Increase in doses of levothyroxine at the age of 3 years and above is useful for distinguishing transient and permanent congenital hypothyroidism

Hinako Yamamura1, Takahide Kokumai1, Akiko Furuya1, Shigeru Suzuki1, Yusuke Tanahashi1, and Hiroshi Azuma1
1Department of Pediatrics, Asahikawa Medical University, Hokkaido, Japan

Abstract. There are no recommended diagnostic criteria for transient congenital hypothyroidism (CH) during early childhood. In this study, we aimed to identify the factors that distinguish permanent (P)- and transient (T)-CH. We retrospectively analyzed the clinical, biochemical, and imaging data of 42 children with a definitive diagnosis of P- or T-CH by re-evaluation tests at our institution from November 1986 to October 2019. Patients who continued levothyroxine (L-T4) treatment after the re-evaluation tests were classified as group P (n = 19), while patients who were diagnosed with T-CH and discontinued L-T4 treatment were classified as group T (n = 23). Initial testing performed during infancy showed that the mean serum TSH and free T4 (FT4) levels did not differ significantly between groups P and T. None of the patients in group T required an increased dosage of L-T4 at the age of 3 yr and above while 85% of the patients in group P required increased dosages of L-T4. Hence, T-CH was suspected in patients who did not require an increase in L-T4 dosage at the age of 3 yr and above.

Key words: congenital hypothyroidism, transient congenital hypothyroidism, permanent congenital hypothyroidism, newborn screening, levothyroxine

Introduction

Congenital hypothyroidism (CH) can result in permanent intellectual disabilities and growth failure if left untreated. Infants with CH are usually detected using the newborn screening test (NBS) and levothyroxine (L-T4) treatments are recommended to be started immediately based on the levels of serum TSH and free T4 (FT4). Children with CH have thyroid hormone deficiency beyond the first year of life and need supplementation of L-T4 until at least 3 yr of age as the thyroid hormone is required for the myelination of the central nervous system. The re-evaluation tests, which can make a definite diagnosis of CH patients detected by NBS, should be carried out by withdrawing the L-T4 treatment (1).

The NBS for CH has revealed that the prevalence of infants with transient CH (T-CH) has been increasing (2). Although the etiology of T-CH, such as iodine deficiency, TSH stimulation blocking antibody (TSBAb), maternal or neonatal iodine exposure, maternal intake of anti-thyroid drugs (2), and genetic mutation of dual oxidase 2 (DUOX2) (3) are known, the causes of T-CH in the majority of patients are unknown. Additionally, it is difficult to predict the clinical course in such patients. There are no recommended diagnostic criteria and guidelines for the withdrawal of treatment for T-CH during early childhood.

Although previous studies have reported the cutoff values of thyroid function tests (TFTs) or L-T4 dosages at certain ages (4–12), the exact conclusion is still unclear. First, there is a significant overlap between permanent CH (P-CH) and T-CH (4–7, 9, 10). Second, in the majority of the studies, the definition of P-CH or T-CH was based on the condition of withdrawing treatment or morphological screening of thyroid glands (4, 6, 7, 10, 12) without re-evaluation tests. Consequently, in this study, we aimed to identify the factors that help to differentiate P-CH and T-CH earlier than re-evaluation tests by comparing the initial TFTs and the changes in L-T4 dosages in two groups that were rigorously diagnosed by re-evaluation tests.
Methods

We retrospectively analyzed the clinical, biochemical, and imaging data of children who were diagnosed with CH and underwent a re-evaluation test from November 1986 to October 2019 at Asahikawa Medical University. We screened a total of 77 patients who were detected through NBS and diagnosed with CH by venous TFTs (Fig. 1). We excluded patients with Pendred syndrome, congenital malformation such as VATER association, and chromosomal disorders such as trisomy 21.

The re-evaluation tests including TFTs, TRH stimulation tests, thyroid ultrasonography, $^{123}$I scintigraphy, thyroid gland iodine uptake ratio, salivary serum ratio of iodine, perchlorate discharge tests, and intelligence quotient (IQ) examinations were performed.

Out of 77 patients, 42 patients who underwent re-evaluation tests were studied (Fig. 1). Others (35 patients) were excluded for the following: the medical records were lacking because of no visit for over 5 yr (n = 3); cases where the patient was too young to undergo re-evaluation tests (1 mo–2 yr 7 mo of age) (n = 9); cases where the patient had failed or uncompleted a re-evaluation test because they had not been tried for ingestion of capsules of $^{123}$I (3 yr 6 mo–6 yr 0 mo of age) (n = 13); cases where the thyroid functions returned to normal without treatment or withdrawal of L-T$_4$ without re-evaluation tests (n = 9); and the diagnosis of mutation in the TSH receptor gene without a re-evaluation test (n = 1).

