

# Prediction of permanent and transient congenital hypothyroidism based on levothyroxine dosages in long-term follow-up patients: a multicenter retrospective study in Japan

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### Introduction

- Congenital hypothyroidism (CH) can be permanent (P-CH) or transient (T-CH). These two CH types are difficult to differentiate prior to treatment initiation. However, previous studies have reported significant differences in the levothyroxine (LT4) dosages for 3-yr-old children with P-CH vs. T-CH (1-7), and seven studies have also identified LT4 dosage cutoff values for differentiating between P-CH and T-CH in 3-yr-old children (1-7).
- Several recent studies in which the oldest patients at the last observation were aged 6 years reported that LT4 dosage was a useful predictor of the duration of hypothyroidism. We also reported in their single-center study that when the LT4 dosage was <2.4 and <1.3 µg/kg/day at ages 1 and 3 years, respectively, T-CH should be suspected (7). However, the thyroid hormone requirement increases during puberty, with some patients with CH requiring an increase in their LT4 dosage during this period.
- In the present study, we retrospectively analyzed CH cases which were observed from the neonatal period past adolescence with the aim of identifying the LT4 dosage cutoff for predicting either P-CH or T-CH.

### Patients and Methods

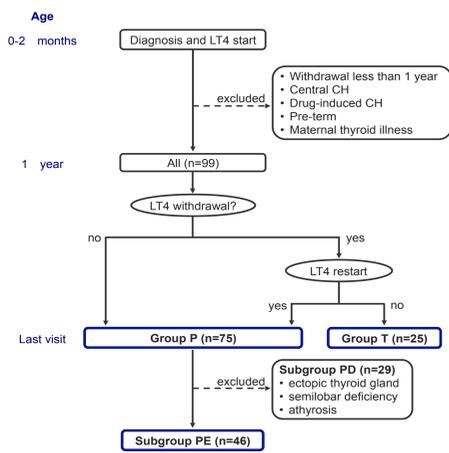


Fig.1. Study flow

- The LT4 dosage and clinical data on 99 patients with CH who were followed at the participating hospitals from the neonatal period to 15 years of age or older were retrospectively analyzed. The participants were divided into the P-CH group ( $n = 75$ ), who were treated with LT4, and the T-CH group ( $n = 24$ ), who were not.

Table 1. Patterns of analysis

<b>Main analysis</b>
-All group P vs. group T
-Group PE vs. group T
<b>Subanalysis</b>
-Group P vs. group T, with patients with a TSH level either below the lower detection limit of the TSH assay or above 10 µIU/mL excluded from group T
-Group P, excluding patients with LT4 <50 µg/day at the last visit, vs. group T
-Group P vs. group T, with 18 patients reported by Higuchi and Hasegawa added to group T

- Group P was further divided into 2 subgroups, a permanent-dysgenesis (PD) and permanent-eutopic (PE) group. In further subanalysis, 2 groups of patients were excluded: patients with a TSH level either below the lower detection limit of the TSH assay or above 10 µIU/mL, and P-CH patients with LT4 <50 µg/day at the last visit (>age 15 years). Another subanalysis added 18 patients with T-CH previously reported by Higuchi and Hasegawa (7) to the 24 patients in group T in the present study.

### Conclusion

- LT4 dosage for CH treatment may be able to predict the permanent and temporary forms of the disease. An LT4 dosage exceeding 4.7 µg/kg/day and below 1.8 µg/kg/day at age 1 year may help predict P-CH and T-CH, respectively.

### References

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### Results

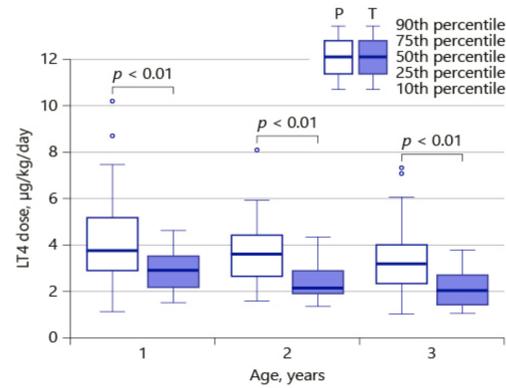


Fig. 2. LT4 dose (µg/kg/day) at ages 1, 2, and 3 years.

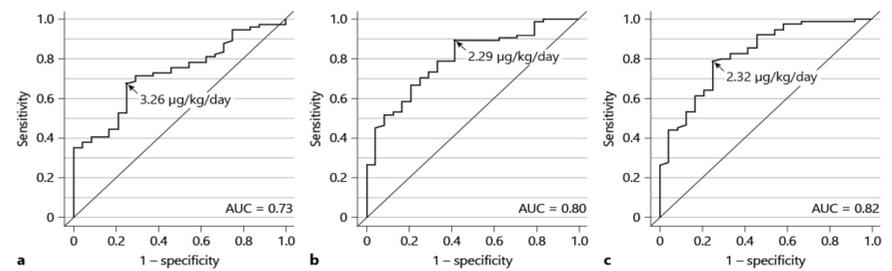


Fig. 3. ROC curves for LT4 dosage at ages 1 (a), 2 (b), and 3 (c) years.

