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What is the ideal thyroid-stimulating hormone (TSH) threshold value in congenital hypothyroidism screening? Twin study

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Abstract

Congenital hypothyroidism is the most common preventable cause of intellectual disability. Therefore, the majority of developed countries have aimed to diagnose cases early through screening programs. In these screening programs, levels of thyroid-stimulating hormone (TSH) and free thyroxine are examined in dried blood spots taken between days 3 and 5 of life. While many countries accept TSH threshold value of 8 mU/L, there is still no consensus on the ideal TSH threshold value. As no twin studies on the TSH threshold value have been conducted previously, this study was planned. Eight pairs of twins were included in the study, with one of the twins having plasma TSH value ≥8 mU/L and the other <8 mU/L, measured between days 3 and 5 of life. The study aimed to investigate whether determining threshold TSH value of 8 mU/L would be beneficial by comparing somatic growth, mental development, and neuromotor development between twins. The age, gender, gestational weeks, birth weights, height, weight, and initial TSH values taken between days 3 and 5 of all cases were recorded. The patients' plasma Vitamin B12, folate, 25-OH Vitamin D, ferritin, and hemoglobin levels were measured. After that, they were evaluated by a child and adolescent psychiatry. Finally, the Denver Developmental Test was applied to the cases. There was no significant impairment in somatic growth, mental development, and neuromotor development in the long-term outcomes of cases with plasma TSH ≥ 8 mU/L compared to those with plasma TSH < 8 mU/L among the twins participating in our study.

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, CH = congenital hypothyroidism, T4 = thyroxine, TSH = thyroid-stimulating hormone.

Keywords: congenital hypothyroidism, screening, thyroxine, TSH

1. Introduction

Congenital hypothyroidism (CH) is the most common cause of preventable intellectual disability. The majority of CH cases arise due to structural anomalies of the thyroid gland (dysgenesis) or defects in hormone biosynthesis despite normal gland structure (dyshormonogenesis). CH is reported in approximately 1 in 2000 to 4000 births.[1] Thyroid hormone plays a crucial role in regulating the functions of almost all organ systems. Therefore, CH affects all organ systems.[2]

In many socioeconomically developed countries, CH has been diagnosed through newborn screening programs for approximately 40 years. Early diagnosis and treatment can prevent late complications, including neurocognitive impairment.[3] However, globally, around 70% of newborns do not undergo screening for CH.[4] Three test strategies are used in screening programs: primary thyroid-stimulating hormone (TSH)–reflex T4, primary T4–reflex TSH, and combined TSH–T4. Most countries use the primary TSH–reflex T4 strategy. Screening examines TSH levels in dried blood spots collected between the 3rd and 5th days. However, congenital central hypothyroidism cases can be missed with this screening strategy.[3] In the Dutch newborn screening program, combined plasma free T4, TSH, and thyroglobulin levels are screened. This allows for the easy detection of central hypothyroidism cases.[5] As countries gain more experience with CH screening, the TSH cutoff values have been lowered. For example, Ireland has accepted a TSH cutoff value of 8 mU/L since 1979.[1] In Japan, the cutoff TSH value in the screening program is accepted as 15 mU/L. In Israel, plasma FT4 levels are screened, and if they are <10th percentile, plasma TSH levels are checked. If plasma TSH levels are >20 mU/L, the infant is referred to a pediatrician.[6] In the UK CH screening program, TSH values of <8 mU/L in dried blood spot samples are considered negative. If repeated samples show >8 mU/L, the infant is referred to a pediatric clinic.[7] Greece, Lithuania, and Norway are other countries that accept the cutoff value of 8 mU/L in dried blood spot samples.[5] In our country, a TSH value of <5.5 mU/L from dried blood spots is considered

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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normal, while a value of >20 mU/L leads to referral to a pediatrician for plasma TSH and free T4 testing. If the TSH value in the dried blood spot is between 5.5 and 20 mU/L, the test is repeated.[8]

There is no consensus on the TSH threshold value in CH screenings. In this study, we compared twins, one with plasma TSH < 8 mU/L and the other with TSH > 8 mU/L. The aim of this study was to answer the question: "Can a plasma TSH cutoff value of 8 mU/L be considered acceptable in CH screening?" Twin cases born in our hospital in the last 6 years were examined and one of the twins included in the study had plasma TSH value of ≥8 mU/L on the 3rd to 5th day of their lives, while the other had plasma TSH value of <8 mU/L. We investigated whether setting a plasma TSH cutoff value of 8 mU/L is beneficial by comparing somatic growth, mental development, and neuromotor development between the twins.

