REVIEW

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Approach to Newborns with Elevated TSH: A Different Perspective from the International Guidelines for Iodine-deficient Countries

Cengiz Kara[1], Hüseyin Anıl Korkmaz[2]

[1]İstinye University Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İzmir Faculty of Medicine, Department of Pediatric Endocrinology, İzmir, Türkiye

Abstract

Lowering of thyroid-stimulating hormone (TSH) cutoffs in newborn screening programs has created a management dilemma by leading to more frequent detection of neonates with elevated TSH concentrations due to false-positive results, transient neonatal hyperthyrotropinemia (NHT), and milder forms of congenital hypothyroidism. Current consensus guidelines recommend starting treatment if the venous TSH level is >20 mU/L in the face of a normal free thyroxine (FT4) level, which is an arbitrary threshold for treatment decisions. In countries such as Türkiye, where transient NHT may be more common due to iodine deficiency (ID) and/or overload, putting this recommendation into daily practice may lead to unnecessary or over treatment, time-consuming long-term follow-up, and increased workload and costs. In this review, we addressed alternative approaches for infants with elevated TSH concentrations detected at newborn screening. The suggested management approach can be summarized as: Infants with mild NHT (venous TSH <20 mU/L) should be followed without treatment. In moderate NHT (venous TSH 20-30 mU/L), treatment or monitoring decisions can be made according to age, TSH trend and absolute FT4 level. Moderate cases of NHT should be treated if age at confirmatory testing is >21 days or if there is no downward trend in TSH and FT4 level is in the lower half of age-specific reference range in the first 21 days. In in-between cases of moderate NHT, thyroid ultrasound may guide treatment decision by determining mild cases of thyroid dysgenesis that require life-long treatment. Otherwise, monitoring is a reasonable option. Infants with compensated hypothyroidism (venous TSH >30 mU/L and normal FT4) or persistent hyperthyrotropinemia (>6-10 mU/L after the neonatal period) should receive L-thyroxine treatment. However, all treated cases of isolated TSH elevation should be closely monitored to avoid overtreatment, and re-evaluated by a trial off therapy. This alternative approach will largely eliminate unnecessary treatment of infants with transient NHT, mostly caused by ID or excess in Türkiye, and will reduce workload and costs by preventing unwarranted investigation and long-term follow-up.

Keywords: Congenital hypothyroidism, neonatal hyperthyrotropinemia, newborn screening

Introduction

Congenital hypothyroidism (CH) refers to thyroid hormone deficiency present at birth, resulting from an impairment of the thyroid axis at the hypothalamic-pituitary (central) or thyroid (primary) level. Primary CH occurs mainly due to developmental defects of the thyroid gland (dysgenesis) or insufficient thyroid hormone biosynthesis (dyshormonogenesis). Thyroid dysgenesis includes ectopy, athyreosis, orthotopic hypoplasia and hemiagenesis (1). Dyshormonogenesis refers to impaired biosynthesis of thyroid hormones in a normally located gland, usually with compensatory goiter (2). Resistance to thyroid-stimulating hormone (TSH) has a special place in the etiology of primary CH, with a phenotypic spectrum varying from severe hypothyroidism with hypoplastic thyroid to mild persistent hyperthyrotropinemia (PHT) with a normal-sized gland (3,4). Central CH is caused by defective stimulation of a normal thyroid gland by TSH due to hypothalamic or pituitary pathologies (5). Since isolated TSH deficiency

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Address for Correspondence: Cengiz Kara Prof. MD, İstinye University Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Türkiye
E-mail: cengiz.kara@istinye.edu.tr, cengizkara68@yahoo.com **ORCID:** orcid.org/0000-0002-8989-560X

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is a rare condition, central CH occurs mostly as part of hypopituitarism (multiple pituitary hormone deficiencies). In addition, CH can be classified as permanent and transient. Permanent CH is a condition of thyroid hormone deficiency that requires lifelong treatment. Transient CH is a temporary deficiency of thyroid hormone production that recovers in the first few months or years of life (1,2). The classification and etiology of CH are given in Table 1.

The term "congenital hypothyroidism" was first introduced by Radwin et al. (6) in 1949 to describe children with severe intellectual disability and growth retardation due to hypothyroidism. In the early 1970s, Klein et al. (7) showed that clinical diagnosis and adequate treatment before three months of age could prevent mental retardation in children with CH, and then successfully implemented laboratory screening for CH, involving the determination of TSH in samples of cord blood (8). Anecdotally, Dussault and Laberge (9) developed a radioimmunoassay for the measurement of thyroxine (T4) on filter paper blood spots, and subsequently initiated the first neonatal mass screening for CH in Quebec in 1973 (10). The introduction of newborn screening programs (NSPs) enabled early diagnosis before the onset of clinical symptoms based on biochemical measurements of TSH and T4 (11). However, the gradual lowering of TSH cutoff levels over time by screening programs has led to the detection of mild cases that exhibit elevated serum TSH concentrations with normal peripheral thyroid hormone (T4 and T3) levels. This condition has been termed compensated or subclinical hypothyroidism (SCH) (12,13,14,15,16). On the other hand, "isolated hyperthyrotropinemia" has been suggested as a more accurate term to describe elevated TSH levels in the presence of normal T4 levels, which does not reflect a true state of hypothyroidism (17,18). Thus, the terms SCH and hyperthyrotropinemia (isolated, neonatal, or persistent) are often used interchangeably (12,19). Herein, we refer to the state of low serum free T4 (FT4) levels as hypothyroidism (20). We believe that when FT4 levels are normal, severe TSH elevation (>30 mU/L for newborns) can be defined as compensated hypothyroidism (or SCH), requiring immediate treatment, whereas mild to moderate TSH elevation (6-30 mU/L for newborns) can be defined as isolated neonatal hyperthyrotropinemia (NHT). Considering literature data (21,22,23), we choose a TSH threshold value of 30 mU/L as the most inclusive definition for NHT given the conditions found in Türkiye, as will be discussed in detail below. No doubt, this definition of NHT includes mild compensated hypothyroidism that can spontaneously resolve during the neonatal period due to iodine deficiency (ID) or overload, but it expresses an approach in favor of the option of monitoring without treatment.