Patients with abnormal findings in re-evaluation tests and continued L-T$_4$ treatment were classified in group P as P-CH, while patients who had normal TFTs in the re-evaluation test and discontinued L-T$_4$ treatment were classified in group T as T-CH. We compared the data of the initial TFTs and changes in L-T$_4$ dosage during the treatment period in the two groups.

Serum TSH, FT3, and FT4 levels were measured by electro chemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Indianapolis, IN, USA) at our institution, Asahikawa Medical University. Of the patients who

![Diagram](https://via.placeholder.com/150)

Fig. 1. Patient population. A total of 42 patients underwent re-evaluation tests (20 boys). Of these, group P comprised 19 patients (8 boys) and group T (12 males) comprised 23 patients (12 boys).
underwent their initial TFTs at other hospitals, 30% of the cases was measured by ECLIA, 41% was measured by chemiluminescent immunoassay (CLIA) (Abbott, Abbott Park, IL, USA), and the measurement system or test was unknown in 29% of the cases. The reference TSH, FT3, and FT4 values for adults were 0.500–5.00 µIU/mL, 0.90–1.70 ng/dL, and 2.3–4.0 pg/mL in ECLIA, and 0.35–4.94 µIU/mL, 0.70–1.48 ng/dL, and 1.71–3.71 pg/mL in CLIA, respectively. We used the actual values noted in the medical records for assessment without using a correction coefficient. The TSH values at the initial diagnosis were set at 100 µIU/mL expeditiously when the upper limit of TSH measurement was 100 µIU/mL at a few hospitals where the patients were diagnosed and were started on L-T4 in the case of neonates.

There were no unified criteria for the increase of L-T4 dosages in all patients. Most patients have been monitored for thyroid function every 1–2 mo until the age of 1 yr and every 3 mo beyond the age of 1 yr. The L-T4 dosages had been increased by a median of 5 µg/d at one time of increasing by their attending physician in each hospital when their serum TSH levels had been more than 5 µIU/mL.

The nominal variables were described with frequencies and percentages and compared using Chi-square tests, when appropriate. The numerical data were expressed as mean± standard deviation or median, when appropriate. The comparisons between the two groups were performed by Student’s unpaired t-test (normally distributed data) or the Mann-Whitney U test (nonparametric data), as a result of the Kolmogorov-Smirnov test. The level of significance was set at P < 0.05. Statistical analyses were performed using the R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

The study design was approved by the Ethics Committee of Asahikawa Medical University (approval number: 18196).

**Results**

Table 1 shows the clinical characteristics of groups P and T. Out of 42 patients who underwent re-evaluation tests, it was observed that the number of patients (n = 23) was higher in group T than in group P (n = 19). Eighty-three percent of all patients were born in the period from 2000 to 2014. There were no significant differences in the sex ratio and frequencies of pre-term and low birth weight between groups P and T, respectively.

In group T, only one patient had maternal thyroid disease (chronic thyroiditis). It was observed that four patients in group T were suspected to be affected with excess iodine exposure (maternal intake of seaweeds or similar extracts or gargling with iodine-containing mouthwash) from their medical records; however, none of them received a definitive diagnosis as excess iodine exposure because they were not tested for urinary iodine in infancy and they required L-T4 treatment until the re-evaluation tests were conducted.

At the initial TFTs, there were no significant differences between groups P and T with respect to the values of serum TSH (122.6 ± 188.6 and 27.3 ± 22.5 µIU/mL), respectively.

