


Evaluation of Transient or Permanent Congenital Hypothyroidism

 Selim Kurtoğlu,¹  Osman Baştuğ,²  Ahmet Özdemir²

¹Department of Pediatric Endocrinology, Memorial Kayseri Hospital, Kayseri, Türkiye

²Department of Neonatal, Health Sciences University, Kayseri City Hospital, Kayseri, Türkiye

ABSTRACT

Congenital hypothyroidism is a common endocrine disease in children. In Türkiye, neonatal screening has been performed since 2007 with a cut-off Thyroid Stimulating Hormone (TSH) level of 5.5 mU/L. The initial treatment period is within the first 14 days. Reevaluation of thyroid function and thyroxine doses is necessary to determine whether the condition is permanent or transient congenital hypothyroidism. Numerous studies and proposals have been published on this topic. This article reviews the publications related to this subject.

Keywords: Congenital hypothyroidism, permanent hypothyroidism, transient hypothyroidism, Iodine, thyroid.



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Address for correspondence:

Osman Baştuğ,
Department of Neonatal, Health Sciences University, Kayseri City Hospital, Kayseri, Türkiye
Phone: +90 352 315 77 00
E-mail: drosman76@hotmail.com

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INTRODUCTION

Congenital hypothyroidism is a global problem with a prevalence between 1/3,000 and 1/4,000.¹ The incidence of this condition is increasing due to environmental factors and the implementation of screening programs.² Early diagnosis through heel lance screening programs and prompt initiation of treatment have significantly reduced the cognitive effects of hypothyroidism. In some cases, congenital hypothyroidism may be temporary (Table 1).³⁻⁵ Infants who undergo treatment are regularly scheduled for follow-up visits, during which the dosage is adjusted. Gradual reduction of dosage during follow-up suggests temporary hypothyroidism. Several studies have been conducted to determine the criteria for diagnosing permanent or temporary hypothyroidism. The aim of this manuscript is to review the parameters used to establish the diagnosis of temporary or permanent congenital hypothyroidism.

Study data were searched using various online databases, including Google, PubMed, and Web of Science. Specific keywords were used during the search, such as transient hypothyroidism, permanent hypothyroidism, free T3, free T4, thyroid stimulating hormone, thyroglobulin, congenital hypothyroidism, thyroid hypoplasia, thyroid volume, iodine, urinary iodine, breast milk iodine, and thyroxine treatment.

Diagnostic Studies, Treatment and Monitoring

Congenital hypothyroidism is diagnosed through abnormal thyroid function tests conducted via heel lance screening or based on clinical findings, such as prolonged jaundice. The primary tests used for diagnosis include free T3 (fT3), free T4 (fT4), and Thyroid Stimulating Hormone (TSH). Additionally, other diagnostic tests may involve thyroid ultrasonography, thyroid scintigraphy,



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Table 1. Transient congenital hypothyroidism

Transient primary hypothyroidism
Endemic iodine deficiency
Prenatal and postnatal iodine overload
Presence of maternal TSHR blocking antibodies
Maternal intake of antithyroid drug (thionamide, D-pencillamine, propranolol, lithium)
Heterozygous THOX2 and DUOX2 mutations
Congenital nephrotic syndrome (Finnish type)
Isolated hyperthyrotropinemia
Transient secondary and tertiary hypothyroidism
Maternal hyperthyroidism
Prematurity and low birth weight
Medications such as dopamine, corticoids, phenytoin, somatostatin analogues
After cardiopulmonary bypass
Deep hypothermia practice
Transient hypothyroxinemia

bone age assessment, thyroglobulin measurement, analysis of iodine levels in the baby's urine and breast milk, as well as genetic analyses. Detailed medical history taking should also explore the use of medications by the mother, maternal radioactive iodine therapy, mode of delivery (cesarean section, episiotomy), and the application of iodine antiseptic on the infant's umbilicus.^{2,6,7}

Thyroid ultrasonography, performed by an experienced radiologist, is used to diagnose conditions such as agenesis, hypoplasia, hemiagenesis, ectopia, hyperplasia, and intrathyroidal ectopic thymus.⁸ It is important to note that unexperienced radiologists may incorrectly report the presence of the thyroid gland in cases of agenesis.

