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Original Article

# Evaluation of the Clinical, Laboratory and Etiological Characteristics of the Patients with Congenital Hypothyroidism

## *Konjenital Hipotiroidi Tanılı Hastaların Klinik, Laboratuvar ve Etiyolojik Özelliklerinin Değerlendirilmesi*

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## ABSTRACT

**Objective:** In this study, we aimed to determine the frequency and etiology of transient and permanent congenital hypothyroidism (CH), and to investigate the role of laboratory data in predicting permanent and transient hypothyroidism.

**Method:** A total of 217 patients (111 girls, 106 boys) on L-thyroxine (LT4) therapy who were diagnosed with CH and followed up for at least 3 years were included in the study. The files of the patients were scanned retrospectively. Thyroid stimulating hormone (TSH), free thyroxine (fT4) levels, thyroid ultrasonography results and treatment doses were noted at the time of diagnosis and 4-6 weeks after treatment was discontinued.

**Results:** Permanent CH was found in 59%, and transient CH in 41% of the cases. The most common causes of permanent, and transient CH were dysgenesis (77.3%), and dyshormonogenesis or unexplained etiology (51.6%), respectively. TSH level at the time of diagnosis was found to be statistically significantly higher in the permanent group, while fT4 levels at the 3rd year were significantly higher in patients with transient CH (p<0.0001, and p=0.002, respectively). LT4 doses were significantly lower in the transient CH group (p<0.0001).

**Conclusion:** Most frequently permanent hypothyroidism due to dysgenesis was detected. It has been shown that high TSH levels at the time of diagnosis, low fT4 levels in the 3rd year of treatment, and LT4 doses at the time of treatment discontinuation are determinative factors in the differential diagnosis made between permanent and transient CH.

**Keywords:** Congenital hypothyroidism, permanent hypothyroidism, transient hypothyroidism

## ÖZ

**Amaç:** Bu çalışmada, konjenital hipotiroidi (KH) tanısıyla takip edilen olgularda geçici ve kalıcı hipotiroidi sıklığının saptanması, KH olgularında etiyolojinin belirlenmesi ve kalıcı-geçici hipotiroidiyi öngörmede laboratuvar verilerinin rolünün araştırılması amaçlanmıştır.

**Yöntem:** Çalışmaya KH tanısı konularak L-tiroksin tedavisi başlanmış ve en az 3 yıl takip edilen 217 hasta (111 kız, 106 erkek) alındı. Hastaların dosyaları geriye dönük olarak tarandı. Tanı anında ve tedavi kesildikten 4-6 hafta sonra bakılan tiroid stimülan hormon (TSH), serbest tiroksin (sT4), tiroid ultrasonografileri ve tedavi dozları not edildi.

**Bulgular:** Olguların %59'unda kalıcı KH, %41'inde ise geçici KH saptandı. Kalıcı hipotiroidilerin en sık sebebi disgenezi (%77,3) iken, geçici konjenital hipotiroidide en sık sebep dishormonogenezis veya açıklanamayan etiyoloji (%51,6) idi. Tanı anındaki TSH seviyesi kalıcı grupta istatiksel olarak anlamlı düzeyde yüksek saptanırken, 3. yıldaki sT4 seviyeleri geçici KH hastalarında anlamlı yüksekti (sırası ile p<0,001 p=0,002). L-tiroksin (LT4) dozları geçici KH grubunda anlamlı ölçüde daha düşüktü (p<0,001).

**Sonuç:** KH'nin en sık nedeninin disgenezise bağlı kalıcı hipotiroidi olduğu görülmüştür. Tanı anındaki yüksek TSH seviyelerinin, tedavinin 3. yılındaki sT4 düşüklüğünün ve tedavi kesimi sırasındaki LT4 dozlarının kalıcı ve geçici KH ayırımında belirleyici olduğu gösterilmiştir.