Current consensus guidelines recommend starting treatment if the venous TSH level is >20 mU/L in the face of a normal FT4 level, which is an arbitrary threshold for treatment decisions (14,15,16). Due to the lack of sufficient evidence, this recommendation is based on expert opinion and has the potential to lead to unnecessary treatments in cases of transient NHT. In countries such as Türkiye, where transient NHT may be more common due to ID and/or overload (24,25,26,27,28,29), putting this recommendation into daily practice may lead to unnecessary treatment, long-term follow-up, and increased workload and costs. Therefore, in this review, we propose an alternative approach for infants with elevated TSH on neonatal screening. To explain the reasons for this alternative approach, we will first discuss the national NSP data and current iodine nutrition status in Türkiye. Next, we focus on the issue of NHT as an unintended consequence of current NSPs. We then present a comprehensive algorithmic approach for the management of newborns with NHT and CH, taking into account both international guidelines (14,15,16) and regional conditions (24-44).

National NSP for CH in Türkiye

The Turkish Directorate of Public Health launched the national NSP for CH in December 2006 (30). In 81 provinces, more than 100 pediatric endocrinology clinics serve as reference centers and deal with the management of newborns referred from the NSP. At the beginning, the cutoff point for capillary TSH was 20 mU/L (serum equivalent). The capillary TSH cutoff value was reduced to 15 mU/L in 2008 and to 5.5 mU/L whole blood (equivalent to 12 mU/L in serum, assuming an average hematocrit of 55%) in 2013 (Table 2). In the current program, the heel-prick blood specimens are routinely collected on filter paper between days 3 and 5 of life. If capillary TSH is ≥20 mU/L whole blood in the first screening specimen, a venous sample is taken immediately for confirmation. When it is between 5.5 and 20 mU/L, a second heel-prick test is performed. A sample taken in the first 48 hours of life before hospital discharge was formerly defined as "early sample", and a new dried blood specimen was requested from these babies (30). However, these early samples were stopped in 2015 due to the high costs and increased workload (31). If capillary TSH is ≥5.5 mU/L for repeat samples, the newborn is recalled for confirmatory tests (Figure 1). The decision whether to treat the babies and to perform further diagnostic tests are at the discretion of the clinician at the referral center.

Although this program has largely eliminated cases of severe mental and growth retardation due to CH, it has also led to the detection of many mild or transient cases

Table 1. Classification and etiology of congenital hypothyroidism

Permanent congenital hypothyroidism

1. Primary hypothyroidism
 a) Thyroid dysgenesis: ectopia, athyreosis, hypoplasia, hemiagenesis
  i) Familial or genetic (2-5% of dygenesis cases): syndrome or associated features
   (1) NKX2.1: Brain-lung-thyroid syndrome (respiratory distress, choreatetosis)
   (2) FOXE1: Bamforth-Lazarus syndrome (cleft palate, chonal atresia, spiky hair)
   (3) PAX8: Hypoplasia, genitourinary anomalies (rare)
   (4) GLIS3: Athyreosis, neonatal diabetes, cystic kidneys, cholestasis
   (5) NKX2.5: Athyreosis/ectopy, congenital heart malformations
   (6) JAG1: Hypoplasia/ectopy, alagille syndrome type 1
   (7) CDC8 (BOREALIN): Ectopy, athyreosis, hemiagenesis
   (8) NTN1 (Netrin1), TUBB1 (Tubulin1): Ectopy
  ii) Sporadic (95-98% unknown etiology)
 b) Dyshormonogenesis: impaired hormone production (±goiter) due to defects in
  i) Iodide uptake by sodium-iodide symporter (NIS-SLC5A5)
  ii) Iodide transport from follicular cell into colloid
   (1) SLC26A4 (PDS): Pendred syndrome (deafness with goiter)
   (2) SLC26A7: Normal hearing
  iii) Iodide organification by TPO
  iv) Hydrogen peroxide generation
   (1) Dual oxidase 2 (DUOX2) or activator/maturation factor 2 (DUOXA2)
   (2) Dual oxidase 1 (DUOX1) or activator/maturation factor 1 (DUOXA1)
  v) Thyroglobulin synthesis (TG)
  vi) Deiodination by iodotyrosine deiodinase/dehalogenase (IYD-DEHAL1)
 c) TSH resistance
  i) Defect in TSH receptor (TSHR): Normal-sized thyroid to severe hypoplasia
  ii) Defect in G-protein signalling (GNAS): Pseudohypoparathyroidism type 1a
 d) Syndromic primary hypothyroidism (usually with normal thyroid morphology)
  i) TBX1: Di George syndorme
  ii) ELN: Williams-Beuren syndrome
  iii) DYRK1A: Down syndrome
  iv) SALL1 (Townes-Brocks), URB1 (Johanson-Blizzard), KMT2D, KDM6A (Kabuki)

2. Central hypothyroidism
 a) Secondary (pituitary) hypothyroidism
  i) Isolated TSH deficiency (TSHβ): Low TSH, pitutary hyperplasia
  ii) TRH receptor resistance (TRHR): Low TSH and prolactin
  iii) Combined pituitary deficiencies (HESX1, LHX3, LHX4, PIT1, PROP1, SOX3, OTX2)
 b) Tertiary (hypothalamic) hypothyroidism
  i) IGSF1: X-linked, low TSH/prolactin, delayed puberty, postpubertal macroorchidism
  ii) TBLX1, IRS4: X-linked, inappropriately normal TSH, sensorineural deafness
  iii) Combined pituitary deficiencies (LEPR, PROK2, FGF8, FGFR1, SOX2, CHD7)

Transient congenital hypothyroidism

1) Primary hypothyroidism
 a) Maternal iodine deficiency (endemic goiter)
 b) Maternal and neonatal iodine exposure
 c) Maternal antithyroid medications (methimazole, propylthiouracil)
 d) Maternal TSH receptor-blocking antibodies
 e) Genetic defects *(DUOX2, DUOXA2, TPO)*

2) Central hypothyroidism
 a) Maternal hyperthyroidism
 b) Prematurity (particularly <27 weeks of gestation)
 c) Drugs: Dopamin, steroids

TPO: thyroid peroxidase, TSH: thyroid-stimulating hormone, FT4: free thyroxine, NHT: neonatal hyperthyrotropinemia

of CH and NHT (27,29). The first published data from the national NSP in Türkiye showed very high incidence rates of possible CH at birth (1:888 in 2008, 1:592 in 2009 and 1:469 in 2010). The recall rates were also high, ranging from 1.9% in 2008 to 3.8% in 2010 (30). However, regional and nationwide studies have shown that more than half of the CH cases were transient (27,29). According to the 2014 NSP data, 7.2% of 1,270,311 newborns screened after 48 hours of life had a capillary TSH level above 5 mU/L (31). This rate was 40.6% among 660,946 newborns screened within the first 48 hours after birth. While the authors emphasized justifiably that mild ID was an ongoing problem in Türkiye [see Table 3 for assessment of iodine status according to World Health Organization (WHO) criteria], these data revealed the existence of a much greater problem for pediatric endocrinologists: tens of thousands of newborn