It is known that various factors, such as puncture site, blood spot size, hematocrit level and birth weight can influence TSH levels in capillary dried blood spots.[9] Therefore, our study was designed based on plasma TSH level measurements rather than dried blood spot samples.

2. Methodology

This study was conducted at Düzce University Research Application and Research Hospital between July and December 2023. We reviewed retrospective data from our hospital. We identified 8 pairs of twins with plasma TSH levels checked between 3rd and 5th days after birth, with 1 twin having TSH level of <8 mU/L and the other >8 mU/L. The age, gender, gestational weeks, birth weights, height, weight, and plasma TSH levels taken between the 3rd and 5th days of the cases were recorded. TSH and sT4 levels were analyzed using the Roche Cobas E602 device and Elecsys TSH kits. This kit utilizes a sandwich method in its working principle. In this method, a 50 µL sample forms a sandwich with a biotinylated, TSH-specific monoclonal antibody and a TSH-specific antibody labeled with a ruthenium complex. During the second incubation, streptavidin-coated particles are added and bound to the solid phase. This reaction mixture is aspirated into a measurement cell, and the microparticles are measured based on their electromagnetic binding to the surfaces of the electrodes. Hemoglobin, ferritin, Vitamin B12, folate, and 25-OH Vitamin D levels were examined. All cases were then evaluated by a child and adolescent psychiatrist in terms of accompanying psychopathologies. Denver II Developmental Screening Test was applied to all cases participating in the study. Cases born before 34 weeks of gestation, intrauterine growth retardation, those requiring resuscitation after birth, patients with CH, individuals with transient TSH elevation, those with chronic diseases, and cases with malnutrition were excluded from the study.

Table 1

Some demographic characteristics and birth/pregnancy features.

		n	%
Gender	Boy	5	31.25
	Girl	11	68.75
Hyperactivity	Yes	4	25.00
	No	12	75.00
Anxiety	Yes	2	12.50
	No	14	87.50
Developmental disability	Normal	16	100.00
	Suspect	0	0.00
Denver developmental test	Normal	12	75.00
	Suspect	4	25.00

Written informed consent was obtained from the parents of the patients.

The Denver II Developmental Screening Test was administered to each child included in the study. This scale evaluates 4 developmental areas in children aged 0 to 6 years: personal-social, fine motor, language, and gross motor. The test began by drawing the "age line" according to the child's age. Evaluation was made with special materials developed for the test, and the child's functional skills were scored by comparing them with their peers. As a result of the scoring; Three types of outcomes were determined: normal, suspicious and abnormal.

This research involving human subjects complied with all relevant national regulations and institutional policies and was conducted in accordance with the tenets of the Helsinki Declaration. This study was approved by Düzce University Faculty of Medicine Ethics Committee (Decision no: 2021/163 Approval Date: 16.10.2023).

3. Statistical analysis

Descriptive statistics were used to present numerical data as mean and standard deviation, while categorical data were presented as frequency and percentage. SPSS 23.0 software package was utilized for the analyses.

4. Findings

A total of 8 twin pairs were included in the study. The average age of the children was found to be 5.25 ± 1.24 years. Upon examining the gender distribution of the children, it was found that 5 were male and 11 were female. Demographic characteristics as well as birth and pregnancy features of all twin pairs are presented in Table 1.

The sociodemographic data of children, including age, gestational age, weight, height, along with laboratory data, showing mean, median, and standard deviation values, are presented in Table 2.

The Denver Developmental Tests, anxiety, and cognitive developments were examined based on the status of plasma TSH levels in all twins, categorized as TSH < 8 mIU/L and TSH ≥ 8 mIU/L. Cognitive development was normal in all twins. Anxiety was present in 1 twin pair. Among the 4 cases with Attention Deficit Hyperactivity Disorder (ADHD), 2 were siblings. The other 2 cases were twins with plasma TSH levels < 8 mIU/L. The Denver Developmental Test results were classified as suspicious in 1 twin pair (Table 3).

Sociodemographic data (such as age, gestational week, weight, and height) and laboratory data were examined for all twins based on the categories of plasma TSH < 8 and TSH ≥ 8 levels (Table 4).

Table 2

Sociodemographic including age, gestational age, weight, height, etc and laboratory data.

