in neonates with mildly elevated TSH levels, TFTs may be more likely to normalize on their own.

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1. Introduction

Congenital hypothyroidism (CH) is typically characterized as an endocrine disorder, and it appears to be the most common preventable cause of mental retardation.[1] A newborn screening test (NST) is used to detect CH, which is confirmed by abnormal levels of serum thyroid-stimulating hormone (TSH) and free thyroxine (free T4) levels. According to the literature, CH occurs in approximately 1 in 3000—4000 live births,[2] but estimates of the incidence of CH vary according to the measurement methods used: the estimated incidence is greater than 1 in 2000—3000 live births in countries that use NST *vs*. approximately 1 in 6700 live births before the screening era.[3]

The NST program for CH, which uses TSH as a biomarker, was introduced in Korea in 1991. It became a free screening in 1997 as a Mother and Child Health project,[4] and the ratio of newborns tested to live births is now over 98% (Table 1). The reported incidence of CH in Korea has been increasing over the past decade, from 1 in 5449 newborns tested in 2004 to 1 in 1231 newborns tested in 2012 (Table 1). Considering that the number of patients with a final diagnosis of CH was based on registration data from the public health center, the actual incidence of CH is estimated to be higher. Screening results for CH are considered positive when the bloodspot TSH concentration exceeds 20 μIU/mL.[2] In Korea, a total of 13 laboratories perform the NST-TSH, and the cutoff levels of TSH vary from 10.0 μIU/mL to 22.5 μIU/mL according to each laboratory protocol.

Treatment with levothyroxine (LT4) for CH must be initiated rapidly to optimize neurocognitive outcomes[1,2] and should be continued to ensure normal growth and development during infancy. However, not all children with CH require lifelong hormone replacement therapy. Some undergo a successful trial-off-therapy at 2 or 3 years of age. Consequently, transient hypothyroidism has become a common condition in parts of the world where NST is routinely provided to all newborns.[5] The current guidelines for the diagnosis and management of CH are well organized,[1] but some details still warrant discussion.[6] For example, the increasing number of premature neonates with thyroid function abnormalities requires distinct diagnostic criteria and treatment protocol. There is also persistent confusion regarding the screening methodology that is most sensitive and cost effective. Because treatment ends before the third year of life in cases of transient hypothyroidism[6] and because studies have highlighted the negative impact of overtreatment with LT4 on developmental outcomes,[7] an earlier trial-off-therapy should be reconsidered in cases of transient hypothyroidism.

In this study, we investigated the clinical characteristics of subjects seen at our center in the past decade who had positive NST results and were found to have transient congenital hypothyroidism (TCH), permanent congenital hypothyroidism (PCH), or transient thyroid function test (TFT) abnormalities. Then, we aimed to determine the factors that predicted TCH *vs*. PCH or transient TFT abnormalities in Korean children.

2. Methods

2.1. Subjects and methods

Between July 2004 and July 2014, 105 subjects (50 boys and 55 girls) from Hallym University Medical Center and Seoul National University Bundang Hospital who had elevated TSH levels on their NST were enrolled. CH was diagnosed for subjects who started LT4 replacement therapy due to low serum levels of free T4 (<0.7 ng/dL) or elevated serum

Table 1 Newborn screening status and the incidence of congenital hypothyroidism in Korea (provided by Planned Population Federation of Korea).

Year	Number of newborn screening tested (n)	Ratio of newborn tested to live births (%)	Positive result of CH in NST (n)	Number of the final diagnosis of CH (n)	Incidence of CH (one patient per newborn tested)
2004	386,889	81.8	not available	71	5449
2005	412,653	94.9	not available	73	5653
2006	433,331	96.7	1349	144	3009
2007	472,055	95.7	1769	149	3168
2008	454,614	97.6	2015	96	4736
2009	439,387	98.8	2221	153	2872
2010	471,632	99.5	2255	163	2893
2011	465,175	98.7	2447	378	1231
2012	482,737	99.6	3028	381	1267
2013	429,759	98.4	2139	317	1356

Abbreviations: NST, newborn screening test; CH, congenital hypothyroidism.

