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INCIDENCE AND CLINICAL OUTCOMES OF CONGENITAL HYPOTHYROIDISM: A RETROSPECTIVE STUDY BASED ON NEWBORN SCREENING DATA FROM MUĞLA PROVINCE, TÜRKİYE

KONJENİTAL HİPOTİROİDİ SIKLIĞI VE KLİNİK SONUÇLARI: MUĞLA İLİNDE YENİDOĞAN TARAMA VERİLERİNE DAYALI RETROSPEKTİF BİR ÇALIŞMA

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ABSTRACT

Objective: To evaluate the incidence, clinical characteristics, and treatment outcomes of congenital hypothyroidism (CH) identified through neonatal screening in Muğla province, with a particular focus on differentiating between transient and permanent CH.

Methods: This retrospective study included 95 infants referred between 2020 and 2022 due to elevated thyroid-stimulating hormone (TSH) levels detected through heel-prick screening. Demographic, clinical, and biochemical data were collected. Infants were classified either as diagnosed and treated CH cases or as having transient TSH elevation without requiring treatment. Among the treated cases, CH was further categorized as transient or permanent based on follow-up findings. The predictive value of the levothyroxine (LT4) dose at six months of age was also analyzed.

Results: The average annual incidence of CH was 114.4 per 100,000 live births. Of the 95 infants, 33 (34.7%) received treatment for CH, while 62 (65.3%) had transient TSH elevation and did not require treatment. Among the treated cases, 19 (57.6%) were diagnosed with permanent CH and 14 (42.4%) with transient CH. The mean LT4 dose at six months was significantly lower in transient cases compared to permanent ones. LT4 dose cut-off value of 3.35 µg/kg/day at six months demonstrated high sensitivity and moderate specificity in predicting transient CH.

Conclusion: The incidence of CH in Muğla province exceeds global averages, with a notable proportion of transient cases. The LT4 dose at six months may serve as a useful marker for differentiating between transient and permanent CH, enabling more individualized follow-up and management strategies.

Keywords: Congenital hypothyroidism, neonatal screening, levothyroxine, transient hypothyroidism, permanent hypothyroidism

ÖZ

Amaç: Bu çalışmada, Muğla ilinde yenidoğan taraması ile saptanan konjenital hipotiroidi (KH) olgularının insidansı, klinik özellikleri ve tedavi sonuçları değerlendirilmiş; geçici ve kalıcı KH ayrımı üzerine odaklanılmıştır.

Yöntem: Bu retrospektif çalışmaya, 2020-2022 yılları arasında topuk kanı taramasında tiroid stimülan hormon (TSH) düzeyi yüksekliği nedeniyle yönlendirilen 95 bebek dahil edilmiştir. Demografik, klinik ve biyokimyasal veriler kaydedilmiştir. Bebekler, KH tanısı alıp tedavi başlananlar ve tedavi gerektirmeyen geçici TSH yüksekliği olanlar şeklinde iki gruba ayrılmıştır. Tedavi başlananlar ise takip sonuçlarına göre geçici veya kalıcı KH olarak sınıflandırılmıştır. Altıncı ayda uygulanan levotiroksin (LT4) dozunun ayırt edici değeri ROC analizi ile değerlendirilmiştir.

Bulgular: Yıllık ortalama KH insidansı 100.000 canlı doğumda 114,4 olarak saptanmıştır. 95 bebeğin 33'üne (%34,7) tedavi başlanmış, 62'si (%65,3) tedavi gerekmemiştir. Tedavi alanlar arasında 19'u (%57,6) kalıcı, 14'ü (%42,4) geçici KH olarak sınıflandırılmıştır. Altıncı ayda LT4 dozu geçici KH grubunda anlamlı olarak daha düşüktü. 3,35 µg/kg/gün kesim değeri, geçici KH'yi %100 duyarlılık ve %63,2 özgüllükle öngörmüştür (AUC: 0,925).

Sonuç: Muğla ilinde KH insidansı küresel ortalamanın üzerindedir ve önemli bir kısmı geçicidir. Altıncı aydaki LT4 dozu, geçici ve kalıcı KH ayrımında faydalı bir belirteç olabilir ve bireyselleştirilmiş takip stratejilerine katkı sağlayabilir.

