Factors associated with permanent hypothyroidism in infants with congenital hypothyroidism

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Abstract

Background Congenital hypothyroidism (CH) is one of the most common endocrine diseases in childhood. A significant proportion of CH cases are transient, but the risk factors for permanent CH (PCH) are not yet well established. The current guidelines suggest using levothyroxine until the age of 3 years, but some studies suggest the possibility of earlier discontinuation. However, few, if any, studies have followed up on the results of early discontinuation. This study aimed to identify predictive factors of transient CH among infants with CH. We also investigated the results in patients who underwent a trial of early discontinuation.

Methods We gathered data regarding infants with CH born between July 2005 and July 2014 by retrospective chart review. Among them, early discontinuation subgroup was defined as those who discontinued levothyroxine before 30 months of age.

Results From the 80 infants (40 males, 40 females) enrolled in this study, 51 were preterm. Nine (11.3%) were diagnosed with PCH. Compared with transient cases, those with PCH were on higher levothyroxine dose at discontinuation (4.3 vs 2.9 µg/kg, P < 0.001). There was no difference in the proportion of permanent cases between preterm and full-term groups. In preterm group, infants with PCH required higher levothyroxine dose at discontinuation than those with transient CH (3.8 vs 2.5 µg/kg, P = 0.018). Levothyroxine discontinuation at a dose of 2.86 µg/kg could suggest PCH (sensitivity, 88.9%; specificity, 71.0%). Among the 9 patients who underwent a trial of early discontinuation, 8 successfully discontinued levothyroxine.

Conclusion The majority of CH patients discontinued levothyroxine successfully, including those who underwent a trial of early discontinuation. Higher levothyroxine dose at the time of discontinuation was found to be a predictive factor for PCH.

Background

Congenital hypothyroidism (CH) is one of the most common endocrine diseases among children, and can cause intellectual impairment [1]. In many cases, CH results from transient abnormalities in the thyroid function rather than permanent dysfunction [2], but current guidelines recommend that levothyroxine treatment be maintained until at least 36 months of age for all infants diagnosed with CH [3]. For parents and infants, taking medication every day for 3 years and undergoing routine blood sampling for follow-up thyroid function tests (TFTs) are difficult tasks. In the United States, more than one-third of children undergoing treatment for CH discontinue treatment within 36 months, some without any medical advice [2]. In addition, the recent evidence suggests that exposure to excess thyroid hormone may be as harmful as hypothyroidism to long-term cognitive development [4, 5]. Therefore, reasonable, individualized, and easy-to-follow guidelines for early discontinuation are needed. Thus, it would be possible to try early discontinuation, especially when there is a high possibility that the patient is experiencing transient CH (TCH).
Several studies have investigated the predictors of TCH. Hypothyroidism is more common among preterm infants than among full-term infants, but a higher proportion of preterm infants with CH may have TCH than full-term infants [6]. The levothyroxine dose at discontinuation trial was also identified as a predictor for permanent CH (PCH) [7, 8]. Several studies proposed possible early discontinuation in some cases, such as those with low levothyroxine dose [9] or preterm infants [10]. However, these were retrospective studies involving a relatively small number of infants, so there is no consensus on the predictors of transient hypothyroidism.

In this study, we investigated the differences between transient and permanent CH groups. We also examined the clinical characteristics and results of infants who underwent a trial of early discontinuation; we tried to identify the predictors of TCH to identify which patients are good candidates to try early discontinuation.

**Methods**

**Subjects**

The subjects were Korean infants diagnosed with CH between January 2005 and December 2015 who started levothyroxine before 3 months of age. Only patients who underwent TFTs for more than 6 months after discontinuation of the treatment were included. Patients with thyroid aplasia/hypoplasia or ectopic thyroid were excluded.

We collected data regarding the patients’ basic demographics, including gestational age, birth weight, sex, age, and weight at each visit. We also collected data regarding the results of neonatal screening and TFTs, and levothyroxine dose.

Neonatal screening tests (NSTs) were performed 2–4 days after birth in full-term infants and within 7 days in preterm infants as per the protocol [11]. NSTs were repeated for all preterm infants or term infants with NST thyroid stimulating hormone (TSH) levels above the cutoff value. A TFT was performed if in the repeat NST, the level of the TSH was abnormal. All TFTs among preterm infants were performed at least 3 times at the ages of 7 days, 2–4 weeks, and prior to discharge from the neonatal intensive care unit. Follow-up tests in outpatient pediatric endocrinology clinics were performed as needed. TSH and free T4 (fT4) levels were measured in peripheral venous blood samples using Electrochemiluminescence immunoassay (ECLA) (Roche Diagnostics Ltd., Swiss) as per manufacturer’s protocol. Hypothyroidism was diagnosed if the fT4 level was below 0.9 ng/dl or if the TSH level was above the cutoff value (>20 µU/ml at any time or >10.0 µU/ml after 4 weeks of age).