levels of TSH (≥10 μIU/mL) with no evidence of acquired hypothyroidism. LT4 replacement therapy was delivered for at least 2 years in CH subjects. TCH was defined when trial-off-therapy was successful and kept TFT results within an acceptable range (TSH <10 μIU/mL and normal free T4 levels) for at least 6 months after the cessation of LT4 medication. PCH was defined when trial-off-therapy failed or subjects were kept on medication beyond the 3 years of age because of thyroid dysgenesis or probable dyshormonogenesis. A transient TFT abnormality was defined when subjects did not require LT4 replacement therapy and their follow-up serum TFTs were normalized (TSH <6 μIU/mL and free T4 ≥0.9 ng/dL after 2 weeks of age). Probable dyshormonogenesis was defined when a large thyroid gland in a eutopic location with increased uptake was seen in imaging studies. The exclusion criteria were as follows: gestational age <37 weeks, an insufficient follow-up period after the diagnosis of CH (less than 2 years), loss to follow-up before trial-off-therapy, loss to follow-up after the trial-off-therapy, and genetic conditions, including Down syndrome. A total of 37 (21 boys and 16 girls), 42 (16 boys and 26 girls), and 26 (13 boys and 13 girls) patients were classified as having TCH, PCH, or transient TFT abnormality, respectively.

The TFT results and treatment histories were analyzed retrospectively. Family history of thyroid disease, such as CH or autoimmune thyroiditis, was investigated. In subjects with CH, initial serum TFT levels were retrieved from the results just before undergoing LT4 replacement therapy. The frequency of dose-up or dose-down was defined as the number of dose changes divided by the total number of TFTs performed between the initiation of LT4 therapy and either an attempted trial-off-therapy or the subject reaching the age of 3 years. The number of days required to normalize free T4 or TSH (free T4 ≥0.9 ng/dL or TSH <6 μIU/mL after 2 weeks of age) was also calculated. Thyroid ultrasonography or a Technetium-99m pertechnetate thyroid scan was performed either at diagnosis or at the trial-off-therapy.

This study protocol was approved by the Institutional Review Board of each center (Hallym University Medical Center and Seoul National University Bundang Hospital).

2.2. Statistics

All data are presented as medians with interquartile ranges. The Mann-Whitney U test or the chi-squared test was used to explore differences between the two groups. Logistic regression analysis was used to determine the predictive factors associated with TCH compared with PCH or transient TFT abnormalities after controlling for other variables. All statistical analyses were performed using PASW Statistics 18.0 for Windows (Chicago, IL). Several parameters that showed significant differences between TCH and PCH or between TCH and transient TFT abnormalities were applied in the ROC curve analysis. To compare receiver operating characteristics (ROC) curves, MedCalc for Windows (version 14.8.1, MedCalc Software, Ostend, Belgium) was used. The optimal cutoff point was defined as the highest Youden index (sensitivity + specificity-1). *P*-values <0.05 were considered significant.

3. Results

3.1. The clinical characteristics of subjects with congenital hypothyroidism (Table 2)

In 79 subjects with CH (37 boys) who were treated with LT4, the median and interquartile ranges of the initial NST-TSH were 27.2 (20.7–57.3) and the initial serum levels of free T4 and TSH were 0.56 (0.24–0.93) ng/dL and 94.4 (44.4–100.0) μIU/mL, respectively. The median age at which LT4 replacement therapy was initiated was 20.0 days, and the initial dose was 10.4 μg/kg/day. The median times required to normalize free T4 and TSH were 21.0 and 34.5 days, respectively. Thyroid sonography or scintigraphy was performed in 78 subjects, and the results were abnormal in 56.4% (n = 44/78) as follows: thyroid agenesis, n = 5; thyroid hypoplasia, n = 7; ectopic thyroid gland, n = 10; probable dyshormonogenesis, n = 20; no uptake on scans with normal glands on ultrasound, n = 2.