In Belgium, the median value of thyroid volume in term-infants with a median urinary iodine level of 68 µg/L was measured as 0.76 ml [mean - SD 0.84 (0.38)]. Hypoplasia was indicated at or below 0.44 ml, while hyperplasia was observed at or above 1.5 ml.⁹ Kurtoglu S et al.¹⁰ measured the median value of thyroid volume as 0.8 ml in term infants. Scintigraphy can be used to diagnose agenesis, ectopic thyroid, and goiter. However, it should be noted that iodine loading and blocking antibodies from the mother may lead to misdiagnosis of agenesis. In such cases, the presence of the thyroid gland should be confirmed through thyroid ultrasound.² Iodine deficiency or loading can be determined by measuring the iodine level in the infant's urine or breast milk. Under normal conditions,

iodine levels in urine and breast milk range from 100 to 200 µg/L. Levels below 100 µg/L indicate iodine deficiency, while levels above 200 µg/L indicate iodine loading.^{11,12} Diagnostic studies may also provide insights into serum thyroglobulin levels, which are involved in the diagnostic process. Very low levels indicate agenesis, moderate increase indicates ectopia, and higher levels indicate iodine deficiency and dishormonogenesis. Hatipoglu N et al.¹³ reported thyroglobulin levels as 3.07 ng/ml in cases of agenesis, 40.92 ng/ml in cases of hypoplasia, 33.1 ng/ml in cases of ectopia, and 499 ng/ml in cases of dishormonogenesis. However, it should be noted that thyroglobulin levels can be elevated in cases of iodine loading.¹² In central hypothyroidism, fT3 and fT4 levels are lower, while TSH may either be low or not elevated enough. In these cases, isolated TSH decrease or combined deficiencies of pituitary hormones may be observed.¹⁴

Thyroxine is used for the treatment of congenital hypothyroidism, with the initial dose ranging from 10 to 15 µg/kg/day (maximum 50 µg/day). The dosage is adjusted based on the age of the patient: 6 to 10 µg/kg/day between months 1 and 6, 5 to 8 µg/kg/day between months 6 and 12, 4 to 6 µg/kg/day between years 1 and 3, 3 to 4 µg/kg/day between years 3 and 10, and 1.75 to 3 µg/kg/day for patients over 10 years of age.¹⁵ It is important to note that higher initial doses may be required in cases of agenesis and severe hypothyroidism, but caution should be exercised to avoid excessively high doses. Previous studies have shown that higher doses of replacement therapy in patients between 6 and 11 years of age may be associated with attention deficit and hyperactivity syndrome.¹⁶ Therefore, Bakker B, Kempers MJ et al.¹⁷ have suggested different initial doses based on the first fT4 levels: 10 to 15 µg/kg/day if fT4 level is at or below 0.3 ng/dl, 8 to 10 µg/kg/day if fT4 level is between 0.3 and 0.6 ng/dl, and 5–8 µg/kg/day if fT4 level is over 0.6 ng/dl.^{17,18} Patients who have started therapy should be called for follow-up visits 2 to 4 weeks after the onset of therapy, every 1 to 2 months until 6 months, every 3 to 4 months between 6 months and 3 years of age, every 6 to 12 months between 3 years and completion of growth, and 4 weeks after dose adjustment. In problematic cases more frequent visits are recommended, and during these visits, serum fT4 and TSH levels are monitored.^{1,15} One or two control visits within the first week are recommended for patients who have started therapy with higher doses.^{17,19} A moderate range of fT4 levels and TSH levels below 6 mU/L indicate the adequate dose of therapy, while a TSH level below 0.8 mU/L indicates a higher dose.²⁰ Some patients who receive an adequate dose of thyroxine may have sufficient levels of fT4 and fT3, but TSH suppression may not be observed. In these cases, a delay in pituitary suppression mechanisms is considered, and combinations of T3+T4 are suggested.²¹

How is the Decision Made for Permanent or Temporary Hypothyroidism?

