Clinical Pediatric Endocrinology

Vol.32 / No.4
October 2023
pp 200–205

Original Article

Utility of basal and peak TSH values in TRH stimulation testing for predicting the long-term therapeutic prognosis of primary congenital hypothyroidism

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Highlights

- This is the first report to examine TRH-T and the long-term prognosis of CH.
- The basal TSH value alone is sufficient for predicting the long-term prognosis.

Abstract. In Japan, most neonates undergo screening for congenital hypothyroidism (CH). A TRH stimulation test (TRH-T) may be performed after initial treatment as a useful method for reevaluating the patient's thyroid status. However, no studies have compared basal and peak TSH values in TRH-T in patients with long-term follow-up. This was a retrospective and observational study. The inclusion criteria were as follows: (1) CH diagnosis based on positive newborn screening, (2) follow-up > 15 yr, and (3) TRH-T after LT4 discontinuation. The participants were divided into a no-treatment group (No-T group) and a treatment group (T group). The No-T and T groups included 14 and nine patients, respectively. The age at TRH-T was 5.38 yr for the No-T group and 4.25 yr for the T group, with no significant difference. The basal and peak TSH levels were significantly lower in the No-T group. The areas under the Receiver operating characteristic curve for basal and peak TSH values were 0.984 and 0.905, respectively. When the basal TSH level was under 4.594 IU/mL, the No-T group had a sensitivity of 1.00 and a specificity of 0.93. Basal TSH levels alone may be sufficient for predicting the long-term therapeutic prognosis of patients with CH.

Key words: TRH stimulation test, congenital hypothyroidism, TSH

Received: March 16, 2023 Accepted: June 3, 2023 Advanced Epub: June 23, 2023

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Introduction

Congenital hypothyroidism (CH) is a general term for congenital thyroid hormone deficiency that occurs during the fetal or perinatal period. Neonatal CH screening has been performed in Japan since 1979 (1–4). The Japanese Society of Pediatric Endocrinology originally issued the "Guidelines for Newborn Screening of Congenital Hypothyroidism" in 1998 (5, 6), which were revised in 2014 and 2021 (1, 7). Currently, most neonates in Japan undergo CH screening and no patients with irreversible intellectual disability or growth retardation due to CH have been identified (3, 4). In Japan, the thyroid stimulating hormone (TSH) value is used for primary CH screening, and the free thyroxine (FT4) value is used in some regions. Although the FT4 value helps diagnose central CH, the present study only discusses primary CH.

CH treatment is performed with oral levothyroxine sodium (LT4), generally starting at approximately 5-15 μg/kg/d, depending on the disease severity (5, 8–10). Some patients with CH who receive continuous LT4 therapy after neonatal screening are considered to have permanent CH, in which thyroid hormone synthesis remains low beyond infancy, while others have transient CH, in which TSH is transiently high and FT4 is low in the neonatal period but later normalizes (5, 11–13). Therefore, LT4 is usually discontinued after 3 yr of age to determine whether patients have transient or permanent CH, unless CH is permanent, as in patients with thyroid agenesis (5, 8, 9).

TRH stimulation tests have undergone reevaluation in Japan and are now described in the guidelines, although the number of facilities performing these tests has been declining. According to the council of the Japanese Society of Pediatric Endocrinology, until 1990, the TRH stimulation test for CH was performed in 95% of facilities in Japan (18). However, with the advent of highly sensitive TSH assays in the 1990's, which can provide immediate information from a small amount of blood, TRH stimulation tests have become obsolete. Most facilities in the U.S. and Europe no longer use the TRH stimulation test, and the guidelines do not mention its clinical utility (9).

At our hospital, the TRH stimulation test is performed in patients with CH to reevaluate their thyroid status and determine whether further treatment is necessary. Prior to testing, LT4 was temporarily discontinued at approximately three years of age for at least four weeks if the LT4 dosage did not increase in the previous year and remained below 2 g/kg/d. A TRH injection of 300 μg/m^2 is then administered intravenously, and TSH is measured every 30 min using chemiluminescence enzyme immunoassay (CLEIA) (Lumipulse®, FUJIREBIO Inc., Tokyo, Japan) or electrochemiluminescence immunoassay (ECLIA) (cobas®, Roche Diagnostics K.K., Tokyo, Japan).

