



# Prediction of Transient or Permanent Congenital Hypothyroidism

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## ABSTRACT

**Aim:** Congenital hypothyroidism (CH) is one of the most common endocrinological problems in the neonatal period. CH, which occurs in 1:3,000-4,000 births, is a preventable cause of mental retardation. In the literature, the most common cause of CH is dysgenesis of the thyroid gland, followed by thyroid dysmorphogenesis. We aimed to determine the prevalence of permanent (P-CH) and transient (T-CH) CH in cases followed up with a diagnosis of CH and to identify a prediction method for persistency.

**Materials and Methods:** We retrospectively analyzed the medical records of 105 children with CH. TSH levels in a screening program, TSH and fT4 levels of the first venous sample, 10-15<sup>th</sup> day of treatment, monthly in the first 6 months, 2-3 monthly until 18<sup>th</sup> months, and 6-monthly until 3 years of age were recorded. L-T4 doses (per microgram per body weight) in each visit were also recorded.

**Results:** From the 105 children (58 males, 47 females) enrolled in this study, 38 (36.2 %) were referred from the National Newborn Screening Program. Treatment was discontinued during the 3<sup>rd</sup> year follow-up period in 44 (41.9 %) of the cases with normal thyroid gland morphology. L-thyroxine (L-T4) therapy was discontinued at a median age of 1.9+1.08 years. TSH levels at the time of diagnosis were higher in the P-CH group, but this difference was not statistically significant ( $p=0.165$ ).

At the sixth month, first and second years of follow-up, L-T4 doses were significantly higher in the P-CH than in the T-CH group ( $p<0.001$ ,  $p<0.001$ ,  $p<0.001$  respectively). TSH levels were also higher in the P-CH group than in the T-CH group ( $p=0.123$ ,  $p=0.038$ ,  $p=0.049$  respectively). Consistent with these results, measured fT4 levels were found to be lower in the P-CH group compared to the T-CH group ( $p=0.431$ ,  $p=0.361$ ,  $p=0.028$  respectively).

**Conclusion:** L-T4 doses at 6, 12 and 24 months may predict transient hypothyroidism in patients with normal thyroid gland morphology before 36 months.

**Keywords:** Congenital hypothyroidism, dysmorphogenesis, screening, thyroid dysgenesis, permanent hypothyroidism, transient hypothyroidism

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## Introduction

Congenital hypothyroidism (CH) is one of the most common endocrinological problems in the neonatal period. CH, which occurs in 1:3,000 to 4,000 live births, is a preventable cause of mental retardation. In a study from Turkey, its prevalence was 1/2,525 (1,2). CH is two times more common in girls than in boys and is classified into 2 types: permanent CH (P-CH) and transient CH (T-CH). P-CH requires life-long levo-thyroxine (L-T4) treatment whereas T-CH shows continuous, normal thyroid function after discontinuation of LT4 treatment. Although the distinction between P-CH and T-CH is clinically one of the most important concerns for the parents of affected children, differentiating between the 2 types in the neonatal period is difficult, and LT4 treatment should be prioritized to avoid mental retardation (3). The majority of P-CH cases were thyroid dysgenesis; followed by ectopic thyroid gland and aplasia/hypoplasia (4). Only 15% of P-CH cases were thyroid dysmorphogenesis (5). T-CH includes; iodine deficiency, excessive iodine exposure, thyroid stimulating hormone (TSH) receptor blocking antibodies transmitted from mother to fetus, and maternal usage of antithyroid drugs (2).

CH is one of the most important causes of preventable mental retardation and constitutes a serious public health problem. Many developed countries have largely eliminated intellectual disability caused by CH owing to newborn screening programs (NSPs) (1). In Turkey, the National NSP (NNSP) for CH (dried blood spot at 48-72 hours of life) was started on December 26, 2006 by the Turkish Directorate of Public Health. According to the NNSP, an infant is considered to have passed the screening test when the blood spot TSH is <5.5 mIU/L. Values between 5.5 mIU/L and 20 mIU/L, are reported for a second evaluation. All cases with a capillary TSH concentration above 5.5 mIU/L in repeat blood samples or above 20 mIU/L in the first sample are referred to the appropriate center for evaluation by venous thyroid function testing, including free thyroxine (fT4) and TSH.

In the present study, we retrospectively analyzed CH cases from the neonatal period up to three years of age in order to determine the prevalence of permanent and transient CH.