The initial NST-TSH levels showed marked differences between the TCH and PCH groups ($P < 0.001$), while the second NST-TSH results did not differ significantly. The initial serum level of TSH was higher ($P = 0.002$) and the time required to normalize TSH was longer ($P = 0.001$) in the PCH group than in the TCH group, but the initial serum levels of free T4 did not differ between the two groups ($P = 0.207$). Significant differences in the serum levels of TSH persisted until the subjects reached 2 years of age and then became similar at 3 years of age. The LT4 doses at 1 year of age (TCH 3.6 *vs.* PCH 4.6 μg/kg/day), at 2 years of age (3.1 *vs.* 4.3 μg/kg/day), and before trial-off-therapy (2.7 *vs.* 4.0 μg/kg/day) were significantly lower in the TCH group than in the PCH group (all, $P < 0.001$). Higher frequencies of dose changes were found in the PCH group compared with the TCH group. Subjects with a family history of thyroid disease comprised 13 of the 37 subjects with TCH (35.1%) and 6 of the 42 subjects with PCH (14.3%); the difference was marginally significant ($P = 0.057$). Abnormal thyroid imaging results were found in 30.6% (n = 11/36) of the TCH subjects (probable dyshormonogenesis, n = 10; no uptake on scans with normal glands on ultrasound, n = 1) and in 78.6% (n = 33/42) of the PCH subjects (thyroid agenesis, n = 5; thyroid hypoplasia, n = 7; ectopic thyroid gland, n = 10; probable dyshormonogenesis, n = 10; no uptake on scans with normal glands on ultrasound, n = 1).

3.2. The trial-off-therapy in subjects with congenital hypothyroidism

Trial off-therapy was performed in 60 subjects with CH. Sixteen of 19 subjects who did not undergo a trial-off-therapy had thyroid dysgenesis or probable dyshormonogenesis, and the others (n = 3) underwent a dose-up at approximately 3 years of age. The median LT4 dose at the trial-off-therapy was higher in the 23 subjects who failed (4.0 μg/kg/day) than in the 37 subjects who succeeded (2.7 μg/kg/day). The median LT4 dose of 19 subjects who did not trial-off-therapy was 3.8 μg/kg/day.

After trial-off-therapy, the median and interquartile ranges of the serum levels of free T4 and TSH of the patients whose trials were successful remained within

acceptable range: 1.35 (1.20—1.49) ng/dL and 5.2 (4.2—7.1) μIU/mL at 6 months, respectively, in the 37 TCH subjects; 1.39 (1.14—1.62) ng/dL and 6.3 (4.2—7.9) μIU/mL at 12 months, respectively, in the 24 TCH subjects. The 23 subjects who failed trial-off-therapy resumed their LT4 medication at 3.4 (1.0—6.8) months after off-therapy at a restarting dose of 3.7 (2.7—4.8) μg/kg/day.

3.3. Predictive factors suggesting TCH *vs.* PCH

Among many parameters, the top 5 with the highest AUC in the ROC curve analysis were the initial NST-TSH level; the LT4 dose at 1, 2, and 3 years of age; and the maximal dose during LT4 replacement therapy. For each parameter, the AUC with a 95% confidence interval (CI), sensitivity, and specificity at the optimal cutoff point were as follows: initial NST-TSH level, 0.817 (0.700—0.903), 72.7% and 83.3% at 31.0 μIU/mL; LT4 dose at 1 year of age, 0.770 (0.658—0.859), 62.5% and 85.71% at 4.4 μg/kg/day; LT4 dose at 2 years of age, 0.831 (0.725—0.909), 60.5% and 97.1% at 4.1 μg/kg/day; LT4 dose at 3 years of age, 0.780 (0.672—0.867), 60.0% and 97.3% at 3.7 μg/kg/day; and maximal LT4 dose, 0.795 (0.687—0.878), 47.6% and 94.3% at 50 μg/day. The ROC curves for the initial NST-TSH levels and LT4 doses at 2 years of age showed no differences ($P = 0.915$, Figure 1). The significant predictive factors that discriminated between TCH and PCH in the logistic regression analysis were the initial NST-TSH level (OR = 1.074, $P = 0.033$), the LT4 dose at 2 years of age (OR = 4.548, $P = 0.012$), and the maximal LT4 dose (OR = 1.104, $P = 0.043$). The initial NST-TSH level also showed good prediction of abnormal thyroid imaging results (OR = 1.062, $P = 0.019$).