Anahtar Kelimeler: Konjenital hipotiroidi, yenidoğan taraması, levotiroksin, geçici hipotiroidi, kalıcı hipotiroidi

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Introduction

Congenital hypothyroidism (CH) is a leading cause of preventable intellectual disability when not diagnosed and treated early. Since affected neonates are typically asymptomatic, clinical recognition without systematic screening is challenging.[1] Newborn screening programs enable early biochemical detection and timely treatment. When levothyroxine (LT4) therapy is initiated within the first two weeks of life, affected children can achieve neurodevelopmental outcomes comparable to those of their healthy peers.[2]

In Türkiye, a nationwide newborn screening program for CH has been in place since 2006 under the coordination of the Ministry of Health. Thyroid-stimulating hormone (TSH) levels are measured from heel-prick blood samples collected between the third and fifth days of life. According to national guidelines, infants with a TSH value >20 µIU/mL in the first sample or >5.5 µIU/mL in a second sample are referred to pediatric endocrinology centers for confirmatory evaluation.[3,4] This structured approach has enabled earlier diagnosis and improved access to treatment.

Before nationwide screening, incidence estimates in Türkiye were based on regional studies, ranging from 1 in 2736 to 1 in 2326 live births.[5,6] Following the program's launch, reported CH incidence rose sharply—reaching 1 in 888 in 2008 and 1 in 469 in 2010.[7] Similar increases occurred in other countries such as the United States and Canada, likely due to enhanced screening protocols and lower TSH thresholds.[8,9] In Türkiye, the screening TSH cut-off was initially set at 20 µIU/mL and later reduced to 10 µIU/mL, allowing earlier detection of borderline and subclinical cases.[10]

As sensitivity has improved, an increasing proportion of infants diagnosed with CH are now identified as having transient rather than permanent disease. This shift is particularly evident in regions where iodine deficiency or perinatal factors contribute to temporary disruptions in thyroid function.[1] Turkish studies report wide variation in the proportion of transient CH among screen-positive infants. For instance, Kara et al. found that 52% of treated infants were ultimately classified as transient, while Asena et al. reported a rate of 24% in a different regional cohort.[10,11] Such variability highlights the importance of early distinction to avoid unnecessary prolonged treatment.

Current guidelines recommend re-evaluation after age three for children without definitive diagnosis, usually via monitored LT4 withdrawal.[1,2] However, in clinical practice, early differentiation remains challenging, as both transient and permanent CH can initially present with similar biochemical profiles. While imaging findings such as thyroid agenesis or ectopy can suggest a permanent etiology, most screen-positive infants have eutopic glands, making diagnosis less straightforward.[10,12,13]

In recent years, treatment response—particularly levothyroxine dosage during follow-up—has been explored as a potential surrogate marker for predicting disease course. Several studies have demonstrated that lower levothyroxine doses at specific intervals are associated with transient CH, though the proposed cut-off values and predictive accuracies vary.[11,14]

This study aimed to evaluate the incidence, clinical characteristics, and outcomes of infants referred with abnormal TSH through newborn screening in the Muğla province of Türkiye over three years. Particular attention is given to the distribution of transient and permanent CH and to the evaluation of early treatment parameters—specifically levothyroxine dose at six months—as potential predictors of disease permanence.

Methods

This retrospective cohort study was conducted to evaluate the incidence and characteristics of CH diagnosed through the neonatal screening program in Muğla province between January 1, 2020, and December 31, 2022. Data were obtained from hospital records of infants who were referred due to elevated TSH levels (>10 µIU/mL) on neonatal screening and were subsequently evaluated clinically and biochemically by a pediatric endocrinologist.