	Mean	Median	SD
Age (year)	5.25	5.50	1.24
First plasma TSH (mIU/L)	7.86	7.25	3.44
Gestational age (week)	36.63	37.00	0.50
Weight (kg)	18.12	17.25	4.19
Height(cm)	111.06	107.50	11.60
Plasma folate (ng/mL)	10.82	9.20	5.48
Hemoglobin (g/dL)	11.41	11.50	0.82
Ferritin (ng/mL)	28.44	25.50	13.64
Plasma Vitamin B12 (pg/mL)	469.50	457.00	123.95
Control plasma TSH (mIU/L)	1.94	1.90	0.90
Plasma free T4 (ng/dL)	1.29	1.30	0.18
Plasma 25-OH vit D (ng/mL)	24.50	21.50	8.51
Birth weight (g)	2.493	2.615	376.83

TSH = thyroid-stimulating hormone.

Table 3

Denver developmental test, anxiety, and cognitive development based on the initial plasma TSH levels of all twins, categorized as TSH < 8 mIU/L and TSH ≥ 8 mIU/L.

		Hyperactivity		Anxiety		Cognitive development		Denver development test	
		Yes	No	Yes	No	normal	Suspect	Normal	Suspect
T1	TSH < 8	1	0	0	1	1	0	1	0
	TSH ≥ 8	0	1	0	1	1	0	1	0
T2	TSH < 8	1	0	1	0	1	0	0	1
	TSH ≥ 8	1	0	1	0	1	0	0	1
T3	TSH < 8	0	1	0	1	1	0	1	0
	TSH ≥ 8	0	1	0	1	1	0	1	0
T4	TSH < 8	1	0	0	1	1	0	1	0
	TSH ≥ 8	0	1	0	1	1	0	1	0
T5	TSH < 8	0	1	0	1	1	0	1	0
	TSH ≥ 8	0	1	0	1	1	0	1	0
T6	TSH < 8	0	1	0	1	1	0	0	1
	TSH ≥ 8	0	1	0	1	1	0	0	1
T7	TSH < 8	0	1	0	1	1	0	1	0
	TSH ≥ 8	0	1	0	1	1	0	1	0
T8	TSH < 8	0	1	0	1	1	0	1	0
	TSH ≥ 8	0	1	0	1	1	0	1	0

TSH = thyroid-stimulating hormone.

5. Discussion

In our study, 8 twin pairs with plasma TSH levels > 8 mU/L and those with < 8 mU/L measured on days 3 to 5 were compared with each other. All participants exhibited normal cognitive development. Anxiety was present in 1 twin pair. ADHD was present in 1 twin, while the other 2 cases with ADHD had plasma TSH levels < 8 mU/L. The Denver Developmental Test results were classified as suspicious in 1 twin pair. There was 1 case where height and weight development were not appropriate for the patient's age. His plasma TSH was also <8 mU/L.

Approximately 70% of CH arises from thyroid dysgenesis (agenesis, hemiagenesis, hypoplasia, ectopy), while 30% is due to dishormonogenesis.[1] A rare cause of CH is central hypothyroidism, which occurs as a result of hypothalamic or pituitary anomalies. It is observed in approximately 1 in 20,000 births.[10]

The normal thyroid tissue secretes 80% of its hormones in the form of prohormone called thyroxine (T4), while 20% exist in the active hormone form known as tri-iodothyronine. These 2 hormones exert their effects through thyroid hormone nuclear receptors, which are highly expressed in the central nervous system, myocardium, skeletal muscle, intestines, bones, liver, kidneys, pituitary gland, and hypothalamus. Since thyroid hormone plays a crucial role in regulating the functions of nearly all organs, CH is a disease that affects all systems.[2]

Cognitive impairment is a common condition in CH. Although the majority of patients who receive timely treatment and appropriate doses achieve normal intelligence levels, it has been reported that some patients continue to experience persistent deficits compared to healthy control groups.[4] In our study, all cases that participated exhibited cognitive development appropriate for their age.

CH often accompanies various neurobehavioral problems. Studies have reported a high prevalence of attention deficit hyperactivity disorder in CH patients.[11] In our study, ADHD was identified in 4 cases among the participants. Two of these cases were siblings, while the other 2 cases had initial plasma TSH levels < 8 mU/L.

Anxiety disorder is another neurobehavioral disorder commonly associated with thyroid diseases. In a study conducted by Ittermann et al, anxiety was reported to be prevalent in hypothyroid patients.[12] In our study, anxiety disorder was identified in 2 siblings.

The Denver Developmental Screening Test is a simple test designed to screen the development of infants and preschool-aged children. It assesses gross motor, fine motor, language, and personal-social development. In a study conducted by Bulus et al, it was reported that there were no significant differences between CH patients and the control group in terms of personal-social skills, fine motor skills, and language development. However, significant delays were observed in gross motor development in the CH group.[13] The Denver test results of the twins participating in our study were similar; with suspected developmental delay identified in 2 pairs of twins.