3.4. The clinical characteristics of subjects with transient TFT abnormality (Table 3)

Of 105 subjects, 26 (24.8%) had transient TFT abnormalities and did not receive LT4 replacement therapy. The initial serum level of TSH was lower, and the free T4 was higher, than those of the TCH group (all $P < 0.001$, Table 3). The second NST-TSH results were also lower in the subjects with transient TFT abnormalities (13.8 μIU/mL) compared with those with TCH (21.1 μIU/mL, $P = 0.003$). The median and

Table 2 Clinical characteristics of the subjects with congenital hypothyroidism.

		TCH	PCH	*P*-value
Number (M:F)		37 (21:16)	42 (16:26)	0.152
Birth weight (kg)		3.4 (3.0—3.6)	3.1 (2.9—3.3)	0.018
Initial NST-TSH (μIU/mL)		22.0 (16.5—25.6)	49.1 (27.5—150.0)	<0.001
Second NST-TSH (μIU/mL)		21.1 (17.9—31.9)	30.5 (18.7—244.1)	0.165
Initial	Age at exam (days)	23.0 (18.0—29.0)	15.0 (12.0—25.0)	0.008
	Free T4 (ng/dL)	0.56 (0.43—0.94)	0.50 (0.19—0.92)	0.207
	TSH (μIU/mL)	50.0 (34.1—100.0)	100.0 (72.1—122.1)	0.002
	LT4 dose (μg/kg/d)	9.9 (8.6—11.8)	10.7 (7.2—12.5)	0.610
At 1 year	Age at exam (years)	1.0 (0.9—1.1)	1.0 (0.9—1.1)	0.606
	Free T4 (ng/dL)	1.50 (1.34—1.61)	1.43 (1.27—1.89)	0.880
	TSH (μIU/mL)	2.2 (1.2—4.0)	4.8 (1.7—10.7)	0.004
	LT4 dose (μg/kg/d)	3.6 (3.0—4.2)	4.6 (3.6—5.4)	<0.001
At 2 year	Age at exam (years)	2.0 (1.9—2.1)	2.0 (1.9—2.0)	0.046
	Free T4 (ng/dL)	1.51 (1.32—1.70)	1.55 (1.32—1.70)	0.610
	TSH (μIU/mL)	2.2 (1.5—3.6)	4.3 (1.7—9.5)	0.007
	LT4 dose (μg/kg/d)	3.1 (2.6—3.5)	4.3 (3.5—5.3)	<0.001
At 3 year	Age at exam (years)	2.7 (2.6—3.0)	2.9 (2.8—3.0)	0.014
	Free T4 (ng/dL)	1.50 (1.39—1.69)	1.57 (1.33—1.69)	0.513
	TSH (μIU/mL)	3.2 (2.3—3.8)	3.8 (2.1—8.6)	0.229
	LT4 dose (μg/kg/d)	2.8 (2.4—3.3)	4.0 (2.9—4.7)	<0.001
At trial-off therapy	Age at exam (years)	3.0 (3.0—3.1)	3.0 (3.0—3.1), n = 23	0.615
	LT4 dose (μg/kg/d)	2.7 (2.2—3.2)	4.0 (2.5—4.7), n = 23	0.001
First FU after off therapy	Days after off therapy (days)	31.0 (30.0—34.0)	31.0 (28.0—34.0), n = 23	0.326
	Free T4 (ng/dL)	1.29 (1.16—1.37)	0.88 (0.64—1.28), n = 23	<0.001
	TSH (μIU/mL)	5.3 (3.9—8.3)	40.7 (15.8—100.0), n = 23	<0.001
Frequency of dose up (%)		9.1 (0.0—11.8)	20.0 (7.8—32.5)	<0.001
Frequency of dose down (%)		4.2 (0.0—10.5)	10.5 (5.8—14.3)	0.003
Maximum LT4 dose (μg/d)		50.0 (40.0—50.0)	50.0 (50.0—75.0)	<0.001
Minimum LT4 dose (μg/d)		33.0 (25.0—40.0)	33.0 (25.0—35.6)	0.716
Free T4 normalization day (days)		20.5 (0.0—27.8)	23.0 (11.0—38.0)	0.189
TSH normalization day (days)		26.0 (21.0—36.8)	59.5 (28.0—89.0)	0.001

Data are expressed as median and interquartile ranges.
Abbreviations: TCH, transient congenital hypothyroidism; PCH, permanent congenital hypothyroidism; NST, newborn screening test; LT4, levothyroxine; FU, follow-up.