## Materials and Methods

### Study Population and Design

This retrospective design study included patients referred from the NNSP and patients diagnosed with CH

at Ege University Pediatric Endocrinology Clinic between January 1<sup>st</sup>, 2014 and December 31<sup>th</sup>, 2017. CH was diagnosed if TSH was >10  $\mu$ U/mL within the first month of life, with low/normal fT4 levels. Patients who were diagnosed in other hospitals, who had premature delivery history, whose first thyroid function tests were unknown, whose treatment was started in other hospitals or who were not followed up for three years for various reasons were excluded from this analysis. Cases with central hypothyroidism were not included in the study.

Demographic measures, auxological measurements, date of birth, admission age, postnatal age, gender, gestational age in weeks and maternal thyroid disease history were extracted from the systematically collected medical records. Other concomitant congenital diseases were recorded. All weight and height standard deviation (SD) score calculations were made by an automatic calculator (3).

TSH levels in a screening program, TSH and fT4 levels of the first venous sample, 10-15<sup>th</sup> day of treatment, monthly in the first 6 months, 2-3 monthly until 18<sup>th</sup> months, and 6-monthly until 3 years of age were recorded. L-T4 doses (per microgram per body weight) in each visit were also recorded. Four and six weeks after the treatment was discontinued, TFT and fT4 were re-evaluated. All serum fT4 and TSH concentrations were measured at least 4 hours after the last L-thyroxine administration.

Thyroid ultrasonography (USG) was performed in all patients. Thyroid glands with a volume less than 0.64 mL (10<sup>th</sup> percentile) were considered to be hypoplastic for the neonatal period, and those with a volume greater than 1.15 mL (95<sup>th</sup> percentile) were considered to be hyperplastic (4). Thyroid scintigraphy was performed in those patients whose thyroid gland could not be visualized by USG. According to thyroid imaging results; thyroid glands were classified as agenesis, hemiagenesis, ectopia, hypoplasia or normal.

Cases with normal thyroid appearance were accepted as thyroid dysmorphogenesis, and other cases were accepted as thyroid dysgenesis. In those patients with normal thyroid gland; discontinuation of treatment was tried at any time until the age of 3, and then having TSH <10 mIU/mL and normal fT4 level for at least 6 months were classified as transient hypothyroidism. Patients with thyroid dysgenesis and/or continued treatment at the end of the third year were classified as permanent hypothyroidism.

Those children who gave assent and whose parents gave signed consent were enrolled in the study. The study was approved by the Ege University Medical Ethics Committee with approval number: 20-12T/24.

### Laboratory Methods

Serum TSH and fT4 levels were measured by electrochemiluminescence immunoassay using Elecsys 2010 modular analytics E170 (Roche Diagnostics, Indianapolis, IN, USA). For cases between 6 days and 3 months; the normal range of TSH is 0.72-11.0  $\mu$ U/mL, and for fT4, it is 0.9-2.2 ng/dL. For older cases; TSH level were considered normal if between 0.27-4.2  $\mu$ U/mL, and fT4 level was considered normal if between 1.1-2.1 ng/dL.

### Statistical Analysis

Analysis was carried out using SPSS for windows 25.0, descriptive statistics are reported using mean  $\pm$  SD for normally distributed variables, and median for skewed data. Groups were compared by independent samples t-test for normally distributed variables and the Mann-Whitney U test for skewed data. Trends across time were analyzed using linear polynomial contrasts (ANOVA). A p-value <0.05 was considered statistically significant, no adjustment was made for multiplicity of statistical tests.

### Results

Out of 192 (101 females, 91 males) patients, 105 patients who met the study criteria were enrolled. Out of these 105 patients, 58 (55.2%) were male, and 47 (44.8%), were female. A history of maternal autoimmune thyroid disease was positive in 34 (32.4%) patients. Mean gestational age was 38.82 $\pm$ 1.42 weeks, and mean birth weight was 3,167 $\pm$ 551 gr. The mean age at diagnosis was 22.3 $\pm$ 21.9 days. The mean serum TSH level was 85.08 $\pm$ 65.60 (2.64-501)  $\mu$ U/mL, and the mean fT4 level was 0.96 $\pm$ 0.35 (0.14-1.67) ng/dL in all patients at admission. Mean screening capillary TSH was 66.30 $\pm$ 48.50  $\mu$ U/mL, first venous TSH was 90.87 $\pm$ 82.48 (7.4-498)  $\mu$ U/mL and first venous fT4 level was 0.87 $\pm$ 0.34 (0.23-1.67) ng/dL in those patients who were referred from the NNSP (n=38; 36.2 %). In the remaining 67 (63.8%) patients, venous TSH levels, obtained for various reasons, were high.