1. Control at Three Years of Age

Patients with congenital hypothyroidism who require treatment are monitored until the age of three, by which time brain development is 90% complete. Thyroxine therapy is discontinued for patients with agenesis, ectopia, or severe hypoplasia. Thyroid hormone levels are assessed after 4 to 6 weeks, thyroid ultrasound is performed, a perchlorate excretion test is conducted, and scintigraphy is performed if not done previously. If thyroid hormone levels are low and TSH is high, permanent hypothyroidism is diagnosed, while normal levels indicate a temporary condition.^{2,22,23}

2. Parameters To Guide the Decision Before Three Years of Age

a. TSH Monitoring with Reduced Thyroxine Dose: Two approaches are recommended for patients who require the same or lower dose despite increased body weight before the age of three. The first suggestion is to reduce the medication dose by half and consider permanent hypothyroidism if the TSH level measured after 30 days is above 20 mU/L.²⁴ The second suggestion is to consider permanent hypothyroidism if the TSH level is above 10 mU/L after reducing the thyroxine dose by 30% for 2 to 3 weeks.²² Additionally, excessive TSH fluctuation during therapy should raise suspicion of permanent hypothyroidism.

b. Initial and Follow-up Serum TSH Levels: Several studies have investigated serum TSH levels before the start of treatment and during monitoring to distinguish between permanent and temporary hypothyroidism cases.

A previous study conducted in our country found that out of 37 patients with hyperthyrotropinemia, 17 developed temporary hypothyroidism. The initial TSH levels were observed to be 11.50 ± 4.59 mU/L in cases of permanent hypothyroidism and 10.48 ± 3.61 mU/L in patients with temporary hypothyroidism. It was also noted that TSH levels remained higher in permanent during the first and second year of therapy. TSH levels were measured as 10.1 ± 4.8 mU/L in permanent cases and 3.80 ± 0.96 mU/L in temporary cases for 30 days after discontinuation of medication.²⁵ Kendirci HN et al.²⁶ in the Pediatric Endocrinology Department at Dr. Sami Ulus Hospital, found that 30% of the 114 infants diagnosed with congenital hypothyroidism had temporary hypothyroidism. Initial serum TSH levels were found to be 42.5 ± 18.3 mU/L in patients with temporary hypothyroidism, while patients with permanent hypothyroidism had TSH levels of 60.7 ± 37.1 mU/L. Another study conducted in the province of Samsun, Türkiye²⁷ included a total of 138 cases with congenital hypothyroidism. Among them, 16 were diagnosed with temporary hyperthyrotropin-

emia, and 63 (52%) cases were classified as temporary congenital hypothyroidism. Serum TSH levels were 91 ± 62 mU/L in patients with permanent hypothyroidism and 67 ± 33 mU/L in patients with temporary hypothyroidism, but there was overlap in the values between the two groups. In Iran, 36% of cases with congenital hypothyroidism were found to be temporary, with initial venous TSH levels of 37.19 ± 30.40 mU/L in permanent cases and 22.93 ± 19.07 mU/L in temporary cases.²⁸ In permanent cases, serum TSH levels were around 6 mU/L during the first years of treatment. However, it increased to 12.9 mU/L after discontinuation for 30 days and reached around 10 mU/L after discontinuation of the therapy for 90 days. In temporary cases, TSH levels were found to be 3.6 ± 1.5 mU/L after discontinuation for 30 days and 3.7 ± 1.3 mU/L after discontinuation for 90 days. A previous study conducted in Korea found the prevalence of temporary hypothyroidism to be 65% with TSH levels of 30.8 ± 18.8 mU/L in temporary cases and 47.1 ± 33.8 mU/L in permanent cases.²⁹ In a study carried out in Israel, TSH levels were found to be 71.5 ± 11.2 mU/L, 49 ± 27.9 mU/L, and 42.5 ± 29.21 mU/L in cases with agenesis/ectopia, eutopic permanent hypothyroidism, and eutopic temporary hypothyroidism, respectively.³⁰ In Macedonia, 45% of 76 patients with congenital hypothyroidism were observed as temporary, with TSH levels of 81.9 mU/L in permanent cases and 22.7 mU/L in temporary cases.³¹ A study involving 58 patients diagnosed with eutopic congenital hypothyroidism in Italy revealed that 34.5% of the cases were diagnosed with temporary congenital hypothyroidism, with initial TSH levels of 73.3 mU/L in permanent cases and 24.24 mU/L in temporary cases.³² Consequently, higher initial TSH levels are expected in patients with agenesis. However, it is not possible to provide an exact predictive TSH value to decide on permanent or temporary eutopic congenital hypothyroidism for every case.^{27,33,34}