Table 2. Changes in TSH cutoff values in the Turkish National NSP

Starting date	Borderline TSH cutoff†	High TSH cutoff†	Reporting unit*
December 2006	20 mU/L	50 mU/L	Serum
July 2008	15 mU/L	50 mU/L	Serum
February 2013	5.5 mU/L	20 mU/L	Whole blood*

†When TSH level is between the borderline and high cutoff points, screening is repeated. When TSH level is above the high cutoff or repeat screening is abnormal, venous sampling is performed for confirmatory testing.
*Filter-paper TSH screening results can be reported per unit of serum or whole blood. Serum equivalent is calculated as 2.2 times the whole blood TSH value, assuming an average hematocrit of 55% for the first days of life. Therefore, a borderline TSH cutoff of 5.5 mU/L whole blood is equivalent to 12 mU/L in serum.
NSP: newborn screening program, TSH: thyroid-stimulating hormone

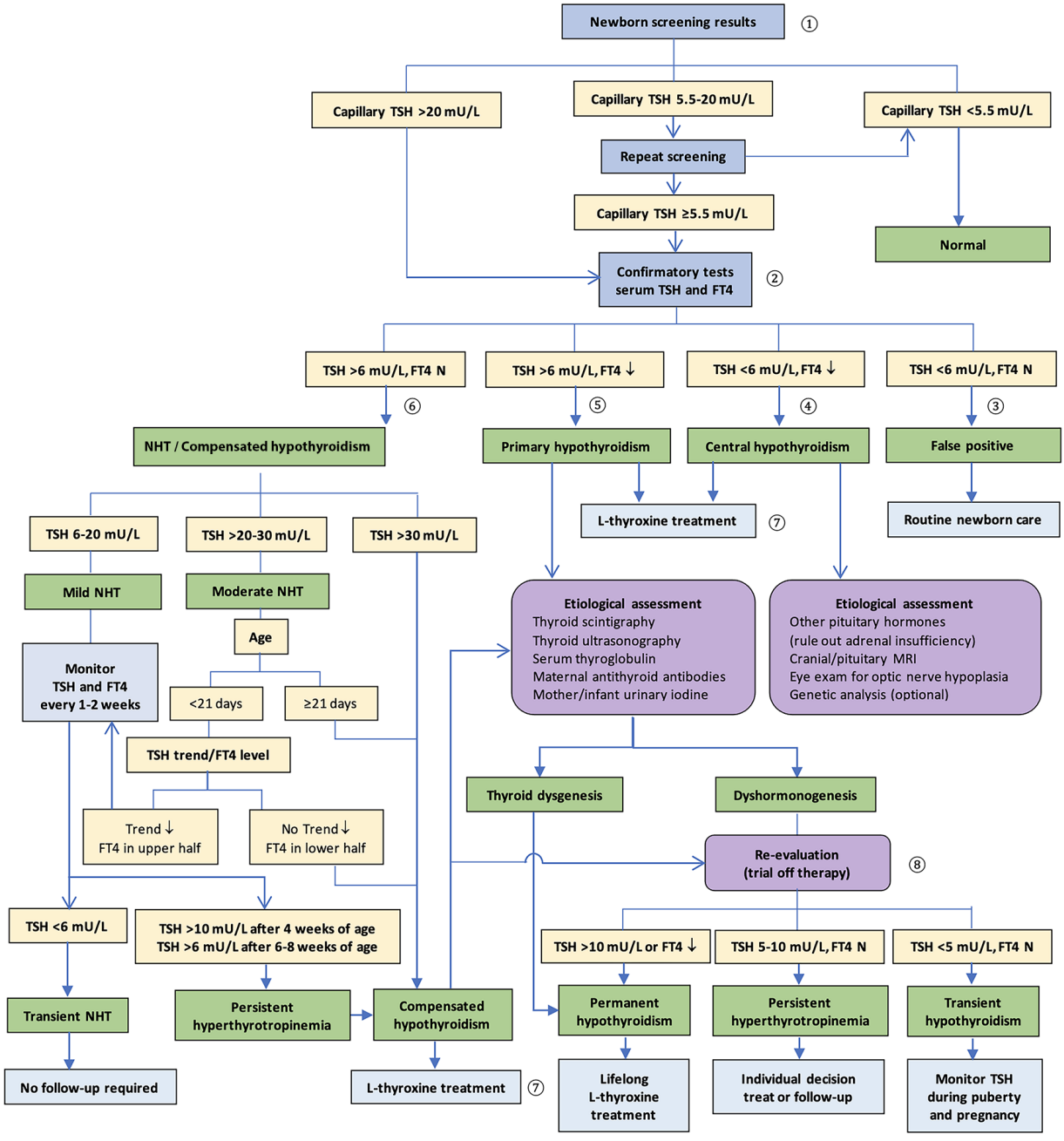

Figure 1. The approach to an infant with TSH elevation on newborn screening (numbers 1 to 8 in the flow diagram refer to the subheadings under the title "An Alternative Approach to the Infants with Neonatal TSH Elevation")

TSH: thyroid-stimulating hormone, FT4: free thyroxine, NHT: neonatal hyperthyrotropinemia

babies are referred to outpatient clinics due to elevated TSH levels. Therefore, an important question was raised: how should we manage newborns with elevated TSH detected by NSP using the low TSH cutoff level of 5.5 mU/L in an iodine-deficient country?

Iodine Problem in Türkiye

WHO and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) recommend four methods for assessing and monitoring iodine intake in a population: urinary iodine concentration (UIC), goiter prevalence, serum/dried blood thyroglobulin and neonatal TSH levels (45,46). Table 3 shows the epidemiological criteria for assessing iodine status based on WHO/ICCIDD recommended indicators in target populations, including school-age children (SAC), pregnant women and newborn infants. The key data from studies of UIC in various target populations in Türkiye are given in Table 4. UIC data for schoolchildren and pregnant women in Table 4 will be discussed together with screening TSH data for newborns.