Thyroid USG was performed in all patients. Based on the findings of thyroid imaging, the morphology of the thyroid glands was classified as follows: 1 (0.9%) hemiagenesis, 3 (2.8%) hypoplasia and 94 (89.5%) of normal morphology (Table I). In 7 (6.6%) cases, the thyroid gland was not visualized in the normal location and thyroid scintigraphy

was performed. Four of these patients had sublingual ectopic thyroid gland and three of them had agenesis on thyroid scintigraphy.

Treatment was discontinued during the 3-year follow-up period in 44 (41.9%) cases with normal thyroid gland morphology. L-T4 therapy was discontinued at a median age of 1.9 $\pm$ 1.08 years. The mean serum TSH level was 3.04 $\pm$ 1.17  $\mu$ U/mL, and the mean fT4 level was 1.37 $\pm$ 0.30 ng/dL at the time of discontinuation. The last dose of L-T4 treatment used was 1.24 $\pm$ 0.45 mcg/kg/day.

At the time of diagnosis, fT4 levels were significantly higher in the T-CH group than in the P-CH group, including thyroid dysgenesis (p=0.037). TSH levels at the time of diagnosis were higher in the P-CH group than in the T-CH group, but this difference was not statistically significant (p=0.165). No significant difference was found between the auxological measurement of T-CH and P-CH patients. The laboratory and auxological measurements of the patients with permanent and transient CH at the time of diagnosed are summarized in Table II. In the P-CH group; TSH values measured in the early period (1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> months) were lower and fT4 values were higher. However, this difference was not statistically significant (Table III).

	<b>Appearance (n)</b>	<b>Rate (%)</b>
Normal thyroid gland morphology	94	89.5
Hypoplastic gland	3	2.8
Hemiagenesis of the gland	1	0.9
Not visualized in the normal location (ectopy/agenesis)	7	6.6

<b>Parameter</b>	<b>Permanent CH (n=61)</b>	<b>Transient CH (n=44)</b>	<b>p-value</b>
TSH levels (N: 0.27-4.2 mIU/mL)	97.11 $\pm$ 76.40	63.22 $\pm$ 50.84	0.165
fT4 levels (N: 1.1-2.1 ng/dL)	0.90 $\pm$ 0.35	1.04 $\pm$ 0.33	<b>0.03</b>
L-T4 dose at onset (mcg/kg/day)	8.68 $\pm$ 3.54	8.01 $\pm$ 3.22	0.322
Weight SDS	-0.45 $\pm$ 1.31	-0.57 $\pm$ 1.19	0.631
Height SDS	-0.46 $\pm$ 1.29	-0.46 $\pm$ 0.81	0.983

CH: Congenital hypothyroidism, TSH: Thyroid stimulating hormone, fT4: Free thyroxine, L-T4: Levo-thyroxine, SDS: Standard deviation score

At the sixth month follow-up, first year follow-up and second year follow-up, L-T4 doses were significantly higher, TSH levels were significantly higher, and serum fT4 levels were significantly lower in in the P-CH group than the T-CH group (Table IV). The LT4 dosage cut-off by receiver operating characteristic (ROC) curve analysis was 1.96 [with sensitivity at 73% and specificity at 82%, area under the curve (AUC)=0.82], 1.56 (with sensitivity at 73%, specificity at 73%, AUC=0.76), and 1.24 µg/kg/day [with sensitivity at 85%, specificity at 73%, AUC=0.84] at ages 1, 2, and 3 years, respectively. The ROC curve is shown in Figure 1.

In subgroup analysis, those cases with thyroid dysgenesis were excluded and the remaining cases were examined in 2 groups as either permanent or transient dyshormonogenesis. There was no significant difference in the TSH, fT4 levels and L-T4 doses at the time of diagnosis between these groups (p=0.424, p=0.069 and p=0.589 respectively) (Table V). At the six-month, one-year and two-year follow-up, L-T4 doses were higher in the permanent dyshormonogenesis group than in the transient dyshormonogenesis group (p=0.020, p=0.015, p=0.143 respectively) (Table VI).

Two cases (1.9%) were Down syndrome and both of these cases had dyshormonogenesis. Fifteen (14.2%) cases had a history of concomitant congenital disease. The most common congenital disease was congenital heart disease (46.6%) (Table VII). Two of the patients (13.3%) with concomitant congenital disease had thyroid dysgenesis, while the others had dyshormonogenesis.