c. Changes in Thyroxine Dose: Kendirci HN et al.²⁶ detected thyroxine levels as 0.6 ± 0.3 µg/kg/day in temporary cases and 2.2 ± 1.3 µg/kg/day in permanent cases. If the thyroxine dose decreases below 1 µg/kg/day during follow-up, thyroxine is discontinued, and normal TSH levels measured three times in a month are considered as temporary hypothyroidism. Kara C et al.²⁷ stated that if a low dose of thyroxine requirement appears below 1.5 µg/kg/day at the beginning and after 6 months, a temporary decision is made to terminate the treatment. Messina MF et al.³³ found the thyroxine dose to be above 4.9 µg/kg/day in the first year and 4.27 µg/kg/day in the second year in permanent cases, whereas it was 1.7 and 1.45 µg/kg/day in temporary cases, respectively. In a study conducted in Israel, the thyroxine requirement in cases with eutopic congenital hypothyroidism within the second year was 3.0 ± 0.3 µg/kg/day in the permanent group and 1.9 ± 0.8 µg/kg/day in the temporary group.³⁰ A study performed in South Korea found that lower thyroxine doses were needed in cases with eutopic temporary congenital hyp-

pothyroidism, and the predictive value for the thyroxine dose was 2.76 µg/kg/day through Receiver Operating Characteristic (ROC) analysis in the third year.²⁹ In an Italian study, it was shown that a daily thyroxine dose of 0.94 µg/kg/day or below in the second year of treatment in cases with congenital hypothyroidism is a highly sensitive predictive value for temporary cases.³² A Macedonian study emphasized that a thyroxine level below 2.6 µg/kg/day at three years of age is an important predictive value for deciding on temporary hypothyroidism.³¹ In Japan, 99 cases were monitored, and it was concluded that a thyroxine requirement over 4.7 µg/kg/day in the first year of treatment should be considered as permanent hypothyroidism, while a requirement below 1.8 µg/kg/day should be considered as temporary hypothyroidism.³⁵ Another study carried out in Japan examined 34 patients with congenital hypothyroidism and highlighted that a thyroxine dose below 2.4 µg/kg/day in the first year and below 1.3 µg/kg/day in the third year are highly predictive for temporary cases.³⁶ Asena M et al.³⁷ investigated 226 cases with congenital hypothyroidism and reported that a thyroxine level at and below 2 µg/kg/day in eutopic cases in the sixth month is a predictive value for temporary cases.

CONCLUSION

In cases diagnosed with congenital hypothyroidism, either through screening or later, thyroid function tests and ultrasound are conducted. Thyroid scintigraphy is performed based on the medical history and ultrasound findings. Serum thyroglobulin and iodine levels are measured in the infant's urine (after the fifth day of life) and breast milk. Common cardiac disorders and other associated malformations observed in patients with hypothyroidism are reviewed. Thyroxine therapy is initiated promptly, and thyroid function is monitored at regular intervals with adjustments made to the thyroxine dose. Patients with thyroid agenesis and ectopia are considered to have permanent hypothyroidism. The age of three is generally preferred to determine whether cases of eutopic congenital hypothyroidism are permanent or temporary. However, changes in the daily thyroxine requirement may provide clues before the age of three. Initial and subsequent TSH values may not be sufficient for deciding on permanent or temporary hypothyroidism.^{2,33,34}

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