**Anahtar kelimeler:** Konjenital hipotiroidi, kalıcı hipotiroidi, geçici hipotiroidi

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## INTRODUCTION

Congenital hypothyroidism (CH) is characterized by thyroid hormone deficiency in newborns and is seen in one in 2,000-4,000 live births. CH, which is the most common endocrine problem of the neonatal period, causes permanent mental retardation if not treated in the early period [1,2]. When CH is evaluated in terms of its underlying cause(s) and disease duration, it is divided into two main subgroups as permanent and transient CH. Permanent CH occurs as a result of thyroid dysgenesis, which is a developmental defect of the thyroid gland, or dyshormonogenesis, which is a defective thyroid hormone production [3]. Transient CH is a condition characterized by the improvement of thyroid hormone deficiency over time and the normalization of thyroid hormone synthesis. The main causes of transient CH are iodine deficiency, prenatal-perinatal iodine overload, maternal thyroid stimulating hormone (TSH) receptor blocking antibodies that can cross the placenta, maternal or neonatal exposure to radioactive iodine or anti-thyroid drugs, and transient dyshormonogenesis [3-5]. Moreover, determining the etiology of CH is important for the duration of the treatment [6]. In permanent CH cases, the treatment is lifelong thyroid hormone replacement. Although treatment can be discontinued earlier in some cases of transient hypothyroidism, treatment of these patients up to 3 years of age and their evaluation at that age are recommended [7-9].

The aim of our study was to determine both the frequency of permanent and transient hypothyroidism in cases diagnosed with CH in our clinic, and the etiology in cases of permanent CH, and to investigate the role of laboratory data in predicting permanent and transient CH.

## MATERIALS and METHODS

Patients who were diagnosed with CH in the neonatal period, treated with L-thyroxine (LT4) and followed up regularly for at least three years in University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital were included in the study. Patients who started treatment in other centers, cases with unknown thyroid function test results at the time of diagnosis, and those who received the diagnosis of CH in our center but continued their treatment in another clinic were not included in our study. Patients that did not attend their follow-up visits for three years for various reasons, and cases that did not reach the age limit of 3 at the time of the study were also excluded. The files of the patients were reviewed retrospectively. The age at diagnosis, gender, gestational week, maternal thyroid disease status, findings at the time of diagnosis, iodine exposure, weight, height, weight and height deviation scores, free thyroxine (fT4), TSH levels, LT4 doses at the time of diagnosis, and at the third year of the treatment and 4-6 weeks after the treatment was discontinued, thyroid ultrasonography (USG) results were recorded retrospectively from their medical records. Patients diagnosed with permanent CH by thyroid USG and/or thyroid scintigraphy were classified as cases with thyroid agenesis, ectopic thyroid gland, and thyroid hypoplasia according to imaging results. Thyroid volumes were calculated and those found below 2 standard deviation score (SDS) were accepted as thyroid hypoplasia. Treatment of the cases was discontinued at the age of three, and serum thyroid hormones were measured 4 weeks after drug discontinuation and the cases with TSH values >10 mIU/L received the diagnosis of permanent hypothyroidism [10].

Approval of Scientific Research Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital was obtained (approval number: 639, date: 09.12.2021).

### Statistical Analysis

Analyses were performed using the Statistical Package for the Social Sciences 18.0 (SPSS). Fitness of quantitative variables to normal distribution was tested with the single-sample Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare data that were not normally distributed, and the chi-square test was used for intergroup comparisons of categorical data. Receiver operating characteristic analysis method was used to determine the threshold value of the LT4 dose at the time of treatment discontinuation as a predictive criterion for making a distinction between permanent and transient CH, and the sensitivity and specificity values were calculated for this threshold value. Descriptive statistics for the data were given as median (minimum-maximum) for non-normally and mean ± SDS for normally-distributed parameters. A p-value of $<0.05$ was considered as statistically significant.

## RESULTS

A total of 217 patients, 106 (48.8%) males and 111 (51.2%) females, were included in the study. The male/female ratio was 0.95. Transient CH was detected in 89 (41%) (35 girls, 54 boys), and permanent CH in 128 (59%) patients (76 girls, 52 boys). The mean ages of the patients at diagnosis