**Table III.** First, 2<sup>nd</sup> and 3<sup>th</sup> month laboratory data of permanent and transient CH cases

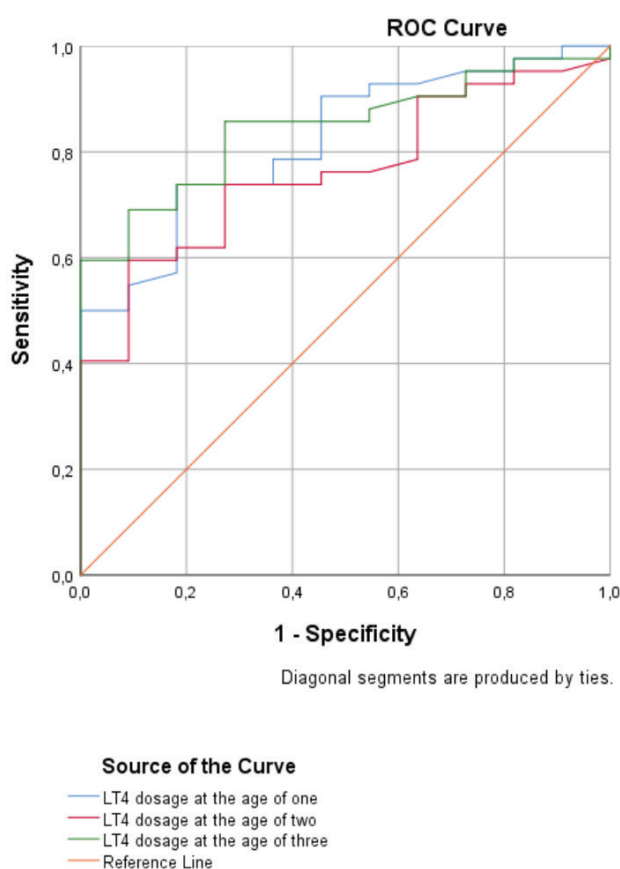
Parameter	Permanent CH (n=61)	Transient CH (n=44)	p-value
1 <sup>st</sup> month TSH levels (N: 0.27-4.2 mIU/mL)	3.75±2.77	2.00±1.63	0.529
1 <sup>st</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	1.70±0.51	1.66±0.45	0.731
2 <sup>nd</sup> month TSH Levels (N: 0.27-4.2 mIU/mL)	2.51±1.51	1.35±1.07	0.140
2 <sup>nd</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	1.56±0.35	1.51±0.29	0.544
3 <sup>th</sup> month TSH levels (N: 0.27-4.2 mIU/mL)	3.67±2.71	1.83±1.57	0.194
3 <sup>th</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	1.44±0.30	1.48±0.24	0.561

CH: Congenital hypothyroidism, TSH: Thyroid stimulating hormone, fT4: Free thyroxine

## Discussion

Our cross-sectional study is one of the most comprehensive retrospective analyzes performed on a national basis to evaluate the data of those cases with either transient or permanent hypothyroidism. Several authors have proposed numerous distinguishing factors between P-CH and T-CH; however, markers for the early detection of T-CH have yet to be validated (5-9).

In studies of CH, P-CH is more frequent than T-CH. In Hashemipour et al.'s (10) study, the prevalence of P-CH was 59.8%, while Scavone et al. (11) reported it to be 65.5%. In a study conducted in Turkey in which 189 cases were analyzed, the prevalence of P-CH was 53.2% (10), while in another study, it was 54 (5). Yanmaz et al. (12) showed a P-CH rate of 41.5%, and they thought that this low frequency may be due to the high consanguineous marriage rate in the study population region. In our study, the rate of permanent hypothyroidism was 58%, and this was similar to other studies in the literature.



**Figure 1.** ROC curve of LT4 dosages  
ROC: Receiver operator characteristic

Traditionally, it is known that 85% of CH is dysgenesis and 15% is dyshormonogenesis. In our study, thyroid dysgenesis was 18% of the permanent hypothyroidism, much lower than expected. Similar to our study, Kara et al. (13) reported this rate to be 61%, and Bezen et al. (14) reported it to be 56.5%. In similar studies in the literature, this rate was reported to be 50-85% (2,5,7,11). However, in a study by Donbaloğlu et al. (15), the rate of thyroid dysgenesis was 33.3%. In a multi-center study conducted

in China, 829 cases detected in CH screening were analyzed retrospectively; thyroid imaging was performed in 664 (80.1%) and thyroid dysgenesis was found in 194 (29.2%) cases (16).