The largest pilot study on neonatal TSH screening in Türkiye was conducted in the early 1990s. When the TSH cutoff was 20 mU/L whole blood, the recall rate and CH incidence were reported as 2.3%, and 1/2736 live births, respectively (32). The high prevalence of elevated TSH levels was attributed to endemic ID in Türkiye. Another regional study found that the incidence of CH at birth was 1/840 using a TSH cutoff of 20 mU/L (37). After the exclusion of transient CH cases, the incidence of permanent CH was 1/2354. The major causes of transient CH are ID and iodine excess (37). The studies by Erdoğan et al. (34) and Erdoğan et al. (35) on goiter prevalence and UIC in SAC before 2000 reported that Türkiye was a moderately ID country, with some severely affected regions (Table 4), which confirmed the data obtained from the previous studies of neonatal TSH screening (32,37).

For correcting ID in Türkiye, a salt iodization program was initiated in 1968 on a voluntary basis. Legislation for mandatory iodization of table salt was passed in 1998, and strictly enforced in 2000. The use of iodized salt corrected ID within a decade in SAC representative of the general population (39), but mild ID persisted in vulnerable groups of the population, such as pregnant women, lactating mothers, and newborn babies (25,26,28,36,38,41,42,43). As noted above, the national NSP data indicate that an ID problem continues (30,31) despite improved iodine intake among the SAC in Türkiye (Table 4) (39,44). A study by Oguz Kutlu and Kara (25) focusing on iodine intake of pregnant women explained the reason for the discrepancy between neonatal TSH levels and UICs in SAC, both of which are indicators of iodine status at the population level (Table 3) (45,46). This study showed that pregnant women living in Ankara, an apparently iodine-sufficient capital city, had a high prevalence of goiter (15%) and a low median UIC (80.5 µg/L), indicating insufficient iodine intake (25). These interesting data demonstrated that iodine nutritional status of SAC does not reflect the iodine supply for pregnant

Table 3. Epidemiological criteria for assessing iodine nutrition of a population based on WHO/ICCIDD recommended indicators (45,46)

Iodine intake	Iodine status	Median UIC (µg/L)	Total goiter rate (%)	Thyroglobulin (ng/mL, DBS)	TSH > 5 mU/L whole blood
School-age children (≥6 years)*					**Newborns**
Insufficient	Iodine deficiency	< 100	≥5	> 40	≥3%
Severity of public health problem	Mild iodine deficiency	50-99	≥30		3-19.9%
	Moderate iodine deficiency	20-49	20-29.9		20-39.9%
	Severe iodine deficiency	< 20	5-19.9		≥40%
Adequate	Adequate iodine nutrition	100-199	< 5	4-40	< 3%
Above requirements	More than adequate†	200-299			
Excessive	Excessive‡	≥300			
Pregnant women**					
Insufficient	Iodine deficiency	< 150			
Adequate	Adequate iodine nutrition	150-249			
Above requirements	More than adequate	250-499			
Excessive	Excessive‡‡	≥500			

*Applies to adults, but not to pregnant and lactating women.
**For lactating women and children < 2 years of age a median UIC of 100 µg/L can be used to define adequate iodine intake, but no other categories of iodine intake are defined. Although lactating women have the same requirement as pregnant women, the median UIC is lower because iodine is excreted in breast milk.
†Likely to provide adequate intake for pregnant/lactating women, but may pose a slight risk of more than adequate intake in the overall population.
‡Risk of adverse health consequences including iodine-induced hyperthyroidism, autoimmune thyroid diseases.
‡‡The term "excessive" for pregnant women means in excess of the amount required to prevent and control iodine deficiency.
DBS: dried whole blood spots, ICCIDD: International Council for Control of Iodine Deficiency Disorders, TSH: thyroid-stimulating hormone, UIC: urinary iodine concentration, WHO: World Health Organization

women. The finding of inadequate iodine nutrition in pregnant women and their offspring was later confirmed in national, multicenter, and large-scale studies (28,42,43).

Although the use of iodized salt in the Turkish population has reached adequate (≥90%) levels (Table 4), salt intake alone has not been enough to meet the increased iodine requirement in pregnant women. Possible reasons for this might be inadequate iodine content of table salts, erroneous consumption of iodized salt, and/or insufficient salt intake. In fact, a surveillance study revealed that only 56.5% of salt samples at the home level had adequate (>15 ppm) iodine content (39), which was well below the minimum target level of 90% recommended by WHO/ICCIDD (46). Another study focusing on the knowledge, attitudes, and behaviors of pregnant women regarding iodized salt consumption found that only 19% stored iodized salt appropriately in lightproof containers and that only 16% added iodized salt properly after cooking into the stewpot or their plate (38). Even if the women correctly consumed adequately (15-40 ppm) iodized salts, their daily salt intake may not be enough to meet the daily iodine requirement. In fact, a person should consume approximately 6-15 g per day of adequately iodized salt to receive the 250-µg iodine recommended by WHO for pregnant women (46). Paradoxically, the WHO recommends a salt intake per person of <5 g/day to reduce the risk of cardiovascular diseases (47). A salt intake below 5 g/day during pregnancy may cause insufficient iodine intake. For this reason, the American Thyroid Association recommends a supplement of 150 µg iodine per day during pregnancy and lactation, in addition to the use of iodized salt (48), but only 5% of pregnant women in our country take iodine supplements (28).

Another important problem in Türkiye is perinatal iodine exposure due to the use of iodine-containing antiseptics for cleaning the perineum before delivery or the umbilical area of the baby. Iodine excess increases neonatal TSH levels and can even induce transient hypothyroidism through the Wolff-Chaikoff effect, usually lasting about 10 days (49). Newborns in iodine-deficient regions may be more susceptible to the Wolff-Chaikoff effect from topical iodine exposure (49). For example, Zonguldak is an iodine-deficient province and povidone-iodine is widely used for antisepsis during delivery. A study conducted in Zonguldak revealed that 61% of 116 newborn babies had iodine excess, even

Table 4. Iodine nutrition status in Türkiye: summary of key studies on urinary iodine concentrations of vulnerable populations