Levothyroxine treatment was initiated after the diagnosis of hypothyroidism, at an initial dosage of 10–15 µg/kg/day. The levothyroxine dosage was adjusted according to the follow-up TFT results. Trial of discontinuation was performed between the ages of 2.5 and 3 years, but in some children early discontinuation was performed at the parent’s discretion. Follow-up TFTs were performed at 1, 6, and 12 months after discontinuation of levothyroxine. Normal TFT results for up to 12 months after
discontinuation of levothyroxine confirmed the diagnosis of TCH. Subjects who failed the levothyroxine discontinuation trial were diagnosed with PCH.

Statistical analysis

The statistical analyses were performed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). The results were expressed as mean and median values, and variability was indicated by the standard deviation and/or range. Continuous data were analyzed using the student's *t*-test or the Mann-Whitney *U* test, and categorical variables were analyzed using the $\chi^2$ test or Fisher's exact test.

We investigated multicollinearity using the variance inflation factor. The variance inflation factor was 1.299, which implied a lack of multicollinearity, so these data were adequate for logistic regression analysis. Thus, logistic regression was performed to identify the predictors of PCH.

To evaluate the optimum cutoff levels of predictors, we performed receiver operating characteristic (ROC) analyses with PCH as the dependent variable. Results with $P < 0.05$ were considered significant.

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**Discussion**

In this study, infants in the discontinuation success group received lower levothyroxine doses during the treatment period than subjects in the discontinuation failure group. Furthermore, the levothyroxine dose at discontinuation was significantly associated with discontinuation failure. A dose of 2.86 µg/kg at discontinuation was the optimal cutoff value that could predict discontinuation failure.

In a previous study conducted by Messina et al. [12] the prevalence of TCH was 36.5%; however, subjects with ectopic thyroid gland were also included in the study. Ghasemi et al. [13] reported that 79.4% of patients with primary CH had TCH, and the prevalence of TCH was 1 in 294 live births. In a study conducted by Eugster et al. [14], among 33 children with primary CH (including 9 with absent or ectopic thyroid), 12 (36%) had TCH. In previous Korean studies, the proportion of TCH among CH patients ranged from 39.4% to 65.0% [6, 7, 9, 15]. In our study, 89.7% of patients with CH were diagnosed with TCH. This high proportion is partially explained by the fact that our study excluded those with ectopic thyroid or thyroid aplasia. Another reason is that our study included a high proportion (63.8%) of preterm infants, among whom transient hypothyroidism is reportedly more common than among full-term infants [16, 17].

The levothyroxine dose required to maintain normal thyroid function is known to be lower in the TCH group than in the PCH group [12, 18, 19], and several studies suggested the use of levothyroxine dose during treatment or at discontinuation as a predictor of PCH. Rabbiosi et al. reported that daily T4 requirement
above 2 μg/kg was a predictor of PCH [8]. Similarly, Lee et al. reported that T4 requirement lower than 2.76 μg/kg/day could predict TCH [7]. In our study, the levothyroxine dose at the third year of treatment was a positive predictor of TCH diagnosis, with a cutoff value of 2.86 μg/kg, which was similar to that reported in previous studies.

It is controversial whether the laboratory finding can predict TCH. Some previous studies suggested that children with TCH had significantly lower initial TSH levels compared to those with PCH [7, 10, 18]. However, other studies have reported that the initial fT4 and TSH levels were not different between TCH and PCH cases [6, 8, 12]. In our study, abnormal TSH levels on NST were more common in the PCH group than in the TCH group, but initial TSH levels showed no difference.

Hypothyroidism is more common among preterm infants than among full-term infants [16, 17]. However, preterm infants with high TSH levels may have TCH rather than PCH, and early reevaluation can be particularly necessary for these patients [17]. In our study, there was no difference in the proportion of TCH patients between the term and preterm groups.