Neonatal screening in Türkiye is a nationwide, government-funded program initiated by the Turkish Ministry of Health, which screens all newborns for congenital hypothyroidism using TSH measurement from heel-prick blood samples collected within the first 48-72 hours of life. The TSH threshold was progressively lowered over time, and a cut-off of 10 µIU/mL is currently used to prompt referral for further evaluation.[7,10]

Live birth data for the corresponding years were obtained from the Turkish Statistical Institute and used to calculate annual incidence rates. [15-17]

For each infant, demographic, clinical, and biochemical parameters were recorded, including sex, birth weight, age at diagnosis, TSH and free T4 levels at presentation, maternal and family history of hypothyroidism, and thyroid ultrasonography findings. Levothyroxine treatment was initiated in infants with persistent TSH elevation (>10 µIU/mL) and/or decreased free T4 levels, in accordance with guidelines.[1,2] The initial LT4 dose ranged between 10-15 µg/kg/day depending on the severity of hypothyroidism.

Patients were classified into two main categories based on their clinical evaluation and treatment course. The first group consisted of infants who were diagnosed with congenital hypothyroidism and initiated on levothyroxine therapy due to persistently elevated TSH levels and/or low free T4 concentrations. The second group included those who exhibited transient neonatal TSH elevation but did not require any treatment following confirmatory testing, as their thyroid function normalized spontaneously without pharmacologic intervention.

Among treated patients, a further distinction was made between permanent and transient CH based on follow-up findings. Children were followed with regular clinical and biochemical assessments. At approximately 3 years of

age, a trial off therapy was performed by discontinuing LT4 for 4–6 weeks, followed by evaluation of serum TSH and free T4 levels. CH was considered permanent if abnormal thyroid function persisted after treatment cessation or if structural thyroid abnormalities (agenesis, ectopy, hypoplasia) were evident on imaging.[1,2] Conversely, CH was defined as transient in children who demonstrated normal thyroid function and did not require LT4 re-initiation during follow-up.

This study was approved by the Medical Sciences Ethics Committee of Muğla Sıtkı Koçman University (Decision date: December 5, 2024; Protocol No: 240222; Decision No: 157).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using both visual methods (histograms, probability plots) and analytical tests (Kolmogorov-Smirnov and Shapiro-Wilk). Variables with normal distribution were presented as mean ± standard deviation, while non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were expressed as percentages. Group comparisons were conducted using the independent samples t-test or Mann–Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables. A p-value of <0.05 was considered statistically significant. The Youden index was used to determine the optimal cut-off value for levothyroxine (LT4) dose in the ROC curve analysis.

Results

Live birth data for the corresponding years were retrieved from the Turkish Statistical Institute (TÜİK): 9,952 in 2020, 9,643 in 2021, and 9,256 in 2022. The annual incidence of CH was calculated by dividing the number of confirmed cases by the total number of live births per year and multiplying by 100,000.

A total of 95 infants were included in the study. Of these, 33 (34.7%) were diagnosed with congenital hypothyroidism and started on levothyroxine therapy, while 62 (65.3%) were followed without treatment due to transient neonatal TSH elevation. Among the 33 treated cases, 19 (57.6%) were classified as permanent CH and 14 (42.4%) as transient CH after follow-up (Table 1).

The mean birth weight of the cohort was 3,169 ± 459.7 grams, and all infants were born at term. The median age at first evaluation was 16 days (IQR: 12). The yearly incidence of CH was 160.7 per 100,000 live births in 2020, 72.6 in 2021, and 108.0 in 2022. The average annual CH incidence over the three years was 114.4 per 100,000 live births, equivalent to 1 in 874. The mean annual incidence of permanent CH was 65.9 per 100,000 (1/1,517), and for transient CH, it was 48.5 per 100,000 (1/2,062).

Thyroid ultrasonography was available for 35 treated infants; 32 had normal thyroid anatomy, 2 had thyroid agenesis, and 1 had thyroid hypoplasia. The median TSH and free T4 values at diagnosis were 81.9 mIU/L (IQR: 48) and 8.6 ng/dL (IQR: 5.4) in treated cases, compared to 13.2 mIU/L (IQR: 8.1) and 18 ng/dL (IQR: 3.4) in untreated cases (p<0.001 for both) (Table 1).