Authors	Study year	Study area	Target population	Number of subjects	Use of iodized salt	Use of iodine supplement	Median UIC (µg/L)	Reference range of UIC	Prevalence of iodine deficiency
Yordam et al. (33)	1997	Yahyalı Ankara	5-24 years 6-15 years	232 2155	None	None	15.7 62.7	100-199	NA
Erdoğan et al. (34)	1997	Black Sea and Ankara	SAC 9-11 years	1226	None	None	21 (14 to 30)	100-199	95%
Erdoğan et al. (35)	1997-1999	Türkiye (20 cities)	SAC 9-11 years	5948	None	None	36 (14 to 78)	100-199	NA
Kurtoglu et al. (36)	2003	Kayseri	Mothers† Newborns	70 70	NA	NA	30.2 23.8	100-199	90% 100%
Kut et al. (38)	2006	Adana	Pregnant w.	141	95%	None	149.7	150-249	50%
Erdoğan et al. (39)	2007	Türkiye (30 cities)	SAC 6-14 years	900	73%‡	None	107 (21 to 338)	100-199	47%
Egri et al. (40)	2007	Malatya	Pregnant w.	824	43%	None	72.3	150-249	99%
Oguz Kutlu and Kara (25)	2008	Ankara	Pregnant w.	168	80%	None	80.5	150-249	73%
Yaman et al. (26)	2012	Zonguldak	Mothers* Newborns	116 116	99%	None	84 279*	100-199	57% 10%*
Celik et al. (41)	2013	Edirne	Pregnant w.	275	97%	None	77	150-249	88%
Oral et al. (42)	2014	İstanbul	Pregnant w.	3487	69%	None	73	150-249	91%
Anaforoğlu et al. (43)	2015	Trabzon	Pregnant w.	864	91%	None	102	150-249	78%
Çelmeli et al. (44)	2015	Antalya	SAC 6-14 years	1594	NA	NA	174.7	100-199	19%
Vural et al. (28)	2018 2020	Türkiye All regions	Pregnant w. Newborns	1444 1444	89%	5.5%	94 96	150-249 100-199	74% 51%

†The median iodine content of breast-milk was 73 µg/L, with 72.9% for the values <100 µg/L. All women delivered spontaneously and had no iodine exposure.
‡Of the 900 household salt samples; 73.5% were iodized, and 56.5% had adequate iodine content (>15 ppm).
*79.3% of the deliveries were caesarean sections (C/S). Iodine-containing antiseptic was used before C/S and normal delivery. Iodine excess (UIC ≥200 µg/L) was 61%.
NA: not available, SAC: school-age children, UIC: urinary iodine concentration, w.: women

though their nursing mothers had ID (Table 4). In this study, the recall rate at screening was found to be 9.5% and three newborns required levothyroxine (L-T4) therapy (26). In conclusion, both maternal ID and perinatal iodine excess are ongoing problems in Türkiye and contribute to the high incidence of elevated neonatal TSH levels.

Unintended Consequence of CH Screening: Neonatal Hyperthyrotropinemia

Newborn screening for CH was first introduced in Canada and USA in the early 1970s (8,9,10). Before the introduction of NSPs, the incidence of CH based on clinical diagnosis ranged from 1/10,000 to 1/7000 live births. The establishment of screening programs has led to an increase in the incidence of CH to 1/3000 to 1/4000 live births (50). Screening strategies and T4-TSH cutoffs have changed over time and thus, the incidence of CH has doubled over the last two decades (27,51,52,53). Although it varies considerably by race and ethnicity, the current incidence of CH is nearly 1/2000 live births worldwide (50,54). The main reason for the increased incidence is mild cases of CH with normal/hyperplastic gland due to dyshormonogenesis (53). Therefore, the rate of dyshormonogenesis in the etiology of permanent CH has increased to 40% (53), as in our patient group from the Black Sea region (27). But, in the eastern region of Türkiye, where consanguineous marriage exceeds 50%, the frequency of dyshormonogenesis in the patients with permanent CH may be as high as 80% (55).

The initial aim of newborn screening was to prevent mental retardation due to severe CH. However, the detection of mostly mild cases of CH and NHT in the current NSPs has led to a management dilemma (56). A systematic review of 46 studies, nine of which investigated the NHT prevalence in a total of 2,715,031 infants, estimated the overall prevalence to be 1/1750 live births, and the calculated NHT:CH ratio was 1.2:1 (19). This meta-analysis showed that in 40% of the NHT cases, serum TSH levels returned to normal without treatment. Of those treated, 11% had to discontinue L-T4 therapy within the first year due to elevated T4 levels. In 30% of the remaining cases, L-T4 treatment was discontinued when TSH level remained normal after re-evaluation at 2-3 years of age (19). In summary, in two-thirds of the NHT cases, TSH elevation resolved in the newborn period or during treatment, but some cases were probably overtreated. Indeed, the Canadian experience reported by Oren et al. (23) showed that 78% (80/103) of infants with mild NHT (TSH 5-30 mU/L) were treated with L-T4, and 45% had evidence of overtreatment (high FT4 and/or low TSH) during follow-up. Moreover, Bongers-Schokking et al. (57) demonstrated that overtreatment of infants with CH during the first two years may be a greater threat to cognitive development than undertreatment. Therefore, overtreatment of NHT may pose a greater risk to later neurodevelopment of these children.

It is also necessary to draw attention to other problematic aspects of transient TSH elevation. Are we doing a good job of identifying mild cases of CH owing to low TSH cutoff at screening, or are we just increasing our clinical workload by detecting mostly false-positive and transient NHT cases? An increase in clinical workload also increases the economic burden by affecting the cost effectiveness of NSPs (58). Let us take the example of Türkiye. Despite a downward trend in recent years, an average of 1,300,000 babies are born in Türkiye each year. Out of 1,292,703 newborns screened with an NSP coverage of 98% in 2015, 13,556 (~1%) were referred for confirmatory testing, and 9950 of them (~73%) were false positives with normal serum TSH and FT4 levels. The remaining 3606 newborns were put in follow-up with suspected CH. Although data on the entire screening program are not available, 6-year follow-up results of 487 infants with elevated screening TSH in 2015 were recently reported by a multicenter study involving 17 pediatric endocrinology centers (29). Serum TSH and FT4 levels were found to be normal in one third of the study group. In addition, 14% had transient NHT that resolved in a median of 35 (21-49.5) days without any treatment. L-T4 treatment was applied to all babies with TSH >20 mU/L and to some babies with milder TSH elevation because the treatment decision was made in accordance with the European guideline (14). Of all treated babies, 54% had transient CH. As a result, only 23% (111/487) of referrals turned out to be permanent CH, 60% of which were due to dyshormonogenesis (29). Since the false-positive rate in this study (33%) was lower than the nationwide rate (73%), the true proportion of permanent CH in the entire screened population might be much lower. In this study, 21%, 42% and 37% of the cases with elevated serum TSH had transient NHT, transient CH and permanent CH, respectively. When this distribution is generalized to the 3606 newborns with elevated serum TSH across all centers, it becomes clear that probably only ~10% of all the 13,556 referrals (n=1334 equal to 37% of 3606) had a final diagnosis of permanent CH. From these figures, an estimated incidence of permanent CH for 2015 can be calculated as 1/969, representing about 2.5-3-fold increase compared to the rates of 1/2736-1/2354 detected with a whole blood TSH cutoff of 20 mU/L (32,37). Moreover, the incidence of transient NHT can be estimated as 1/1708 (for 757 cases, equal to 21% of 3606 infants with elevated serum TSH), which is consistent with meta-analysis data from nine studies (19).