Few, if any, previous studies have followed up the results of early discontinuation trial. In a study conducted by Lim et al., 39 infants with very low birth weight discontinued L-T4 therapy at around 2 years of age, all of whom retained normal thyroid function without medication [10]. In our study, among 9 patients who tried to discontinue levothyroxine early (before 30 months of age), all except one successfully discontinued treatment. This result suggests that the majority of infants with CH may not require 3 years of levothyroxine treatment as per the current guidelines [12].

One of the strengths of our study is that it involved a relatively large number of infants, including both full-term and preterm infants. Another strength is that this was a single center study, including only those with eutopic thyroid glands, to minimize differences between the groups. And we compared the characteristics of PCH and TCH group in preterm infants, which has not been investigated. Also, we described the results of early discontinuation trial, though the number of patients was small.

The limitation of our study is that it was retrospective. It is possible that children in the early discontinuation group tried early discontinuation because their thyroid function was controlled successfully. However, there were no significant differences in levothyroxine dose or laboratory findings during treatment between the two groups. The TCH rate might have been underestimated because we included only those who took levothyroxine until 30 months of age. And the number of early discontinuation group is small, so we couldn’t draw success rate of early discontinuation or postulate predictive factor of early discontinuation success. Also, long-term follow-up of cognitive function and growth is necessary to compare long-term consequences between the groups. Nevertheless, our study provide useful data that support to try early discontinuation with low levothyroxine requirement, in both preterm and term infants.

**Conclusions**
We found that the majority of infants with CH, including those who underwent early trial of discontinuation, successfully discontinued levothyroxine. The levothyroxine dose at the time of discontinuation seems to be associated with permanent hypothyroidism. Early discontinuation with careful monitoring of thyroid function would be an option for those receiving low levothyroxine dose.

**Abbreviations**

CH: congenital hypothyroidism; PCH: permanent congenital hypothyroidism; TFTs: thyroid function tests; TCH: transient congenital hypothyroidism; NSTs: neonatal screening tests; TSH: thyroid stimulating hormone; FT4: free T4.

**Declarations**

- Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board of Gyeongsang National University Hospital (approval no. 2018–01–018). The need for informed consent was waived by the institutional review board due to the retrospective nature of the study, and that data were anonymized with randomly assigned case numbers.

- Consent for publication

Not applicable.

- Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

- Competing interests

The authors declare that they have no competing interests.

- Funding

None

- Authors’ contributions

Conceptualization and methodology: Park ES. Formal analysis, writing, original draft preparation: Yoon JY. Writing - review and editing: Park ES. Approval of final manuscript: all authors.

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Tables

Table 1. Demographic and auxologic characteristics of participants

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| Characteristic                  | All patients (n = 80) | Off trial success (n = 71) | Off trial failure (n = 9) | Early off trial (n = 9) | On-time off trial (n = 71) | P   |
|--------------------------------|----------------------|----------------------------|--------------------------|-------------------------|----------------------------|-----|
| Male, n (%)                   | 40 (50.0)            | 35 (49.3)                  | 5 (55.6)                 | 1                       | 35 (49.3)                  |     |
| GA (weeks)                    | 33.6±4.6             | 33.6±4.5                   | 34.0±5.8                 | 33.6±4.5                | 33.7±4.7                   | 0.95|
| Age (treatment initiation, weeks) | 3.4±3.1             | 3.2±2.3                    | 5.5±6.8                  | 3.0±2.5                 | 3.5±3.2                    | 0.687|
| Age (discontinuation trial, months) | 34.5±4.6         | 34.6±4.4                   | 33.9±5.9                 | 23.7±3.9                | 35.9±2.2                   | <0.001|
| Wt (at birth, kg)             | 2.1±0.9              | 2.0±0.9                    | 2.3±1.1                  | 2.1±0.8                 | 2.1±0.9                    | 0.956|
| Wt (at treatment initiation)  | 2.5±1.0              | 2.4±1.0                    | 3.1±1.3                  | 2.3±0.9                 | 2.5±1.0                    | 0.518|
| Wt (at discontinuation)       | 12.8±1.8             | 12.8±1.8                   | 13.4±1.8                 | 11.7±1.6                | 13.0±1.8                   | 0.047|

Abbreviations: Wt, weight; GA, gestational age

Quantitative data are expressed as the mean ± SD (standard deviation), and qualitative data are expressed as frequency (%)