It is well-known that thyroid hormones play a crucial role in somatic growth. While some studies report that early treatment in CH patients leads to achieving normal linear growth, Heyerdahl et al reported that the linear growth of CH patients is delayed.[14,15] In our study, the cases were generally similar to their twins in terms of height and weight. A difference between siblings was observed in only 1 pair of twins. The patient with plasma TSH < 8 mU/L had weight and height percentiles above the 99th percentile, while their sibling's weight was at the 40th percentile and height at the 78th percentile.

The hemoglobin, ferritin, Vitamin B12, folate, 25-OH Vitamin D, control plasma TSH, and free T4 levels of the twins participating in our study were quite similar. Mitchell et al reported in their study involving 1604 twins and siblings that plasma 25-OH Vitamin D levels in twins were correlated throughout the year.[16] Nilsson et al reported in their study involving 216 monozygotic and dizygotic twin pairs that plasma folate, B12 Vitamin, plasma TSH, and free T4 levels showed high correlation.[17]

In newborn screening programs, setting the threshold value too low increases false positives, which can create workforce and economic disadvantages.[18] Furthermore, studies have reported that false positives in newborn screenings can cause long-term anxiety in families.[19] Setting the threshold too high, on the other hand, leads to false negatives, resulting in delays in the diagnosis and treatment of CH. There is currently no consensus on the optimum TSH threshold value.[18] Twin studies are known to be important for evaluating the contribution of genetic and environmental factors to a specific disease.[20] Twin studies can also provide valuable insights for determining the plasma TSH cutoff value.

It was determined that the long-term results of linear development, neuromotor development and cognitive development of patients with plasma TSH > 8 mU/L were not retarded compared to patients with <8 mU/L. According to our study, a higher plasma TSH level should be determined for CH screening.

Table 4

Sociodemographic data (age, gestational week, weight, height, etc) and laboratory data of all twins based on the categories of first plasma TSH values < 8 mIU/L and TSH ≥ 8 mIU/L levels.

		Weight (kg)	Height (cm)	Folat (ng/mL)	Hb (g/dL)	Vit B12 (pg/mL)	Control TSH (mIU/L)	Free T4 (ng/dL)	25(OH) vit D (ng/mL)
T1	TSH < 8	29	122	16.7	12.4	327	2.6	1.7	24
	TSH ≥ 8	18	114	13.0	12.3	469	2.9	1.6	22
T2	TSH < 8	18	111	18.0	12.5	396	1.5	1.4	16
	TSH ≥ 8	17	108	20.0	12.0	428	1.9	1.4	17
T3	TSH < 8	24	133	11.8	11.7	505	1.9	1.0	19
	TSH ≥ 8	24	134	11.5	11.8	528	2.1	1.1	17
T4	TSH < 8	19	120	4.5	10.5	446	2.5	1.3	18
	TSH ≥ 8	19	118	6.1	11.0	414	2.8	1.3	21
T5	TSH < 8	15	99	5.9	11.6	655	1.3	1.2	22
	TSH ≥ 8	16	101	4.6	11.4	490	1.3	1.2	22
T6	TSH < 8	16	106	9.3	10.0	465	.8	1.2	21
	TSH ≥ 8	16	105	6.8	9.7	449	.9	1.3	20
T7	TSH < 8	14	97	9.1	11.2	628	2.1	1.3	39
	TSH ≥ 8	14	98	7.8	11.1	732	4.2	1.1	36
T8	TSH < 8	18	107	18.2	12.0	312	1.2	1.3	38
	TSH ≥ 8	16	104	19.8	11.3	268	1.1	1.2	40

TSH = thyroid-stimulating hormone.

6. Conclusion

Twin studies are highly valuable due to their ability to control for numerous variables. Given the lack of consensus on the TSH threshold value in CH screenings, we conducted this twin study. To our knowledge, no twin studies have been conducted specifically to determine the TSH cutoff value. In this study, we compared twins with plasma TSH values above and below 8 mU/L, measured within the first 3 to 5 days after birth. Long-term outcomes regarding somatic growth, intellectual development, and neuromotor development showed no significant differences between twins with plasma TSH levels ≥ 8 mU/L and those with levels < 8 mU/L in our study.

7. Limitation

The number of cases is the limitation of our study.

Author contributions

Conceptualization: Fatih Kurt, Kenan Kocabay.
Data curation: Fatih Kurt.
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Investigation: Fatih Kurt, Busra Olcay Oz, Kenan Kocabay.
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