Another issue is that a possible diagnosis of CH can cause great anxiety for family members and guardians. Long-term parental psychological reactions to false-positive screening tests for CH were documented years ago (59). Therefore, the follow-up and treatment of NHT cases with suspicion of CH may cause more concern for families. The data of the multicenter study (29) can also be evaluated from this perspective. The anxiety experienced by nearly 10,000 families due to a false positive result in 2015 is worth considering. Also, if the alternative approach suggested in this article had been applied, the outcome for at least some babies treated with a diagnosis of CH might have been different. Detection of transient NHT without treatment instead of transient CH could have significantly reduced parental stress.

The main problem here is that it is not known whether missing the babies with isolated TSH elevation or leaving them untreated will have adverse developmental effects at later ages. In addition, it is unknown whether L-T4 treatment improves neurodevelopmental outcomes, but overtreatment of NHT may have harmful effects (57). Many physicians choose to "play it safe" and treat babies with NHT (19), whereas available data on the effects of NHT on subsequent development are inconclusive and conflicting (60,61,62,63). For example, Cuestas et al. (60) found suspected developmental delay in 23 % (15/65) of the children with transient NHT at elemental school entry using a 10-question phone survey. Although this rate was higher than 11 % (21/185) in the control group, which implies developmental repercussions of NHT, the developmental assessment in this study was solely based on the subjective evaluations of parents. A population-based record-linkage study by Lain et al. (61) showed an association between poor educational or developmental outcomes and mildly increased neonatal TSH concentrations, which were below screening cutoff of 20 mU/L whole blood (particularly between 12 and 20 mU/L). This valuable study might justify lowering TSH cutoffs to detect milder forms of CH that may be detrimental to brain development. However, an important limitation of this anonymized study was the lack of data on definitive diagnosis, such as transient NHT or transient and permanent CH, which does not allow for a direct link between NHT and any neurodevelopmental outcome. In contrast, Trumpff et al. (62) found that neonatal TSH concentrations between 5 and 15 mU/L were not associated with impaired psychomotor development at preschool age. In this study, in which psychomotor development was assessed at home by a psychologist blinded to TSH values, psychomotor scores did not differ between children with neonatal TSH < 5 (n = 181) and > 5 mU/L (n = 103). A recent study by West et al. (63) also found that mild TSH elevation of 8-14 mU/L at newborn screening was largely transient, and that childhood neurocognitive performance of these children (n = 65) was similar to that of their siblings with normal neonatal TSH. Despite some shortcomings such as small sample size (especially for those with TSH levels close to 14 mU/L), and the absence of data regarding definitive diagnosis, follow-up, and treatment, this study suggests that mild neonatal TSH elevation has no clinically meaningful long-term negative effects. Finally, a systematic review of nine studies on NHT revealed no poor developmental outcome in any of the 94 subjects (19). Nevertheless, the exact neurodevelopmental risks posed by NHT remained unclear because 82 % of these infants received L-T4 treatment. Consequently, the optimal approach to NHT treatment is still a matter of debate, and whether to treat these infants is not a simple decision. A more comprehensive approach to newborns with elevated TSH levels is needed, which is the focus of this article.

An Alternative Approach to Infants with TSH Elevation on Screening

Treating every infant with mild to moderate TSH elevation would be overmedication, especially if other important determinants for the treatment decision were not taken into account, such as FT4 level (in the lower or upper half of the reference range) and TSH trend (increase or decrease by capillary measurement) (56). The possibility of unnecessary treatment is higher in Türkiye and similar countries where ID and excess problems that may cause transient NHT are relatively common (24-43,64,65). For this reason, we consider that in addition to serum FT4 level and TSH trend, the degree of TSH elevation should be evaluated more carefully during the newborn period. To avoid overtreatment in iodine-deficient countries, serum TSH level can be graded as mild (6-20 mU/L), moderate (20-30 mU/L) and severe (> 30 mU/L). In case of severe TSH elevation, L-T4 treatment is started immediately for compensated hypothyroidism, but mild to moderate TSH elevation, which we call isolated NHT, can be managed differently. Namely, mild NHT can be monitored without L-T4 treatment. In moderate NHT, the decision for treatment or follow-up can be made on an individual basis according to the age at confirmatory testing, the absolute FT4 level and TSH trend (Figure 1) (66). Indeed, the Indian Society of Pediatric and Adolescent Endocrinology has recently published its own guideline that recommends the use of higher TSH thresholds for confirmation and treatment of CH (67), compared to the American Academy of Pediatrics' CH guideline (16). In this publication, due to the lack of strong evidence for the treatment of mild CH (that can be thought of as the equivalent of isolated NHT), the authors stated that both guidelines can be followed in terms of the TSH threshold for L-T4 initiation.

The Thyroid Working Group of the Turkish Society for Pediatric Endocrinology and Diabetes recently conducted a survey among its members to question possible attitudes towards alternative approaches to the management of CH. This survey has shown that pediatric endocrinologists in Türkiye do not prefer to treat the infants with mild TSH elevation (< 20 mU/L), and when moderate TSH elevation (up to 40 mU/L) was offered as an option, the majority did not initiate treatment (68). As a result, management of neonatal TSH elevation may vary depending on local conditions. The flow diagram in Figure 1 illustrates such an algorithmic approach to the infants with elevated TSH on neonatal screening. The cornerstones of the approach are explained below, in accordance with the numbers indicated in Figure 1:

1. Capillary TSH screening: Initial part of the algorithm reflects the routine implementation of the current NSP. Please see the section of the national NSP for CH in Türkiye for details.

2. Venous TSH and FT4 measurement: For confirmation, serum TSH and FT4 levels should be measured. Most confirmatory tests are performed at weeks 2 to 3 of life, at which time the upper limit of normal range for serum TSH levels falls to anywhere between 6 and 10 mU/L. According to laboratory methods, the upper limit of TSH in newborns varies between 4.3 and 12.6 mU/L (69). Furthermore, the reference ranges for FT4 levels vary greatly depending on assay methods, with the lower limits ranging from 0.6 to 1.4 ng/dL in the newborn period (69). Therefore, TSH and FT4 levels must be evaluated according to the age- and assay-specific reference ranges.