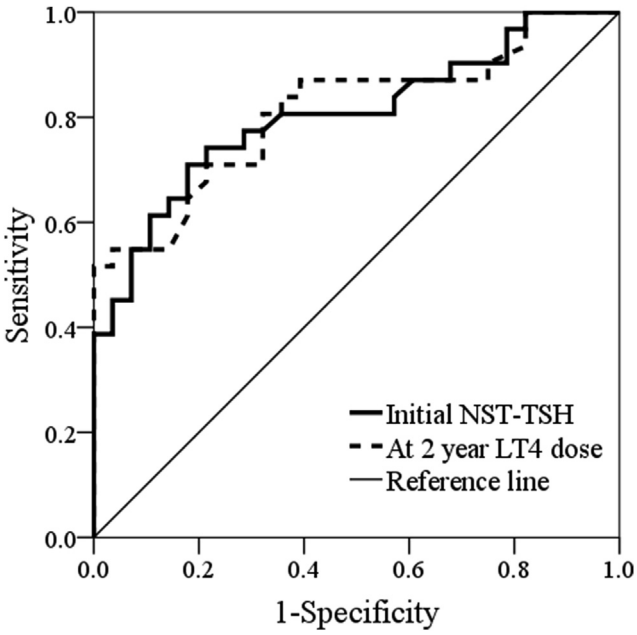

Figure 1 As the ROC curves show, both the initial NST-TSH level and the levothyroxine dose at 2 years of age were predictive factors discriminating between transient and permanent congenital hypothyroidism ($P = 0.915$).

interquartile range of the time required before TSH values fell below 6 μIU/mL were 35.5 (24.0—61.0) days for the subjects with transient TFT abnormalities. The last follow-up TFTs (free T4 and TSH) at 5.5 (2.7—17.3) months of age were 1.29 (1.13—1.49) ng/dL and 4.0 (2.8—4.7) μIU/mL, respectively. The free T4 nadir was 1.21 (1.09—1.40) ng/dL and the TSH peak was 9.8 (5.4—20.8) μIU/mL during the follow-up. Four out of 26 (15.4%) subjects had a family history of thyroid disease, which was not significantly different from the results for the TCH group ($P = 0.147$).

3.5. Predictive factors suggesting TCH compared with transient TFT abnormalities

For each parameter, the AUC with a 95% CI, sensitivity and specificity at the optimal cutoff point was as follows: initial NST-TSH level, 0.711 (0.563—0.831), 80.0% and 68.4% at 15.5 μIU/mL; second NST-TSH level, 0.828 (0.643—0.942), 83.3% and 81.8% at 17.3 μIU/mL; initial serum level of free T4, 0.945 (0.852—0.987), 85.7% and 91.7% at 1.06 ng/dL; and initial serum level of TSH, 0.913 (0.813—0.970), 85.7% and 88.5% at 27.2 μIU/mL. The comparison of the ROC curves for the initial serum levels of free T4 and TSH showed no differences ($P = 0.792$), but in the logistic regression analysis, only the initial serum level of free T4 (OR = 0.008, $P = 0.009$) was significant for discriminating between transient TFT abnormalities and TCH.

4. Discussion

In the present study, CH was diagnosed in 75.2% (TCH 35.2% and PCH 40.0%) of the newborns who had a positive NST. The rest (24.8%) of the newborns with an elevated NST-TSH showed transient TFT abnormalities that normalized without LT4 medication. Both TSH levels and medication histories differed between the TCH and PCH patients. The factors that best predicted TCH compared with PCH were the initial NST-TSH result, the LT4 dose at 2 years of age, and the maximal LT4 dose during the follow-up period. With the exception of the PCH subjects, the low initial serum level of free T4 was the most important factor discriminating the subjects who need LT4 medication from those who do not although they all have positive screening results.