No previous studies have analyzed the TRH stimulation test results in terms of long-term CH prognosis. Therefore, we examined the results of TRH stimulation testing in patients with CH with long-term follow-up to determine whether basal and peak TSH levels could be used as criteria for long-term LT4 discontinuation.

Materials and Methods

Patients

This study included patients with CH followed up at our hospital as of April 2021 who met all the inclusion criteria and none of the exclusion criteria. The inclusion criteria were as follows: (1) CH diagnosis based on positive neonatal screening results with treatment starting within the first two months of life, (2) follow-up until age 15 yr or older, and (3) TRH stimulation test after discontinuation of therapy. The exclusion criteria were as follows: (1) presence of a syndrome known to affect thyroid function (e.g., Down syndrome) and (2) lack of consent to participate in the study.

Study design

The present study was a retrospective observational study based on patients' medical records. The following parameters were investigated: patient background (sex, date of birth, gestational week, birth weight, presence or absence of abnormalities in the neonatal mass screening test, family history of thyroid disease, and date of last visit), TRH stimulation test results (TSH values at 0, 30, 60, 90, and 120 min in the TRH stimulation test), medications (dose and duration of LT4 therapy, time of discontinuation, and current dosage), and presence or absence of side effects on the TRH stimulation test.

CLEIA was used to measure serum TSH, and some values obtained by ECLIA were converted using the following formula: {(CLEIA conversion value) = 0.761 × (value measured by the ECLIA method) + 0.002} (unpublished in-house data).

Methods

The participants were divided into a no-treatment (No-T group) and a treatment group (T group). The No-T group consisted of patients who had not received LT4 for more than one year at age 15 yr or older, while the T group consisted of patients who were unable to discontinue LT4 at age 15 yr or older. The primary endpoint was the difference in the peak TSH value in the TRH stimulation test between the groups. The secondary endpoint was the difference between the groups in the basal TSH value and TSH (peak TSH value – basal TSH value) on the TRH stimulation test and the cutoff values of the peak TSH value, basal TSH value, and the ΔTSH value separating the groups. Log-transformed values for each TSH value are shown.

doi: 10.1297/cpe.32.2023-0020

Statistical analysis

The results were expressed as the mean ± SD or the median and range. Comparisons between the two groups were performed using Student's t-test (for normally distributed data) or the Mann–Whitney U test (for nonparametric data), as appropriate. The frequency rates were compared using the chi-square test. The correlation between quantitative variables was assessed using Pearson's correlation analysis. Statistical significance was set at P = 0.05. Receiver operating characteristic (ROC) curve analysis was also used to establish the cutoff value for the TRH stimulation test results of the two groups.

All participants provided informed consent to participate in the study prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Tokyo Metropolitan Children's Medical Center (2021b-25, July 2, 2021).

Results

Patients' baseline data

Twenty-three patients were included in the study: 14 in the No-T group and nine in the T group. There were no differences in sex, age (days) at the first visit, age at TRH stimulation test, age at the last visit, LT4 dosage per body weight before TRH stimulation testing, or washout period of LT4 between the groups (**Table 1**). The age at TRH loading test was 5.38 yr for the No-T group and 4.25 yr for the T group, with no significant difference. In the No-T group, 12 patients remained off LT4 after TRH stimulation. Two patients resumed LT4 after the TRH stimulation test but later discontinued treatment (see below).

TSH values on the TRH stimulation test

All peak TSH values in the TRH stimulation test were obtained at the 30-min timepoint. The median (range) peak TSH value (μIU/mL) differed significantly between the groups at 19.318 (7.039–98.41) and 42.135 (26.140–476.0) in the No-T group and T group, respectively (**Fig. 1**). The median (range) basal TSH levels (IU/mL) also differed significantly at 2.870 (0.820–5.73) and 8.360 (4.594–190.0) in the No-T and T groups, respectively (**Fig. 2**). Similarly, the median (range) TSH values differed significantly between the groups at 17.518 (6.219–92.68) and 37.541 (17.78–286.0) (**Fig. 3**).