3. False positive result: Although screening TSH is high, confirmatory test results may be normal. This very short-lasting hyperthyrotropinemia is classified as false positives at CH screening, and should not be considered transient NHT (19,56). Newborn screening before 24 to 48 hours of life causes an increase in false positive results because of the physiological TSH surge after birth. If confirmatory TSH and FT4 levels are normal, there is no need for additional testing and monitoring. Routine well newborn care is sufficient (16).

4. Normal TSH-low FT4: In central hypothyroidism, FT4 is low, and TSH is usually at normal or clearly low levels. However, sometimes there may be mild TSH elevation (5), not exceeding 20 mU/L in newborns (10 mU/L in children), and these cases may be captured in programs that use a low TSH threshold value as in our country (20). In cases of central CH, pituitary magnetic resonance imaging should be performed for etiologic evaluation. Genetic defects that may cause isolated or multiple pituitary hormone deficiencies may be investigated. In differential diagnosis, low T4 syndrome of prematurity and non-thyroidal illness (euthyroid sick) syndrome should be kept in mind. Both conditions mimic central hypothyroidism with low FT4 and TSH levels. Follow-up without treatment is generally recommended in such premature and/or sick babies (70). However, if treatment has been started, it should be stopped and thyroid tests should be repeated after the clinical condition improved.

5. High TSH-low FT4: This combination establishes a diagnosis of primary CH, which requires immediate initiation of L-T4 therapy. Nevertheless, if TSH levels are slightly high (< 20 mU/L), the possibility of central hypothyroidism should still be considered (20). Indeed, the patient may have multiple pituitary hormone deficiencies and coexisting central adrenal insufficiency. Initiation of L-T4 treatment with the thought of primary CH may trigger an adrenal crisis by accelerating cortisol metabolism and clearance (15). In babies with mildly elevated TSH, the adrenal axis should be checked before treatment. Another clue to central CH is that TSH levels fall below normal limits when FT4 levels return to normal with treatment.

Primary CH may occur due to thyroid dysgenesis or dyshormonogenesis (Table 1). After starting L-T4 treatment without delay, the etiology of CH should be determined to ensure a definitive diagnosis of underlying causes, such as ectopic thyroid or athyreosis that require lifelong treatment (15). Both scintigraphy and ultrasonography (US) are recommended for thyroid imaging because each method has some drawbacks in the diagnosis of thyroid dysgenesis (71). Scintigraphy is the best imaging tool to determine ectopic thyroid tissue, which is the most common cause of primary CH in iodine-replete populations (1). However, concerns about radiation exposure and increasing costs may limit the use of scintigraphy. The recent attitude survey revealed that 90 % of pediatric endocrinologists in Türkiye prefer US alone as an imaging modality (68). This choice seems reasonable in order not to expose a large population to radioisotopes in an iodine-deficient country where transient CH and NHT are more common than permanent CH (29). Of note, US is an observer-dependent method, and require an experienced operator, a high-resolution device and special probe in newborns (20). A synchronous evaluation of urinary iodine levels of both infant and mother provides a more accurate assessment of iodine status (26). Serum thyroglobulin measurement may contribute to etiological evaluation; undetectable levels indicate true athyreosis and undetectable or low levels a synthesis defect. Finally,

genetic testing may provide a definitive diagnosis and alter long-term treatment decisions (72).

6. High TSH-normal FT4: This pattern is present in both compensated hypothyroidism and isolated NHT (12,13,17,18,19). In this group, our management approach can be summarized as follows:

• Mild NHT (TSH < 20 mU/L): Follow-up without treatment. Retest after 1-2 weeks.

• Moderate NHT (TSH 20-30 mU/L): Decide based on age, TSH trend and FT4 level.

- Start L-T4 treatment if age at confirmatory thyroid function testing is > 21 days.

- Start L-T4 treatment if serum TSH level shows no downward trend from screening TSH and FT4 level is in the lower half of the reference range in the first 21 days.

- Retest TSH and FT4 at weekly interval if serum TSH shows downward trend from screening TSH, and FT4 level is in the upper half of the reference range.

- Consider deciding based on thyroid imaging in in-between cases; for example, those with a downward trend in TSH but FT4 in the lower half, or *vice versa*.

- Start L-T4 treatment in any case if family is very concerned about high TSH.

• Compensated hypothyroidism (SCH) (TSH > 30 mU/L): Start L-T4 treatment.

• PHT or SCH (TSH > 10 mU/L after neonatal period): Start L-T4 treatment.

- Consider retesting if TSH level is between 6 and 10 mU/L, with a downward trend (TSH level maybe normal up to 10 mU/L depending on assay method).

The etiology of isolated hyperthyrotropinemia is complex. It may result from delayed maturation of the hypothalamic-pituitary-thyroid (HPT) axis, or several transient or permanent thyroid abnormalities. With increasing HPT maturation, molar TSH/FT4 ratio gradually decreases with age, from 15 in the midterm fetus, to 4.7 in term infants, and 0.97 in adults (73). The cold-stimulated TSH surge at birth causes a marked increase in T4 secretion, and HPT axis reaches a new equilibrium by 2-20 weeks (73). The markedly increased TSH concentration at birth (the TSH surge) returns to normal within 24-48 hours. Hence, TSH screening in the first 48 hours causes more false positives. However, in some babies, TSH levels normalize with a delay after confirmatory tests. This condition is characterized by high TSH and FT4 levels and does not require treatment. Indeed, transient NHT is mostly caused by maternal ID and/or perinatal iodine overload. A meta-analysis of six studies from Italy (n = 2), Türkiye (n = 2), Belgium (n = 1) and Japan (n = 1) showed that 46 % of babies with NHT had iodine excess and 16 % had ID (19). Two Turkish studies in the meta-analysis reflect the iodine problem in Türkiye (21,26). For that reason, a history of iodine overload during perinatal period should be questioned. In addition to iodine problems, maternal TSH receptor (TSHR) blocking antibodies and anti-thyroid drugs may cause transient NHT as well as transient CH (Table 1).