Table 2. Clinical characteristics of the study cohort

	Group P PD (n = 29)	PE (n = 46)	Group T (n = 24)	p value (P-CH vs. T-CH)
Female sex, n (%)	24 (83)	27 (59)*	14 (58)	0.54
Mean gestational age (range), weeks	39.9 (36-42)	39.4 (34-42)	39.2 (35-41)	0.36
Median birth weight (IQR), kg	3.03 (±0.46)	3.09 (0.45)	2.87 (0.49)	0.08
<b>At diagnosis</b>				
Median serum TSH (IQR), µIU/mL	293 (103-566)	27.9 (13.7-88.6)*	25.7 (14.9-59.2)	0.04
Median serum fT4 (IQR), ng/dL	0.60 (0.22-0.77)	1.20 (0.91-1.40)*	1.00 (0.64-1.20)	0.74
LT4 dose at start (mean ± SD), µg/kg/day	10.2±2.07	8.26±3.34*	6.31±3.62**	<0.01
Age at LT4 cessation (range), years	15.5-27.0	15.0-28.0	6.5 (2.2-18.0)	<0.01
Age range at last visit, years	15.5-27.0	15.0-28.0	14.8-22.1**	<0.01
Gene mutation, n	9	13	8	
TPO, n	0	1	0	
TSHR, n	0	2	1	

\*  $p < 0.05$  for group PD; \*\*  $p < 0.05$  for group PE. PD, permanent-dysgenesis subgroup; PE, permanent-eutopic subgroup.

### Discussion

- This study demonstrated that the LT4 dosage at ages 1 and 2 years predicted whether LT4 treatment of CH patients would be permanent or transient. The LT4 dosage at ages 1 and 2 years may help differentiate P-CH from T-CH. To the best of our knowledge, this study is the first to focus on the final prognosis of CH patients who were followed from the neonatal period past adolescence.
- Messina examined only patients with a eutopic thyroid gland whereas our study cohort originally included both patients with a eutopic thyroid gland (PE group) and other patients with hypothyroidism (PD group). It is worth noting that our analysis using only PE and T-CH patients yielded similar results to those of Messina et al (1).
- One of the limitations of this study is its longitudinal and retrospective design, which may have omitted some T-CH patients. In order to settle this issue, further analysis was done (data not shown), but the results were essentially the same.

Table 3. Summary of the studies differentiating between P-CH and T-CH

Significant factors	Insignificant factors	P-CH or T-CH predictors	Composition	Reference
LT4 dosages at 1, 2, and 3 yr		LT4 dosage = 2.70 (1 and 2 yr) and 2.05 (3 yr) µg/kg/d	P-CH agenesis or ectopic (n = 61), eutopic (n = 18), T-CH (n = 46)	1
Initial TSH level, LT4 dosages at 1, 2, and 3 yr	Sex, birth wt, gestational age, age at treatment initiation, fT <sub>4</sub> and T <sub>3</sub> levels, initial LT4 dosage	LT4 dosage at 3 yr = 2.76 µg/kg/d	P-CH (n = 35), T-CH (n = 65)	2
Initial fT <sub>4</sub> and TSH levels, thyroid gland size or position, LT4 dosages by age 3 yr	Body wt, gestational age, sex	LT4 dosage at 90 d = 30 µg/d	P-CH (n = 161), T-CH (n = 159)	3
Initial TSH and T <sub>4</sub> levels, LT4 dosages at the initial visit and 1, 2, and 3 yr	Sex, birth wt, gestational age, age at treatment initiation	Initial TSH level = 30.5 IU/mL, LT4 dosage at 3 yr = 2.6 µg/kg/d	P-CH agenesis (n = 21), ectopic (n = 13), hypoplastic (n = 4), eutopic (n = 4), T-CH (n = 34)	4
LT4 dosage during the first 2 yr	Sex, age at diagnosis, body wt, maternal pregnancy history, birth parameters, perinatal history	LT4 dosage at 6 mo = 2.2 µg/kg/d	P-CH agenesis or ectopic (n = 58), eutopic (n = 67), T-CH (n = 17)	5
LT4 dosages at 6 and 12 mo, first-degree family members	Sex, ethnicity, neonatal problems, iodine status, initial CH severity, thyroid gland size or position	LT4 dosage = 3.2 (6 mo) and 2.5 (12 mo) µg/kg/d	P-CH hypoplastic (n = 3), eutopic (n = 35), T-CH (n = 45)	6
LT4 dosages at 1 and 3 yr	Sex, gestational age, age at diagnosis, body wt, initial TSH and fT <sub>4</sub> levels, thyroid gland size or position	LT4 dosage = 2.4 (1 yr) and 1.3 (3 yr) µg/kg/d	P-CH hypoplastic (n = 3), ectopic (n = 1), eutopic (n = 15), T-CH (n = 15)	7

fT<sub>4</sub>, free T<sub>4</sub>; LT4, levothyroxine; CH, congenital hypothyroidism; P-CH, permanent congenital hypothyroidism; T-CH, transient congenital hypothyroidism.