The median treatment initiation age was 20 days (IQR: 16), and the mean starting dose of levothyroxine was 10.9 ± 4.1 µg/kg/day. At 6 months, the mean dose was 2.3 ± 0.5 µg/kg/day in the transient group and 3.6 ± 0.7 µg/kg/day in the permanent group (p<0.001) (Table 2). The ROC curve analysis revealed that a levothyroxine dose ≤3.35 µg/kg/day at 6 months predicted transient CH with 100% sensitivity and 63.2% specificity (AUC: 0.925; 95% CI: 0.84–1.00; p<0.001) (Figure 1).

Table 1. Comparison of demographic and clinical characteristics between infants diagnosed with Congenital Hypothyroidism and those with transient neonatal TSH elevation

Parameter	CH Group (n = 33)	Transient TSH Elevation (n = 62)	p-value
Sex (Female/Male)	18 / 15	22 / 40	0.07
Family history of hypothyroidism (%)	9 (27.3%)	11 (17.7%)	0.27
Maternal hypothyroidism history (%)	11 (33.3%)	32 (51.6%)	0.08
Birth weight (g), mean ± SD	3145 ± 487.5	3182 ± 447.7	0.61
Age at initial evaluation (days), median (IQR)	20 (14.5)	14 (9.2)	**<0.001**
TSH (mIU/L), median (IQR)	81.9 (48.0)	13.2 (8.1)	**<0.001**
Free T4 (ng/dL), median (IQR)	8.6 (5.4)	18.0 (3.4)	**<0.001**
Thyroid ultrasound findings (n)	28	7	**<0.001**
Normal	25	7	
Agenesis	2	0	
Hypoplasia	1	0	

P-values were calculated using the Mann–Whitney U test for non-normally distributed variables (presented as median and IQR) and the independent samples t-test for normally distributed variables (presented as mean ± SD).

IQR: interquartile range, SD: Standard deviation, CH: Congenital Hypothyroidism, TSH: thyroid-stimulating hormone

Table 2. Comparison between permanent and transient congenital hypothyroidism within the treated group

Parameter	Transient CH (n = 14)	Permanent CH (n = 19)	p-value
Sex (Female/Male)	9 / 5	9 / 10	0.33
Family history of hypothyroidism (%)	4 (28.6%)	5 (26.3%)	0.88
Maternal hypothyroidism history (%)	5 (37.4%)	6 (31.6%)	0.80
Birth weight (g), mean ± SD	3174 ± 464	3124 ± 515	0.07
Age at initial evaluation (days), median (IQR)	17 (13.7)	26 (14.0)	0.08
TSH (mIU/L), median (IQR)	72.5 (71.0)	95.0 (41.0)	0.21
Free T4 (ng/dL), median (IQR)	8.1 (5.6)	8.7 (6.2)	0.82
Thyroid ultrasound findings (n)	14	14	0.05
Normal	14	11	
Agenesis	0	2	
Hypoplasia	0	1	
Initial levothyroxine dose (µg/kg/day), mean ± SD	11.5 ± 4.6	10.5 ± 3.6	0.49
LT4 dose at 6 months (µg/kg/day), mean ± SD	2.3 ± 0.5	3.6 ± 0.7	**<0.001**

P-values were calculated using the Mann–Whitney U test for non-normally distributed variables (presented as median and IQR) and the independent samples t-test for normally distributed variables (presented as mean ± SD).
IQR: interquartile range, SD: Standard deviation, CH: Congenital Hypothyroidism, TSH: thyroid-stimulating hormone, LT4: levothyroxine