*P < 0.05

**Table 2.** Laboratory findings and levothyroxine dose

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| Characteristic                  | All patients | Off trial failure | Off trial success | P     | Early off trial | On-time off trial | P     |
|--------------------------------|--------------|------------------|------------------|-------|-----------------|-------------------|-------|
|                                | (n = 80)     | (n = 9)           | (n = 71)         |       | (n = 9)         | (n = 71)          |       |
| NST                            |              |                  |                  |       |                 |                   |       |
| TSH (µU/ml)                    | 21.0±58.3    | 70.9±96.1        | 13.9±48.1        | 0.141 | 4.9±4.4         | 22.4±60.6         | 0.525 |
| T4 (µg/dl)                     | 6.8±3.2      | 7.6±4.1          | 6.7±3.2          | 0.557 | 7.3±1.9         | 6.7±3.4           | 0.674 |
| TSH >20 IU/L                   | 9 (13.8)     | 5 (62.5)         | 4 (7.0)          | 0.001* | 0               | 9 (15.3)          | 0.584 |
| T4 <5 µg/dl                    | 12 (21.8)    | 1 (20.0)         | 11 (22.0)        | 1     | 0               | 12 (24.0)         | 0.574 |
| Initial TSH (µU/ml)            | 31.7±32.0    | 49.5±31.7        | 29.4±31.7        | 0.075 | 17.5±12.2       | 33.5±33.3         | 0.009* |
| Initial fT4 (ng/dl)            | 1.2±0.4      | 1.0±0.4          | 1.2±0.4          | 0.437 | 1.3±0.2         | 1.1±0.4           | 0.162 |
| TSH >20 µU/ml                  | 39 (49.4)    | 5 (55.6)         | 34 (48.6)        | 0.737 | 5 (55.6)        | 34 (48.6)         | 0.737 |
| fT4 <0.9 ng/dl                 | 22 (30.1)    | 2 (40.0)         | 20 (29.4)        | 0.634 | 0 (0)           | 22 (34.4)         | 0.049* |
| TSH at off trial (µU/ml)        | 3.4±3.0      | 5.7±3.7          | 3.1±3.7          | 0.295 | 3.8±2.3         | 3.4±3.1           | 0.682 |
| fT4 at off trial (ng/dl)        | 1.5±0.2      | 1.5±0.2          | 1.5±0.2          | 0.796 | 1.4±0.2         | 1.5±0.2           | 0.138 |
| Initial T4 dose (µg/kg/day)     | 11.2±2.5     | 10.7±2.5         | 11.4±2.5         | 0.442 | 12.1±2.0        | 11.2±2.5          | 0.306 |
| T4 dose (1 year) (µg/kg/day)    | 3.7±1.4      | 4.3±1.4          | 2.5±1.4          | <0.001 | 3.3±1.7        | 3.7±1.3           | 0.419 |
| T4 dose (2 years) (µg/kg/day)   | 3.1±1.2      | 4.9±1.2          | 3.5±1.2          | 0.002 | 2.4±0.3         | 3.2±1.2           | 0.234 |
| T4 dose at off trial (µg/kg/day)| 2.8±1.2      | 4.3±1.2          | 2.9±1.2          | 0.001 | 2.5±0.7         | 2.8±1.2           | 0.44  |
| Off trial failure              | 9 (11.3)     | 9 (100%)         | 0 (0%)           | -     | 1 (11.1)        | 8 (11.3)          | 1.000 |

Abbreviations: Wt, weight; GA, gestational age; TSH, thyroid stimulating hormone; T4, thyroxine; fT4, free thyroxine; NST, neonatal screening test
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*P < 0.05

Table 3. Results of binary logistic regression analysis of factors associated with transient congenital hypothyroidism (n = 80, $R^2 = 0.258$)

| Variable                | $\beta$ | Standard error | Wald statistic | $P$   | Odds ratio |
|-------------------------|---------|----------------|----------------|-------|------------|
| Constant                | -5.884  | 1.769          | 11.058         | <0.001| 0.003      |
| T4 dose at off trial    | 1.028   | 0.483          | 4.522          | 0.033 | 2.795      |
| NST TSH >20 µU/ml       | 1.811   | 1.077          | 2.830          | 0.093 | 6.119      |

Abbreviations: NST, neonatal screening test; TSH, thyroid stimulating hormone; T4, thyroxine

Figures
Figure 1

Receiver operating characteristic curve of various thresholds of levothyroxine for predicting transient congenital hypothyroidism. A levothyroxine dose of 2.86 µg/kg at the off trial may lead to discontinuation failure with a sensitivity of 88.9% and specificity of 71.0%, and an area under the ROC curve of 0.849

Supplementary Files
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