were 24.61±19.05 days in patients with transient CH and 24.02±22.82 days in patients with permanent CH. There was no statistically significant difference according to age between two groups (p=0.706). Clinical and laboratory findings of the patients with CH are shown in Table 1. Thyroid dysgenesis was detected in 99 (77.3%) of the patients with permanent CH. Among the patients with thyroid dysgenesis, thyroid agenesis was found in 28 (28.2%), thyroid hypoplasia in 63 (63.6%), and ectopic thyroid gland in 8 (8.08%) patients. In addition, among patients with transient CH, iodine exposure due to umbilical wound care was detected in 14.6% (9 female, 4 male; total 13 patients), isolated TSH elevation in 14.6% (7 female, 6 male; total 13 patients) history of maternal anti-thyroid medication in 10.1% (6 female, 3 male; total 9 patients), prematurity in 8.9% (2 female, 6 male; total 8 patients), dyshormonogenesis or unknown etiology in 51.6% of the cases. Two of the premature cases were born by normal vaginal delivery and the rest of the premature babies were born by cesarean section. Thyroid gland dimensions were within normal limits in all premature cases based on thyroid USG findings L-T4 dosage at diagnosis was 8.95±3.19 mcg/kg/day in patients with transient CH and 10.93±2.56 mcg/kg/day in patients with permanent CH. LT4 dosages used in 3-year-old (mcg/kg/day) patients with transient CH and permanent CH were 1.25±0.45; 2.76±0.93; respectively (p<0.001). Clinical and laboratory findings of patients with permanent and transient CH are shown in Table 2.

**Table 1. Clinical and laboratory findings of patients with congenital hypothyroidism**

| Clinical and laboratory findings | n=217 |
|---|---|
| Gender (n, %)<br>Female<br>Male | <br>111 (51.2%)<br>106 (48.8%) |
| Age at Diagnosis (days) | 24.6±21.3 |
| TSH (at diagnosis) (mIU/L) (n=0.51-4.30) | 86.9±32.8 |
| fT4 (at diagnosis) (ng/dL) (n=0.93-1.77) | 0.57±0.58 |
| LT4 dosage at diagnosis (mcg/kg/day) | 10.8±2.9 |
| TSH (at 3 years old) (mIU/L) (n=0.51-4.30) | 4.46±7.6 |
| fT4 (at 3 years old) (ng/dL) (n=0.93-1.77) | 1.32±0.4 |
| LT4 dosage at 3 years old (mcg/kg/day) | 2.64±1.07 |

TSH: Thyroid stimulating hormone, fT4: Free T4, LT4: L-thyroxine

A LT4 dose of 1.90 mcg/kg/day was found to be the best cut-off value as a predictive criterion for distinguishing between permanent and transient CH (89.1% sensitivity and 91.0% specificity) with a discriminative ability of 0.948±0.15 (95% confidence interval: 0.919-0.977, p<0.001).

## DISCUSSION

CH is the most common endocrine problem in the neonatal period, and early diagnosis and treatment are important in terms of preventing mental retardation and motor dysfunction. Moreover, differential diagnosis made between permanent and transient CH will prevent unnecessary treatment in patients with transient CH, and will avoid inadequate treatment in patients with permanent CH [11].

Various prevalence rates of permanent CH (Gaudino et al. [12]: 62%, and Hashemipour et al. [13]: 59.8%), and

**Table 2. Clinical and laboratory findings of patients with permanent and transient congenital hypothyroidism**

| | Transient congenital hypothyroidism (n=89) | Permanent congenital hypothyroidism (n=128) | p-value |
|---|---|---|---|
| Gender (n, %)<br>Female<br>Male | <br>35<br>54 | <br>76<br>52 | - |
| Age at diagnosis (days) | 24.6±19.1<br>(min-max: 4-90) | 24.0±22.8<br>(min-max: 3-150) | 0.524 |
| TSH (at diagnosis) (mIU/L) (n=0.51-4.30) | 55.12±33.33 | 90.34±23.46 | <0.001 |
| fT4 (at diagnosis) (ng/dL) (n=0.93-1.77) | 0.80±0.44 | 0.56±0.65 | 0.550 |
| L-T4 dosage at diagnosis (mcg/kg/day) | 8.95±3.19 | 10.93±2.56 | <0.001 |
| TSH (at 3 years old) (mIU/L) (n=0.51-4.30) | 3.09±1.91 | 4.60±9.47 | 0.160 |
| fT4 (at 3 years old) (ng/dL) (n=0.93-1.77) | 1.52±0.55 | 1.31±0.35 | 0.002 |
| L-T4 dosage at 3 years old (mcg/kg/day) | 1.25±0.45 | 2.76±0.93 | <0.001 |