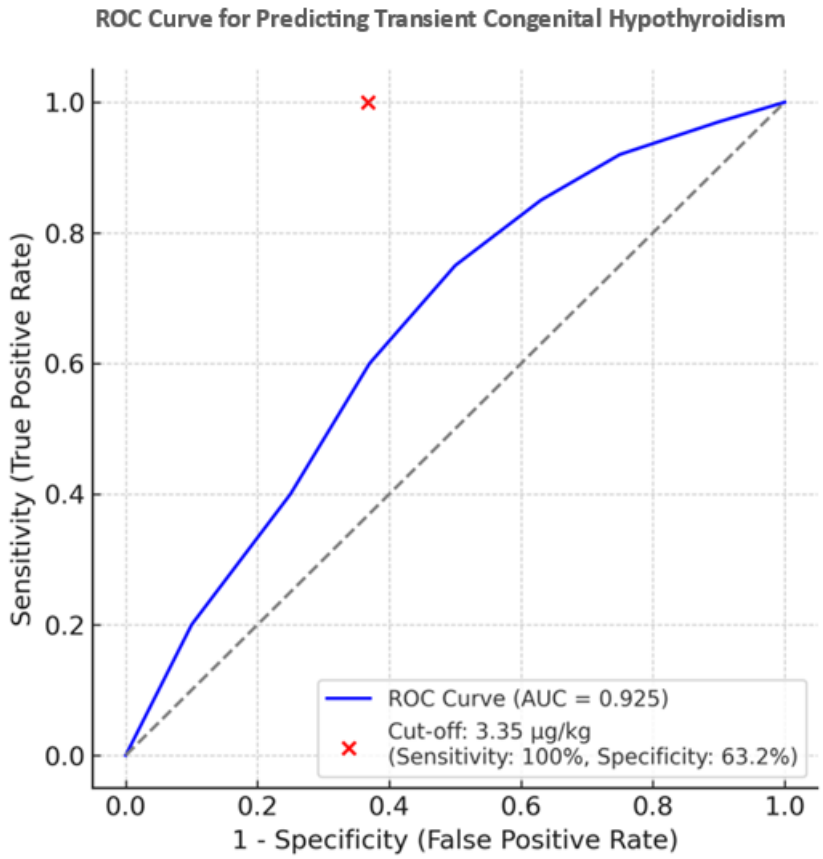

Figure 1. Receiver Operating Characteristic (ROC) Curve for Predicting Transient Congenital Hypothyroidism Based on the Levothyroxine Dose at 6 Months. The optimal cut-off value of the levothyroxine dose at 6 months for predicting transient congenital hypothyroidism was determined to be 3.35 µg/kg/day, with a sensitivity of 100%, specificity of 63.2%, and an area under the curve (AUC) of 0.925 (95% confidence interval: 0.84-1.00; p<0.001).

Discussion

The incidence of CH observed in this province during the years 2020-2022 was approximately 114 per 100,000 live births (1 in 874), which is notably higher than the classically reported global range of 1:2000 to 1:3000 births. This elevated incidence is consistent with previously published national screening reports from Türkiye and with findings from other iodine-deficient regions, such as parts of Iran, where incidence rates have been reported as high as 1:500 to 1:800.[7,18] In Türkiye, national newborn screening data showed a marked increase in CH detection after the implementation of universal screening in 2006, with incidence rates rising from 1:888 in 2008 to 1:469 in 2010.[7] Our findings align with this trend and may reflect both methodological changes and region-specific risk factors.

A key factor contributing to the rising CH incidence is the progressive lowering of TSH cut-off values used in neonatal screening. In Türkiye, the threshold was reduced from 20 to 10 µIU/mL, increasing the likelihood of detecting milder or transient forms of CH.[10] Similar effects have been observed internationally in countries that lowered screening thresholds.[9] Additionally, factors such as prematurity and low birth weight-frequently observed in regions with limited prenatal care-have been associated with increased rates of false-positive results in newborn screening programs, likely due to immature hypothalamic-pituitary-thyroid axis function.[18] Genetic and familial factors also play a role, especially in populations with high rates of consanguinity, where dyshormonogenesis and other hereditary defects are more prevalent.[19]

In our cohort, 57.6% of infants diagnosed with CH were classified as having permanent hypothyroidism, while 42.4% had transient CH. This distribution closely mirrors the findings of other Turkish studies, which report transient CH rates between 40% and 60% among screen-detected cases.[10,11] Notably, a recent multicenter Turkish study also reported a 53.6% rate of transient CH, highlighting the consistency of these rates across different regions and emphasizing the national relevance of our findings.[20]