ROC curve analysis

The ROC curve analysis using peak TSH values showed an area under the curve (AUC) of 0.905 (95% CI: 0.777–1.000) (**Fig. 4**). The detection power was maximal

Table 1. Basic parameters of the No-T and T-groups

	No-T group (n = 14)	T group (n = 9)	P value
Sex (males)	4	2	0.75
Age (d) at first visit	22	21	0.95
Age (yr) at time of TRH loading test	5.38	4.25	1.00
Age (yr) at last visit	15.7	17.6	0.07
Levothyroxine sodium dosage pre-TRH loading test (μg)	1.39	2.04	0.18
Washout period of levothyroxine sodium (d)	38	47	0.80

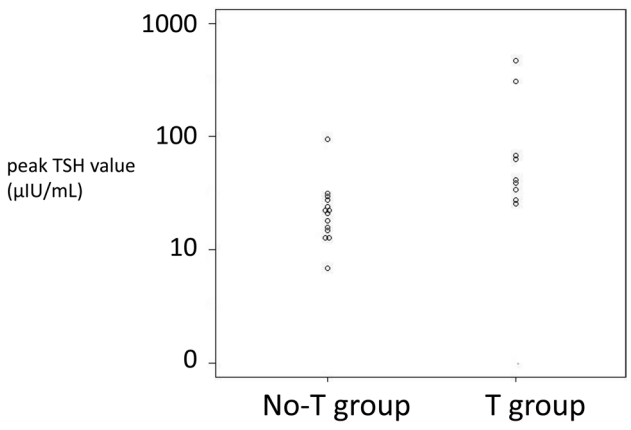

Fig. 1. Distribution of the peak TSH value (μIU/mL). The vertical axis is logarithmic.

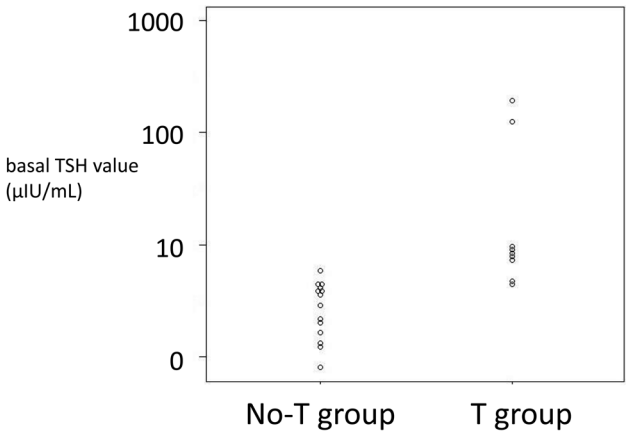

Fig. 2. Distribution of the basal TSH value (μIU/mL). The vertical axis is logarithmic.

doi: 10.1297/cpe.32.2023-0020

when the peak TSH value was 26.14 μIU/mL, and the No-T group was detected with a sensitivity of 1.00 and specificity of 0.79. ROC curve analysis using basal TSH level showed an AUC of 0.984 (95% CI: 0.947–1.000) (**Fig. 5**). The detection power was maximum when the TSH level was 4.594 IU/mL, and the No-T group was detected with a sensitivity of 1.00 and specificity of 0.93. Conversely, the point at which the T group was differentiated with a sensitivity of 1.00 was when the TSH value was 7.390 IU/mL, and the specificity was 0.78. ROC curve analysis using the ΔTSH value had an AUC of 0.849 (95% CI: 0.688–1.000) (**Fig. 6**). The detection power was maximal when the TSH level was 20.614, and the No-T group had a sensitivity of 0.89 and specificity of 0.71.

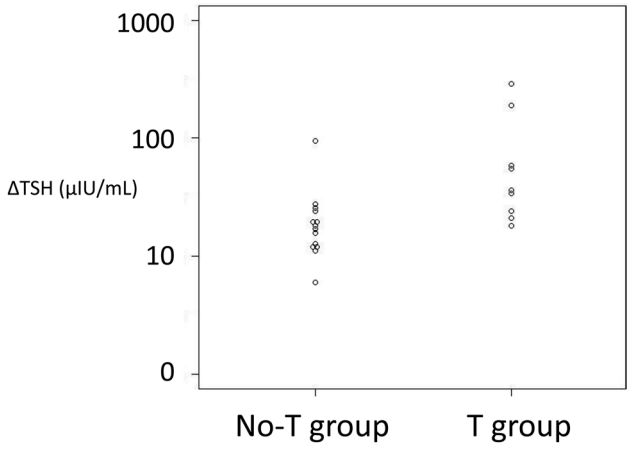

Fig. 3. Distribution of the ΔTSH value (μIU/mL). Of note is that the vertical axis is logarithmic.