Thyroidal morphological abnormalities including large ectopic thyroid, hemiagenesis and hypoplasia may underlie persistent NHT or SCH (74,75,76). Therefore, thyroid imaging can be performed to decide on treatment or follow-up in babies with NHT. While the presence of thyroid dysgenesis requires initiation of L-T4 therapy, normal-sized gland *in situ* cases can be followed without treatment. However, since neonatal TSH elevation is a frequently encountered condition in our country, radiologic examinations performed in every case impose a huge financial burden on families and social security institutions (20). Therefore, we recommend performing thyroid US in infants with moderate NHT, especially in those with discrepancy between TSH trend and FT4 level as mentioned above. In addition, genetic variations in *TSHR*, thyroid peroxidase and dual oxidase 2 may be responsible for isolated NHT (19), which usually persists in later life in the picture of PHT or SCH. This condition will be discussed in the re-evaluation section.

7. Treatment: L-T4 treatment should be started immediately when the diagnosis of CH is confirmed, within the first two weeks of life if possible. The recommended starting doses of L-T4 is 10-15 µg/kg/day, but the dose should be meticulously adjusted to avoid overtreatment according to FT4 level. Indeed, CH can be classified as severe [FT4 < 0.4 ng/dL (< 5 pmol/L)], moderate [FT4 0.4-0.8 ng/dL (5-10 pmol/L)], and mild [FT4 > 0.8 ng/dL (> 10 pmol/L)] (14,15). In severe CH, most likely resulting from athyreosis or complete dyshormonogenesis, L-T4 dose should be the highest (15 µg/kg/day). In moderate CH, possibly caused by an ectopic or hypoplastic thyroid or partial dyshormonogenesis, a dose of ~10 µg/kg/day would be more appropriate. In mild CH and SCH, the dose should be reduced to 5-10 µg/kg/day. In daily practice, a full-term infant with a birthweight over 3 kg should be treated with L-T4 at a dose of 37.5 to 50 µg/day for moderate to severe CH, respectively. For SCH, L-T4 dose of 25 µg/day is usually adequate. Monitoring of treatment requires regular measurements of serum FT4 and TSH levels. If high dose L-T4 is started, thyroid tests should be checked in the first week to avoid overtreatment. Otherwise,

the L-T4 dose can be adjusted with measurements taken every 1 to 2 weeks until TSH levels return to normal limits. TSH level should be kept within the age-specific reference range and care should be taken not to suppress it. Serum FT4 level should be kept in the upper half of the age-specific reference range.

8. Re-evaluation: Re-evaluation of the HPT axis is indicated in CH with gland *in situ*. The guidelines of the European Society of Pediatric Endocrinology and the American Academy of Pediatrics recommend a trial off therapy after the age of 2-3 years (14,15,16). However, treatment may be discontinued earlier in the presence of conditions known to cause transient hypothyroidism, such as maternal blocking antibodies, and ID or overload. Despite low doses of L-T4, suppression of TSH necessitates earlier discontinuation of treatment (27). There is no need for re-evaluation in infants with thyroid ectopia or agenesis, or with TSH elevations that requires an increase in L-T4 doses during follow-up, as the definitive diagnosis is permanent CH (77).

A trial off therapy should be performed in children with normal, large, or small sized and normally located thyroid glands, or in children who have not had a thyroid imaging before starting treatment and whose L-T4 doses have not been increased during the follow-up period. Routinely, after L-T4 therapy is stopped for one month, a full evaluation is made with biochemical tests and imaging. If FT4 level becomes low, and/or TSH level rises over 10 mU/L at the end of this period, permanent CH is confirmed and treatment is restarted (16). It should be remembered that compensatory transient TSH elevation may occur after long-term L-T4 treatment in some overtreated children. Therefore, if FT4 level is within normal limits and TSH increases up to 15 mU/L in the first month of re-evaluation, monitoring is an option (78). If TSH level remains >10 mU/L in the third month of follow-up, treatment is reinstituted.

At re-evaluation, if FT4 and TSH levels are within normal limits in the first month of the trial off therapy, thyroid tests are repeated at the third and sixth months (77). If the values remain within the normal range, a diagnosis of transient CH is established. In these cases, TSH level should be checked during puberty and pregnancy periods when metabolic needs increase.

The third possibility, PHT, is characterized by normal FT4 and mild TSH elevation (5-10 mU/L), and occurs in about one-third of cases at re-evaluation (78). The management of PHT is another matter of debate, but most practitioners elect to treat cases of PHT, as in NHT (16). In fact, most of children with PHT have been already treated with a diagnosis of NHT/SCH since the neonatal period. Therefore, these children may have to receive lifelong treatment, even though there is no proven benefit. Leonardi et al. (74) showed that TSH levels returned to normal by age 9 years in 68 % of children with mild PHT detected at CH screening. In this study, the children with ongoing PHT had thyroid morphological and/or genetic abnormalities. Likewise, we observed that TSH levels normalized between the ages 5 and 9 years in some children with mild PHT who had no morphological or genetic abnormalities. However, the children whose PHT did not resolve had heterozygous variants in the *TSHR* gene (72). In summary, PHT may be a condition that resolves spontaneously in late childhood, possibly due to extremely delayed maturation of the HPT axis, or may be the result of an underlying structural or genetic defect. Therefore, treatment decision in PHT cases should be made on an individual basis.

Conclusion

Transient NHT is a common condition in Türkiye, and mostly occurs due to ID and overload problems in pregnant women and their offspring. Therefore, the recommendation to start treatment for every infant with a TSH level >20 mU/L may not be applicable. Monitoring of babies with mild to moderate TSH elevation will generally be an appropriate approach to avoid overtreatment. L-T4 treatment should be reserved for newborns with TSH >30 mU/L, and infants with PHT. However, all treated cases of NHT/PHT should be re-evaluated by a trial off therapy after two years of age. Nevertheless, it should be kept in mind that transient NHT or CH caused by ID or excess may resolve in a short time, which may require earlier discontinuation of treatment. This alternative approach will largely eliminate unnecessary treatment of infants with transient neonatal TSH elevation, and will reduce workload and costs by preventing unwarranted investigation and long-term follow-up.

Ethics

Footnotes

Authorship Contributions

Concept: Cengiz Kara, Hüseyin Anıl Korkmaz, Design: Cengiz Kara, Hüseyin Anıl Korkmaz, Data Collection or Processing: Cengiz Kara, Hüseyin Anıl Korkmaz, Analysis or Interpretation: Cengiz Kara, Hüseyin Anıl Korkmaz, Literature Search: Cengiz Kara, Hüseyin Anıl Korkmaz, Writing: Cengiz Kara, Hüseyin Anıl Korkmaz.

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