A major challenge in clinical practice is distinguishing transient from permanent CH early in the course of treatment, ideally before age three. Identifying infants who do not require lifelong LT4 therapy can prevent overtreatment and reduce caregiver burden. In our study, we evaluated the predictive value of LT4 dose at 6 months of age. ROC curve analysis identified a cut-off value of 3.35 µg/kg/day, with 100% sensitivity and 63.2% specificity for predicting transient CH (AUC: 0.925). This result is consistent with existing literature showing that lower LT4 requirements in early infancy are associated with transient disease. For example, Oron et al. reported that a 6-month LT4 dose of ≤2.2 µg/kg/day predicted transient CH with moderate sensitivity and specificity.[21] Similarly, Özer et al. found that an LT4 dose of <2.0 µg/kg/day at the time of treatment discontinuation predicted transient CH with high specificity (94.5%), further validating the role of LT4 dosing in guiding clinical decisions.[20] Chen et al., in a large cohort study, proposed a 24-month LT4 dose threshold of <2.9 µg/kg/day for predicting transient CH.[22]

While our cut-off value of 3.35 µg/kg/day demonstrated excellent sensitivity, its specificity was moderate, indicating that some infants with permanent CH also maintained euthyroidism on low LT4 doses by 6 months. In our cohort, approximately one-third of permanent CH cases had LT4 needs below the identified threshold. This limitation has been similarly reported in other studies, where infants with mild permanent CH-especially those with eutopic thyroid glands-may initially appear transient.[20,21] Moreover, up to 62-86% of infants with mildly elevated TSH and normal ultrasound findings have been shown to have permanent hypothyroidism upon long-term follow-up.[13] These findings highlight that no early marker is perfectly reliable when used in isolation, and that clinical, biochemical, and imaging data must be integrated cautiously. Current international guidelines endorse a cautious approach. The American Academy of Pediatrics (AAP) recommends that in all cases where a definitive diagnosis of permanent hypothyroidism has not been established, LT4 treatment should be continued until 3 years of age, followed by a 4- to 6-week discontinuation to reassess thyroid function.[23] Similarly, the European Society for Pediatric Endocrinology (ESPE) suggests that a child with a eutopic gland and a 6-month LT4 dose below 3.0 µg/kg/day may be considered for earlier re-evaluation, though only under close clinical supervision.[2] In our study, most clinicians adhered to a conservative approach; the median age for treatment discontinuation among transient CH cases was approximately 2.4 years. This practice balances patient safety with the desire to avoid unnecessary prolonged therapy and is in line with international recommendations. Nevertheless, monitoring LT4 requirements throughout infancy remains a valuable tool to support individualized care planning.

In summary, our findings from Muğla province confirm a relatively high incidence of congenital hypothyroidism, consistent with national data from Turkey and reports from other iodine-deficient populations.[9,10,18] A substantial proportion of cases (42.4%) were transient, emphasizing the importance of distinguishing between transient and permanent forms to optimize treatment duration. Our analysis supports the use of LT4 dose at six months of age as a practical and sensitive early predictor of transient CH, in agreement with both national and international studies.[11,20,21] While early dose thresholds should not replace formal re-evaluation at 2–3 years of age, they can provide valuable guidance for individualized follow-up.

To our knowledge, this study is among the few that have comprehensively evaluated CH incidence and treatment outcomes in the southwestern Aegean region of Türkiye, providing valuable regional data to complement national reports. These findings reinforce the clinical relevance of early dose monitoring and may support the development of individualized follow-up protocols. A key limitation of

our study is its retrospective, single-center design and relatively small sample size, which may affect generalizability. In addition, iodine status and genetic testing data were not available, limiting the ability to determine underlying etiologies. Long-term neurodevelopmental outcomes were also not assessed, which may have provided a more comprehensive evaluation of treatment efficacy. Further multicenter studies with long-term follow-up are warranted to validate early predictive markers and improve CH management strategies across different populations.

Ethical Approval

This study was approved by the Ethics Committee of Muğla Sıtkı Koçman University Faculty of Medicine (Date: 05.12.2024, Protocol No: 240222, Decision No: 157). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest

There is no conflict of interest to declare.

Author Contributions

GCY: Study conception and design, data analysis, manuscript drafting, final approval; GG: Data collection, literature review, manuscript revision; ES: Methodological supervision, interpretation of results, critical revision of the manuscript.

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