### Table 1. Clinical characteristics of permanent (P)-CH group and transient (T)-CH group

|                      | Group P (n = 19) | Group T (n = 23) | P value |
|----------------------|-----------------|-----------------|---------|
| Sex (male/female)    | 8/11            | 12/11           | 0.516   |
| Gestational age (wk) | 39.0 ± 1.5      | 37.8 ± 2.8      | 0.099   |
| Pre-term (<37 wk)    | 1 (5%)          | 4 (17%)         | 0.255   |
| Birth weight (g)     | 3,007 ± 578     | 2,778 ± 657     | 0.243   |
| Low birth weight (< 2,500 g) | 2 (11%) | 5 (22%) | 0.369   |
| Initial thyroid function test (TFTs) |  |  |  |
| Median age (days)    | 18.0            | 19.5            | 0.147   |
| Serum TSH (µIU/mL)   | 122.6 ± 188.6   | 27.3 ± 22.5     | 0.15    |
| Serum FT4 (ng/mL)    | 1.0 ± 0.4       | 1.2 ± 0.4       | 0.099   |
| Serum FT3 (µg/dL)    | 3.7 ± 1.0       | 3.8 ± 0.8       | 0.881   |
| Initial L-T4 dosage (µg/kg/d) | 8.3 ± 2.8 | 6.3 ± 2.7 | 0.127   |
| Last L-T4 dosage before re-evaluation test (µg/kg/d) | 2.9 ± 1.2 | 1.6 ± 0.6 | < 0.001 * |

**Re-evaluation test**

|                      | Group P (n = 19) | Group T (n = 23) | P value |
|----------------------|-----------------|-----------------|---------|
| Median age of tests (yr) | 5.9             | 5.8             | 0.571   |
| Body height (SD)      | −0.1 ± 1.0      | +0.0 ± 1.0      | 0.746   |
| Obesity index (%)     | +6.4 ± 16.4     | +3.0 ± 11.1     | 0.471   |
| IQ                   | 93.9 ± 11.2     | 99.5 ± 12.4     | 0.217   |
| Base of serum TSH (µIU/mL) | 45.5 ± 43.9 | 3.2 ± 1.3 | < 0.001 * |
| Serum FT4 (ng/mL)     | 0.8 ± 0.5       | 1.3 ± 0.2       | < 0.001 * |
| Serum FT3 (µg/dL)     | 2.9 ± 1.5       | 4.0 ± 0.6       | 0.008   |
| Peak of serum TSH (µIU/mL) (TRH stimulation test) | 106.9 ± 68.2 | 23.2 ± 8.5 | < 0.001 * |

* p value < 0.05.
μIU/mL, p = 0.150), FT4 (1.0 ± 0.4 and 1.2 ± 0.4 ng/dL, p = 0.099), and FT3 (3.7 ± 1.0 and 3.8 ± 0.8 pg/mL, p = 0.881), respectively.

The initial dosages of L-T4 did not differ significantly between groups P and T, respectively (8.3 ± 2.8 µg/kg/d [group P], 6.3 ± 2.7 µg/kg/d [group T], p = 0.127). However, the final dosages before the re-evaluation tests of group T were significantly lower than those of group P (2.9 ± 1.2 µg/kg/d [group P], 1.6 ± 0.6 µg/kg/d [group T], p < 0.001).

The median ages at the re-evaluation tests of groups P and T were 5.9 and 5.8 yr, respectively (p = 0.571). In group P, there were nine patients with thyroid dysgenesis (six patients with agenesis/hypogenesis and three patients with ectopic thyroid) and 10 patients with thyroid dyshormonogenesis (3 patients with iodide organification defects). Seven patients of dyshormonogenesis were diagnosed with subclinical CH based on high serum TSH, normal serum FT4, and excessive response in the TRH stimulation test; however, no abnormal findings in other examinations were noted. There were no significant differences in the initial and final dosages of L-T4 between patients with dysgenesis and with dyshormonogenesis (8.3 ± 3.3 vs. 8.1 ± 2.4 µg/kg/d, p = 0.650, and 3.3 ± 1.1 vs. 2.6 ± 1.5 µg/kg/d, p = 0.281, respectively) in group P. In group T, three patients were diagnosed with an iodide organification defect using the perchlorate discharge test. There were no significant differences in the body height, obesity index, and IQ during the re-evaluation test between groups P and T. The TFTs and the peak TSH in the TRH stimulation test at re-evaluation differed significantly between groups P and T.

Table 2 shows the changes in the L-T4 dosages during the treatment period. The records of L-T4 dose increments of three patients were not available in each group. No increase in L-T4 dosages during the whole treatment period was observed in 10 patients (50%) in group T, while observed only in one patient (6%) in group P. There was a significant association between requiring increased L-T4 dosages and being in group P (Chi-square tests, p = 0.005). At the age of 3 yr and above, 11 patients in group P (85%) required increasing dosages of L-T4, while none in group T required increasing dosages. When increasing the L-T4 dosage over the age of 3 yr was set as a predictive factor between groups P and T, the sensitivity and specificity were 85% and 100%, respectively.