TSH: Thyroid stimulating hormone, fT4: Free T4, LT4: L-thyroxine, min: Minimum, max: Maximum

transient CH (Messina et al. [14]: 36.5%, and Ghasemi et al. [15]: 79.4%), have been reported. On the other hand, Park et al. [16] determined the frequency of transient CH in children without dysgenesis as 65%. In various studies conducted in our country, the incidence rates of permanent CH ranging between 25-75% have been reported [11,17-22]. In our study, in line with the literature, we determined the rate of permanent CH as 59%. The frequency of transient and permanent CH differed between studies in our country. The variations in the frequency of consanguineous marriages by region, inclusion criteria (term vs preterm), the use of different TSH threshold values in the definition of transient CH, and iodine deficiency, iodine overload, or transmission of TSH receptor-blocking antibodies from the mother to the fetus can play an important role in these different frequency rates reported regarding transient and permanent CH. In the literature, thyroid dysgenesis (85%) is reported as the most common while thyroid dyshormonogenesis (10-15%) as the second most common cause of permanent CH [3]. In studies conducted in our country, thyroid dysgenesis was found in 34-55.6% of permanent CH cases [11,17,21]. In our study, we detected thyroid dysgenesis in 77.3% (n=99) of patients with permanent CH. Among the patients with permanent CH, thyroid hypoplasia was the most common cause, with a frequency of 63%. On the other hand, in the current study, the female-male ratio was 111/106 in all cases diagnosed with CH, consistent with previous studies in our country [11,18,22]. In addition, transient CH was found more frequently in male and permanent hypothyroidism in female cases.

The mean age at diagnosis has been reported to be between 11 and 18 days, and the mean age at diagnosis in our study was 24.6±21.3 [3,22-24] days. This difference in age at the time of diagnosis in this study may be due to premature cases, isolated TSH elevations, iodine exposure, and the inclusion of cases with CH due to maternal hypothyroidism.

In the literature, levels of TSH, and fT4 at diagnosis and follow-up have been studied and different results have been obtained in transient and permanent CH groups. Studies on TSH, fT4, fT3 and LT4 levels at the time of diagnosis and during follow-up have been conducted to differentiate between patients with permanent CH and transient CH and different results have been obtained [11,13,16,17,18,20-22,25-27]. In our study, serum TSH levels at the time of diagnosis were found to be significantly higher in the permanent CH group, but without any difference in fT4 levels. While there was no difference between the two groups in terms of TSH levels in the third year of treatment, fT4 was found to be significantly higher in the patients with transient CH. According to these results, we think that higher TSH levels at the time of diagnosis can be evaluated in favor of permanent CH, while higher fT4 levels in the third year of treatment may be evaluated in favor of permanent CH.

Many studies have determined that the dose of LT4 used in the treatment is higher in patients with permanent CH than in cases with transient CH [11,17,18,21,28-30]. In our study, in line with the literature, we observed that patients with permanent CH used higher LT4 doses during follow-up. In the literature, different cut-off values for LT4 doses ranging between 1.6-2.1 mcg/kg/day have been reported during treatment cessation [11,14,16,22,31]. In our study, the threshold value for LT4 dose during treatment discontinuation, which was determined as a predictive criterion for the differential diagnosis between permanent and transient CH, was 1.90 mcg/kg/day.

### Study Limitations

The most important limitations of our study are its retrospective design and the relatively low number of cases. In addition, we failed to evaluate iodine deficiency or excess that may affect thyroid functions, trans-placental transmission of maternal thyroid autoantibodies, and maternal drug use that may affect thyroid functions.

## CONCLUSION

In summary, in our study, the frequency of transient CH was 59%, and the most common cause of permanent CH was dysgenesis. Among the predictive criteria in the differential diagnosis between transient and permanent CH, TSH value at the time of diagnosis, fT4 and LT4 doses at the 3rd year of the treatment were found to be statistically significant.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Ethics Committee (approval number: 639, date: 09.12.2021).

**Informed Consent:** Retrospective study.

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

### Author Contributions

Surgical and Medical Practices: Ö.N., B.Ö., Concept: Ö.N., B.Ö., Design: Ö.N., B.Ö., Data Collection and/or Processing: Ö.N., B.Ö., Analysis and/ or Interpretation: Ö.N., B.Ö., Literature Search: Ö.N., B.Ö., Writing: Ö.N., B.Ö.

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