In a study from Japan, 99 cases were analyzed for TSH level and L-T4 dose at the time of diagnosis. These parameters were higher in the P-CH group (17). In our study group, in accordance with this data in the literature, the fT4 level at the time of diagnosis was

**Table IV.** Follow-up and treatment data of the cases with permanent and transient congenital hypothyroidism

Parameter	Permanent CH (n=61)	Transient CH (n=44)	p-value
6 <sup>th</sup> month TSH levels (N: 0.27-4.2 mIU/mL)	5.91±3.62	1.97±0.97	0.123
6 <sup>th</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	1.52±0.70	1.64±0.76	0.431
6 <sup>th</sup> month L-T4 dose (mcg/kg/day)	2.74±1.02	1.98±0.94	<b>0.000</b>
6 <sup>th</sup> month weight SDS	-0.21±1.25	-0.01±0.94	0.430
6 <sup>th</sup> month height SDS	-0.23±1.28	-0.04±0.94	0.346
12 <sup>th</sup> month TSH Levels (N: 0.27-4.2 mIU/mL)	4.24±4.02	2.29±1.09	<b>0.038</b>
12 <sup>th</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	1.35±0.24	1.40±0.23	0.361
12 <sup>th</sup> month L-T4 dose (mcg/kg/day)	2.42±0.97	1.72±0.45	<b>0.000</b>
12 <sup>th</sup> month weight SDS	-0.23±1.17	-0.23±0.83	0.774
12 <sup>th</sup> month height SDS	-0.18±1.13	-0.12±1.02	0.794
24 <sup>th</sup> month TSH Levels (N: 0.27-4.2 mIU/mL)	4.29±4.27	2.71±1.26	0.490
24 <sup>th</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	1.41±0.21	1.30±0.21	<b>0.028</b>
24 <sup>th</sup> month L-T4 dose (mcg/kg/day)	2.24±1.28	1.50±0.39	<b>0.009</b>
24 <sup>th</sup> month weight SDS	-0.22±1.25	-0.09±1.26	0.289
24 <sup>th</sup> month height SDS	-0.52±1.20	-0.31±0.87	0.446

CH: Congenital hypothyroidism, TSH: Thyroid stimulating hormone, fT4: Free thyroxine, L-T4: Levo-thyroxine, SDS: Standard deviation score  
Significant p-values are shown in bold

**Table V.** Baseline characteristics of infants with permanent and transient dyshormonogenesis cases

Parameter	Permanent dyshormonogenesis cases (n=50)	Transient dyshormonogenesis cases (n=44)	p-value
TSH levels (N: 0.27-4.2 mIU/mL)	82.8±63.8	63.8±51.3	0.424
fT4 levels (N: 1.1-2.1 ng/dL)	0.92±0.35	1.04±0.33	0.069
L-T4 dose at onset (mcg/kg/day)	8.42±3.53	8.04±3.26	0.589
Weight SDS	-0.43±1.35	-0.62±1.17	0.472
Height SDS	-0.4±1.30	-0.45±0.82	0.676

TSH: Thyroid stimulating hormone, fT4: Free thyroxine, L-T4: Levo-thyroxine, SDS: Standard deviation score