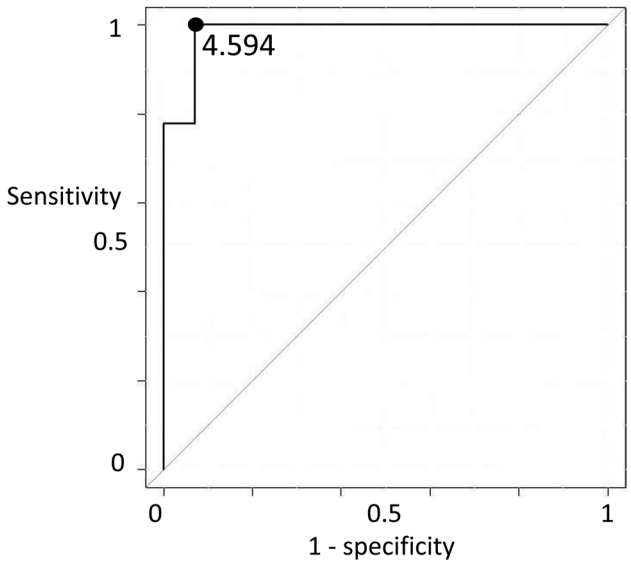

Fig. 5. ROC curve of the basal TSH value on the TRH stimulation test (● marks the point of maximal detection power).

An outlier in whom the basal and peak TSH values were not useful

One outlier patient in terms of basal TSH level was referred to our hospital because neonatal screening detected a TSH value of 29.3 μIU/mL. The patient was administered LT4 supplementation on day 52. The TRH stimulation test was performed at the age of 5 yr and 8 mo. Basal and peak TSH levels were 5.73 μIU/mL and 98.41 μIU/mL, respectively. Since the LT4 dosage was 0.44 μg/kg/d at age 15 yr, a TRH stimulation test was performed again after LT4 discontinuation and found the basal and peak TSH values to be 1.9 μIU/mL and

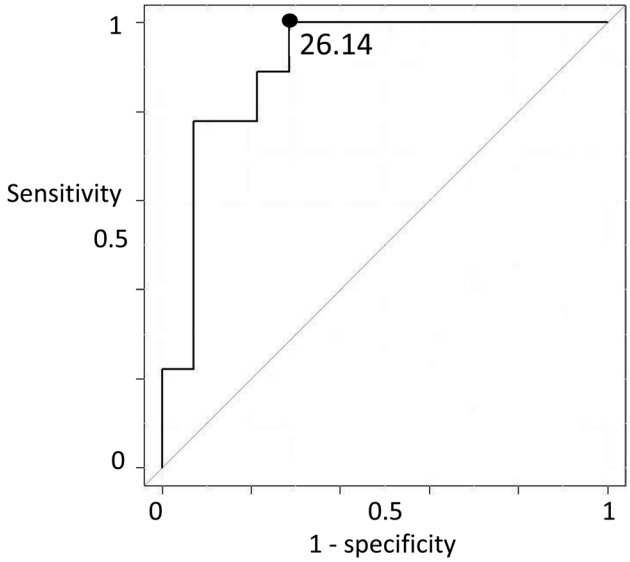

Fig. 4. ROC curve of the peak TSH value on the TRH stimulation test (● marks the point of maximal detection power).

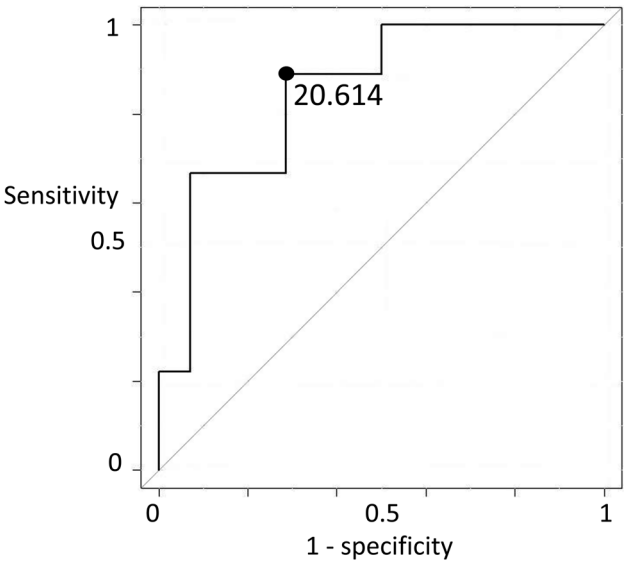

Fig. 6. ROC curve of the ΔTSH value on the TRH stimulation test (● marks the point of maximal detection power).