We compared the time period from the last L-T4 increase before the age of 3 yr to the next increase between group P (12 patients) and group T (9 patients) whose records regarding the dosages of L-T4 had been available completely (Fig. 2). Six patients in group P required an increase before 4 yr of age again (cases P7–P12). One patient (case P6) needed only a single instance of increase after 3 yr of age. As a result, 58% of group P required an increase between 3 yr 0 mo and 4 yr 0 mo of age. Four cases of group P (cases P1–4) did not require an increase in L-T4 dosages between 3 yr 0 mo and 4 yr 0 mo of age and required increases from 4 yr 8 mo to 5 yr 3 mo. One patient (case P5) required an increase in L-T4 at 1 year 8 mo of age and had not been increased since then. In patients who required an increase in the L-T4 dosages at any age before re-evaluation tests, the mean of dosages at the age of 3 yr were 58.8 µg/d (3.9 µg/kg/d) in group P and 30.0 µg/d (2.2 µg/kg/d) in group T, respectively. When the cutoff value of L-T4 dosage at 3 yr of age was set at 45 µg/d, the sensitivity and specificity of discriminating between P-CH and T-CH were 100% and 91.7%, respectively. Additionally, upon considering the cutoff value of L-T4 dosage per kilogram body weight at 3 yr of age as 3.4 µg/kg/d, the sensitivity and specificity were 100% and 75.0%, respectively. However, there was a lack of data about body weight in the cases T6, T8, P3–4, and P11–12.

One patient required no increase in the L-T4 dosage during the whole treatment period in group P. The thyroid function of this patient had been stable with 35 µg/d of L-T4 ever since the beginning of the supplementation. In the re-evaluation test, she was diagnosed with permanent CH (subclinical CH) due to high serum TSH (7.35 µIU/mL) and a heightened response in the TRH stimulation test (peak TSH was 44.7 µIU/mL), while no imaging test or organification defect findings were observed.

### Table 2. Increase in L-T4 dosages during treatment

| Age          | Whole period | Required increase | No increase | Lack of data |
|--------------|--------------|------------------|-------------|--------------|
| Group P (n=19) | 15           |                  | 1           | 3            |
| Group T (n=23) | 10           |                  | 10          | 3            |

### Table 2. Increase in L-T4 dosages during treatment

| Age          | Whole period | Required increase | No increase | Lack of data |
|--------------|--------------|------------------|-------------|--------------|
| Group P (n=15) | 0            |                  | 1           | 3            |
| Group T (n=10) | 4            |                  | 3           | 1            |
In this study, we analyzed the data of patients who were diagnosed with CH by re-evaluation tests to identify the factors that aid in the distinguishing of P-CH and T-CH. There was a significant association between requiring increased L-T4 dosages at the age of 3 yr and above and being P-CH. In contrast, it was difficult to predict T-CH by the results of the initial TFTs or the initial dosages of L-T4.

There are inconsistent results regarding whether the initial TFTs can predict P-CH or T-CH (4–8). Cho et al. set the cutoff of serum TSH at initial TFTs as 28.4 µIU/mL to diagnose T-CH with eutopic thyroid gland (6). In contrast, others reported that there was no significant difference between P-CH and T-CH in the initial TFTs (8). In this study, although group T had lower serum TSH and higher serum FT4 levels in the initial TFTs than group P, there were some overlaps between the two groups. Therefore, there are no clear diagnostic criteria for using the initial TFTs.

With reference to the prediction of T-CH by increasing L-T4 dosages, Messina et al. reported that none of the individuals with T-CH had required any increase in the L-T4 dosages over time, whereas 89% of the individuals with P-CH needed some dose increase during the same period (9). However, they did not refer to the details of the L-T4 dosage changes. In contrast, we demonstrated the changes in the L-T4 dosages and the age at which increasing doses were required. Notably, half of the patients in group T required no increase throughout the observation period and the others had no increase at the age of 3 yr and above. The present study revealed that increasing L-T4 dosages over the age of 3 yr is a simple and efficient indicator that can distinguish between P-CH and T-CH with the sensitivity and specificity of 85% and 100%, respectively.