**Table VI.** Follow-up and treatment data of the cases with permanent and transient dysmorphogenesis cases

	<b>Permanent dysmorphogenesis cases (n=50)</b>	<b>Transient dysmorphogenesis cases (n=44)</b>	<b>p-value</b>
Parameter	2.97±2.68	1.99±0.97	0.391
6 <sup>th</sup> month TSH levels (N: 0.27-4.2 mIU/mL)	1.54±0.77	1.65±0.76	0.506
6 <sup>th</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	2.70±1.05	2.00±0.95	<b>0.002</b>
6 <sup>th</sup> month L-T4 dose (mcg/kg/day)	<b>1.18±0.24</b>	<b>0.97±0.01</b>	0.559
6 <sup>th</sup> month weight SDS	-0.15±1.18	-0.01±0.94	0.447
6 <sup>th</sup> month height SDS	3.98±3.84	2.37±1.02	0.417
12 <sup>th</sup> month TSH levels (N: 0.27-4.2 mIU/mL)	1.32±0.20	1.40±0.23	0.112
12 <sup>th</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	2.29±0.88	1.74±0.45	<b>0.015</b>
12 <sup>th</sup> month L-T4 dose (mcg/kg/day)	<b>1.20±0.35</b>	<b>0.84±0.23</b>	0.586
12 <sup>th</sup> month weight SDS	-0.25±1.20	-0.17±0.99	0.751
12 <sup>th</sup> month height SDS	4.47±4.39	2.77±1.23	0.660
24 <sup>th</sup> month TSH levels (N: 0.27-4.2 mIU/mL)	1.42±0.22	1.31±0.21	<b>0.042</b>
24 <sup>th</sup> month fT4 levels (N: 1.1-2.1 ng/dL)	2.01±1.01	1.47±0.36	0.143
24 <sup>th</sup> month L-T4 dose (mcg/kg/day)	<b>1.17±0.19</b>	<b>1.28±0.10</b>	0.313
24 <sup>th</sup> month weight SDS	-0.48±1.07	-0.33±0.88	0.559

TSH: Thyroid stimulating hormone, fT4: Free thyroxine, L-T4: Levo-thyroxine, SDS: Standard deviation score  
Significant p-values are shown in bold

**Table VII.** Congenital anomalies accompanying congenital hypothyroidism

	<b>Number</b>	<b>Rate (%)</b>
Tetralogy of Fallot	2	13.3
Pulmonary stenosis	2	13.3
Aortic coarctation	1	6.6
Atrioventricular septal defect	1	6.6
Double outlet right ventricle	1	6.6
Cleft palate	1	6.6
Tracheoesophageal fistula	2	13.3
Duodenal atresia	1	6.6
Anal atresia	1	6.6
Horseshoe kidney	1	6.6
Posterior urethral valve	1	6.6
Meningomyelocele	1	6.6

significantly lower in the P-CH group compared to the T-CH group. However, the TSH levels and L-T4 doses were not statistically significant higher in the P-CH group as was seen in several other studies (6,18). Similarly, Tamam et al. (19) reported that TSH levels were significantly higher and fT4 levels were significantly lower at the time of diagnosis in the P-CH group than in the T-CH group. In another study, fT4 levels were lower in patients with P-CH in accordance with the etiology of the patients (12). In a study from Brazil, it was shown that initial TSH levels cannot be determinative in making a distinction between the transient and permanent disease types (20).

Itonaga et al. (17) reported that the dose of L-T4 used in the first and second years of follow-up was higher in the P-CH group. Furthermore, they showed that CH patients with an LT4 dosage >3.26 µg/kg/day at age 1 year, >2.29 µg/kg/day at age 2 years and >2.32 µg/kg/day at age 3 years were likely to have P-CH (17). In a study in Turkey, drug doses in the sixth month, first and second year were significantly higher in the P-CH group (12). In our study,



similar to the literature, LT4 doses at the sixth month, first and second year were significantly higher in the P-CH group. The cut-off values we obtained were similar to other studies (6,17). However, although those patients in the P-CH group used higher doses of medication, their first and second year TSH levels were higher than the T-CH group. This finding is not expected under appropriate treatment and we speculate that there may have been problems with treatment compliance.

### Study Limitations

Our study has some limitations such as its retrospective design, no free T3 levels, thyroglobulin and urine iodine levels and the lack of complete data regarding maternal drug intake and the use of iodine during delivery.

### Conclusion

Our cross-sectional retrospective study is one of the comprehensive analysis performed on a national basis to evaluate the data of cases with transient or permanent hypothyroidism. We are conscious that these results will not modify the current standard of practice but we believe that our data, supported by other studies, may allow for earlier discrimination between T-CH and P-CH. In conclusion, the results of this study show that fT4 levels at diagnosis and the L-thyroxine dose at the sixth month, first and second year can be used to distinguish between T-CH and P-CH.

### Ethics

**Ethics Committee Approval:** The study was approved by the Ege University Medical Ethics Committee with approval number: 20-12T/24.

**Informed Consent:** Those children who gave assent and whose parents gave signed consent were enrolled in the study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: F.E., Design: F.E., S.Ö., Data Collection or Processing: H.G.B., A.A., E.E., Analysis or Interpretation: H.G.B., A.A., E.E., Z.V., Literature Search: S.Ö., D.G., Project Administration: Ş.D., Writing: F.E., H.G.B., A.A., E.E., D.G.

**Conflict of Interest:** The authors declared no conflict of interest.

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