The reported incidence rate of CH has been increasing in the United States over the past 2 decades,[8] and Korea is showing a similar pattern (Table 1). The reported prevalence of TCH in the literature varies from 20.0%—66.5%,[9—15] largely because the definition of TCH differs among studies. In some cases, authors do not distinguish between transient TFT abnormalities and TCH.[5] Additionally, the inclusion criteria, such as preterm neonates, thyroid gland status, or chief complaints that lead to TFTs, are diverse, and ethnic differences among study populations may also account for differences in results.[16] In the present study, TCH was revealed in 35.2% of the newborns with elevated NST-TSH levels and in 46.8% of CH subjects who began taking LT4 medication. Kemper et al.[17] analyzed the data detected from NSTs such as the one used for our study population and found that TCH accounted for 38% of CH cases. Therefore, considering that we excluded preterm infants in this study, the prevalence of TCH might be higher than previous reports indicate.[15,17] CH is a heterogeneous disorder that includes thyroid gland agenesis, dysgenesis, and eutopic thyroid glands. The female-to-male sex ratio among newborns with thyroid agenesis or dysgenesis, which is the most common cause of CH, is

Table 3 Comparison of clinical characteristics of the subjects between transient congenital hypothyroidism and transient thyroid function test abnormality.

	TCH	TFT abnormality	*P*-value
Number (M:F)	37 (21:16)	26 (13:13)	0.785
Initial NST-TSH (μIU/mL)	22.0 (16.5—25.6)	14.5 (12.4—21.9)	0.014
Second NST-TSH (μIU/mL)	21.1 (17.9—31.9), n = 18	13.8 (12.1—17.3), n = 11	0.003
Initial age at exam (days)	23.0 (18.0—29.0)	18.0 (11.8—23.0)	0.016
Initial Free T4 (ng/dL)	0.56 (0.43—0.94)	1.46 (1.28—1.60)	<0.001
Initial TSH (μIU/mL)	50.0 (34.1—100.0)	9.8 (5.4—18.9)	<0.001

Data are expressed as median and interquartile ranges.
Abbreviations: TCH, transient congenital hypothyroidism; TFT, thyroid function test; NST, newborn screening test.

typically 2:1[18]; it was 1.6:1 in our subjects with PCH. However, the sex ratio among our subjects with CH (1.1:1) suggests that a significant proportion might have TCH. In other words, the incidence of PCH over the past decade might be relatively stable when preterm infants are excluded.

One of many reasons for the increased incidence of CH was the recent lowering of the NST-TSH cutoff levels.[19–21] The reduction of screening thresholds compared with initial values allows more sensitive detection of CH and earlier intervention. However, because there was no untreated control group among the subjects with mild TSH elevations, it is not clear whether early treatment would benefit them in terms of their learning and school performance.[22] The cutoff levels of the NST-TSH were lowered to 12 μIU/mL from 20 μIU/mL at Hallym University Medical Center and Seoul National University Bundang Hospital in 2012 and 2011, respectively. However, considering the optimal NST-TSH cutoff point of 31 μIU/mL that was used in this study, a readjustment of the cutoff levels of the NST-TSH may be necessary. In other words, it might be safe to refer to the guidelines,[1,2] which still suggest an NST-TSH cutoff level of 20 μIU/mL. Other reports have suggested initial serum TSH cutoff levels of 28.4 μIU/mL[23] and 34.0 μIU/mL.[13] The filter-paper TSH level is approximately half the concentration in serum,[2] and our study revealed an initial serum TSH cutoff level of 68.9 μIU/mL (data not shown). Although those values are higher than those reported in other studies,[13,23] our results may be closer to recent guidelines. Deladoëy et al. also reported that lowering the TSH cutoff at retesting did not significantly increase the incidence of the severe types of CH, such as athyreosis, ectopy, and dyshormonogenesis.[24] The original purpose of screening for CH was to identify severe cases in which a benefit was clear,[24] which also supports our suggestions for cutoff values.