However, this indicator has some limitations in the clinical setting. First, one patient (Fig. 2 case P5) was overlooked because the age of the last increment of L-T4 dosage was below 3 yr of age. Second, we may have to observe patients above the age of 3 yr because

---

**Fig. 2.** L-T4 dosages of patients who required increases until re-evaluation tests. The number in parenthesis on the right of the cases (T1–P12) represents the L-T4 dosages at 3 yr of age (µg/d). After the age of 3 yr, seven patients (cases P6–12) in group P (58%) required an increase before 4 yr of age, while no patients of group T required an increase. Four patients (cases P1–4) needed no increase until 4–5 yr of age after the age of 3 yr. One patient (case P5) required an increase in the dosage at 1 yr 8 mo of age and continued with that dose until the age of the re-evaluation test.
four patients (cases P1–P4) required an increment in the L-T₄ dosage after 4 yr of age. To overcome this problem, it may be useful to consider the dosage of L-T₄ itself. When we set the cutoff of L-T₄ dosage at 3 yr of age at 45 µg/d in our patients, the sensitivity and specificity to distinguish between P-CH and T-CH were 100% and 91.7%, respectively. With respect to the cases of P1–5 as above, the dosages at the age of 3 yr were 45–90 µg/d and these patients with P-CH were suspected to be distinguished by dosages of L-T₄.

Recent studies have also demonstrated the cutoff of L-T₄ dosages with P-CH and T-CH (6, 9, 11, 12). In Japanese patients, Higuchi et al. showed the cutoff of L-T₄ dosages suspicious of T-CH as 2.4 µg/kg/d at the age of 1 yr and 1.3 µg/kg/d at the age of 3 yr (11). Itonaga et al. detected that an L-T₄ dosage above 4.7 µg/kg/d and below 1.8 µg/kg/d at age of 1 yr helps the prediction of P-CH and T-CH, respectively (12). Consequently, the combination of an increasing L-T₄ dosage and the dose of L-T₄ should be considered to predict the presence of P-CH or T-CH. We also detected the mean of L-T₄ dosages suspicious of T-CH in our patients, the sensitivity and specificity are often normalized after infancy or during the school age period (13). The patients with DUOX2 mutations show iodide organification defects during infancy but present negative findings in the perchlorate discharge test after infancy (14). Consequently, we speculate that the present case in group P who required no increase in the L-T₄ dosage during the observation period may progress toward normal thyroid function, similar to T-CH patients with DUOX2 mutations.

All the patients included in group T exhibited no morphological defects in the thyroid gland. This indicates that it is unnecessary to perform invasive examinations of re-evaluation tests except ultrasonography for the screening of morphological abnormalities when the patient required no increase in the L-T₄ dosages at the age of 3 yr and above. It is beneficial for patients with CH who withdraw the L-T₄ supplementation in their early childhood to reduce ambulant visits and to alleviate burden-associated examinations or treatment.

Conclusions

We analyzed the clinical data of children with CH who were definitively diagnosed by re-evaluation tests. We found that the increase in the dose of L-T₄ at the age of 3 yr and above is a useful indicator to discriminate between P-CH and T-CH at earlier ages before the re-evaluation tests.

Conflict of interests: The authors have none to declare.

References

1. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, et al. ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAE Congenital Hypothyroidism Consensus Conference Group. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab 2014;99:363–44. [Medline] [CrossRef]
2. Kanike N, Davis A, Shekhawat PS. Transient hypothyroidism in the newborn: to treat or not to treat. Transl Pediatr 2017;6:349–58. [Medline] [CrossRef]
3. Maruo Y, Takahashi H, Soeda I, Nishikura N, Matsui K, Ota Y, et al. Transient congenital hypothyroidism caused by biallelic mutations of the dual oxidase 2 gene in Japanese patients detected by a neonatal screening program. J Clin Endocrinol Metab 2008;93:4261–7. [Medline] [CrossRef]
4. Kara C, Günindii F, Can Yilmaz G, Aydin M. Transient congenital hypothyroidism in Turkey: an analysis on frequency and natural course. J Clin Res Pediatr Endocrinol 2016;8:170–9. [Medline] [CrossRef]
5. Nair PS, Sobhakumar S, Kailas L. Diagnostic re-evaluation of children with congenital hypothyroidism. Indian Pediatr 2010;47:757–60. [Medline] [CrossRef]
6. Cho MS, Cho GS, Park SH, Jung MH, Suh BK, Koh DG. Earlier re-evaluation may be possible in pediatric patients with eutopic congenital hypothyroidism requiring lower L-thyroxine doses. Ann Pediatr Endocrinol Metab 2014;19:141–5. [Medline] [CrossRef]
14. The Japanese Society for Pediatric Endocrinology (JSPE). Pediatric Endocrinology (2nd Edition). Tokyo: SHINDAN TO CHIRYO SHA, Inc; 2016. p. 432–33 (in Japanese).