doi: 10.1297/cpe.32.2023-0020

29.938 μIU/mL, respectively. After this test, the patient did not receive LT4.

Two patients who discontinued LT4 after a resumption period

Two patients discontinued LT4 after having resumed treatment: Patient 1, discussed above and patient 2, who was referred to our hospital because neonatal screening detected a TSH value of 19.7 μIU/mL on a re-test and therefore began receiving LT4 supplementation from day 27. A TRH stimulation test was performed at the age of 5 yr and 3 mo, when her LT4 dosage was 20 g/d. Basal and peak TSH value were 3.60 μIU/mL and 20.50 μIU/mL, respectively. Three months after the TRH stimulation test, the TSH level increased to 4.9 μIU/mL, and LT4 was resumed at the discretion of the attending physician. At 10 yr of age, LT4 was discontinued again and no TRH stimulation test was performed. Because there was no TSH elevation thereafter, the patient remained off the treatment.

Discussion

The present study was the first to examine the results of TRH stimulation tests along with the long-term course of CH. The basal TSH, peak TSH, and TSH levels in patients with CH aged 15 yr who did not require treatment were significantly lower than those in patients who required treatment. The results of the ROC curve analysis showed that the basal TSH value had high sensitivity and specificity, suggesting that an evaluation of basal TSH in the outpatient setting is sufficiently predictive of the CH course and that a TRH stimulation test is not required.

One patient was an exception and had a high basal and peak TSH value but later discontinued LT4 therapy. The patient's TRH stimulation test findings at the age of 15 fell within the reference range for basal TSH values, and there was no need for further long-term resumption of treatment. This finding suggests that the patient's thyroid function may have improved over time. The *DOUX2* mutation is known to be the most frequent genetic abnormality underlying transient CH in the Japanese population; however, no genetic analysis was performed in this case.

The reference values for the TRH stimulation test in Japan are based on the thyroid function in normal children. A previous study using immunoradiometric assay (IRMA) of children with short stature and normal thyroid function found that the distribution of the basal and peak TSH values was 0.2–5.4 and 3.6–26.8 μIU/mL, respectively (14, 15). Another study using ECLIA for the TRH stimulation test reported that the 5–95th percentile of the TSH value in children with short stature and normal thyroid function was 0.8–4.2 μIU/mL for the basal value and 5.3–26.1 μIU/mL for the peak value (16). These reports indicate that TSH reaches its peak within 15–30 min, and that the peak TSH values fell within 10–35 μIU/mL (17). The validity of the criteria for the TRH stimulation test in children with CH with long-term follow-up remains unclear.

The number of facilities conducting TRH stimulation tests has been decreasing, making it difficult to conduct large-scale studies on the utility of TRH testing in predicting the long-term prognosis of patients with CH. Adverse effects of TRH stimulation include nausea, pulsation, and cardiac discomfort (19).

This study had some limitations. First, this was a single-center study with a small number of eligible patients. For the following conditions (AUC = 0.90, power = 0.90, significance level = 0.05, ratio of normal to abnormal = 1:1, one-sided test), the number of cases required for ROC curve analysis was seven cases each; we believe that our study exceeds that number and is therefore useful to some extent. Second, the criteria for the discontinuation of CH treatment were not strictly predetermined. However, all patients were followed up until 15 yr of age or older. Therefore, the need for treatment was verified. In contrast, dropout cases, if any, were not evaluated because the scope was limited to those with long-term follow-up.

Conclusion

Although the TRH stimulation test is useful for determining the need for long-term treatment of CH, the basal TSH level alone is sufficient for this purpose.

Conflict of interests: The authors declare no conflicts of interest.

Acknowledgments

We are grateful to James R. Valera for his assistance in editing this manuscript.

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 doi: 10.1297/cpe.32.2023-0020