The initial LT4 doses were approximately 10 μg/kg/d in all CH subjects; however, significant dose differences between the TCH and PCH groups (1.0 μg/kg/d at 1 year and 1.2 μg/kg/d at 2 and 3 years of age) were found afterward, although the doses were lowered during the follow-up for both groups. Many authors emphasize the LT4 dose as the discriminant marker between TCH and PCH. Cho et al. reported that LT4 doses over 3.3 μg/kg/d at 1 and 2 years of age indicated a higher chance of developing PCH.[23] Hong et al.[9] and Unuvar et al.[10] reported that the only difference between TCH and PCH was the LT4 dose required, and they reported LT4 doses at 2 years of age of 2.6 μg/kg/d for TCH and 4.5 μg/kg/d for PCH[9] and 2.2 μg/kg/d for TCH and 2.9 μg/kg/d for PCH,[10] respectively. Hong et al.[9] also reported that LT4 doses after as little as 6 months of treatment were significantly lower in PCH patients than in TCH patients. Bekhit et al.[25] showed maximal LT4 doses of 50–125 μg/day for PCH and less than 50 μg/day for TCH, which were consistent with our study. Among several parameters related to medical histories, the LT4 dose at 2 years of age and the maximal dose were important discriminating factors in our study; therefore, we suggest that when a subject with an initial NST-TSH level below twice the cutoff level takes an LT4 dose $<$50 μg/d during the treatment period, TCH is more likely to be diagnosed, especially when the dose is $<$4.1 μg/kg/d at 2 years of age.

In the present study, we included the 3rd group, transient TFT abnormalities; therefore, cases of TCH should not be confused with cases of transient hyperthyrotropinemia. The recent protocols published by the American Academy of Pediatrics, the American Thyroid Association, Lawson Wilkins Pediatric Endocrine Society, and the European Society for Pediatric Endocrinology are well organized[1,2] but leave many questions unanswered. When TSH levels are between 6–20 μIU/mL and free T4 levels are normal, guidelines recommend playing it safe by providing LT4 treatment during early childhood.[2,3] However, our study suggests that when the free T4 level is above 1.06 ng/dL with a mildly elevated TSH level below 27.2 μIU/mL, starting LT4 medication immediately might not be the best option because of the probability of overtreatment, increased medical costs, or parents' concerns during the treatment period. Especially, the initial free T4 level should be carefully looked because its role in the decision of treatment or not is important.

Our study has several limitations. First, long-term follow-up of subjects with TCH is limited. We included patients who had undergone at least 6 months of follow-up after off-therapy and 12 of the 27 TCH subjects were lost at 12 months of follow-up. Considering that at long-term follow-up, children are more likely to have stopped treatment, our rates might be underestimated. Second, the number of subjects with transient TFT abnormalities was small; therefore, further research with an extended sample size is needed to confirm our findings. Despite these weaknesses, our study results are meaningful because we tried to exclude various other medical conditions, such as jaundice, acute illness and preterm birth, which can influence the TFTs. Compared with the general population, preterm children are more likely to have TCH.[12,21] As reported in the literature, thyroid dysfunction in preterm newborns often improves rapidly and spontaneously, without the need for hormonal treatment.[26] Lim et al. also reported that thyroid dysfunction in very low birth weight infants was common in their cohort and that most cases were transient.[27]

Current guidelines recommend early treatment with LT4 (when possible, at less than 2 weeks of age) if CH is diagnosed; once treatment is started, re-evaluation is not recommended until the age of 3 years or older.[1] This recommendations are based on the fact that myelination of the brain is completed by 36–40 months of age,[28] and the belief that the child grow and develop normally with sufficient treatment duration. However the cause of TCH is multifactorial; thus, it is not clear how long LT4 therapy is needed for TCH. Most TCH subjects have normal thyroid glands, and LT4 replacement for this population is generally continued until 2 years of age in case of iodine excess,[5] which is more common in Korea than deficiency as the transient cause of CH.[29] More than one-third of children treated for CH have discontinued treatment within 36 months, which is inconsistent with current guidelines. Therefore, re-evaluation following a one-month drug-free period at the end of 2 years of age might be considered.

In conclusion, because both NST-TSH levels and treatment histories are important for predicting a successful trial-off-therapy, earlier re-evaluation of children younger than 3 years of age might be possible when their initial NST-

TSH levels and maximal or 2-year LT4 doses are low. Moreover, when the initial serum level of free T4 is above average values in neonates with mild TSH elevation, TFT results could normalize without LT4 medication. Finally, based on an optimal cutoff point analysis, NST-TSH levels could be readjusted to prevent unnecessary or excessive treatment of TCH.

Conflict of interest

The authors declare that they have no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements) that might be considered to represent a conflict of interest in connection with this study.

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