Characteristics of Delayed Thyroid Stimulating Hormone Elevation in Neonatal Intensive Care Unit Newborns

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Objectives To elucidate the incidence, clinical characteristics, and short-term outcome of delayed thyroid stimulating hormone (TSH) elevation (dTSH) in a large cohort of newborns admitted to the neonatal intensive care unit.

Study Design Data were gathered from a cohort of 13 201 newborns admitted to the neonatal intensive care unit born between January 1, 2008, and October 31, 2014, who underwent TSH measurements because of low T4 levels on the second screen. The data from the newborn screening program included gestational age, birth weight (BW), T4 levels, and short-term outcome.

Results Of 13 201 newborns, 333 (1:40) presented with dTSH (TSH >15 IU/L). dTSH had a peak proportion at gestational age of 37-39 weeks, and 66% of the patients had BW >1500 g. T4 levels in the 333 patients were negatively correlated with TSH levels (R = –0.505; $P < .001$), and significantly lower than levels in the other newborns: 5.9 ± 2.8 vs 7.6 ± 1.7 μg/dL; $P < .001$. TSH levels in dTSH newborns were already higher on the initial screen compared with the other newborns: 8.3 ± 5.2 vs 4.2 ± 3.7 IU/L; $P < .001$. Fifty-eight percent of 193 patients with dTSH were started on levothyroxine treatment.

Conclusions dTSH has a higher incidence than previously reported, especially among newborns with BW >1500 g. Relatively high TSH and low T4 levels on the initial and second screen respectively are predictors for dTSH. Levothyroxine treatment is required in most cases. *(J Pediatr 2016;178:135-40).*

Neonatal screening programs were designed to detect congenital hypothyroidism within the first 72 hours after birth to enable prompt treatment of affected infants.[1] In specific subpopulations of neonates, however, the initial screening may be insufficient, and additional screening is required a few weeks later to reveal a late rise of thyroid stimulating hormone (TSH).[1] In an early study of 71 infants with congenital hypothyroidism, delayed TSH elevation (dTSH) was common among low birth weight (LBW) newborns (mostly extremely LBW [ELBW]; <1000 g) who presented initially with low T4 but normal TSH (nTSH) levels.[2] This report initiated several large-scale, population-based retrospective studies that were based on a neonatal screening database in New England[3,4] and other newborn screening programs.[5-7] These studies reported that dTSH prevalence was very low among normal BW (NBW; >2500 g) newborns and increased by an order of magnitude in the subgroups of LBW (1500-2499 g) and very LW (VLBW; 1000-1499 g) newborns,[3,4] being the highest among ELBW newborns.[7] In addition, a disproportionate number of infants with dTSH were premature.[5]

Accordingly, the guidelines of both the European and the American pediatric and endocrinology societies recommend a second screening for LBW and VLBW neonates, preterm neonates with gestational age (GA) of less than 37 weeks, and ill and preterm neonates admitted to the neonatal intensive care unit (NICU).[1,8] Several small-scale reports claimed that dTSH was mostly transient.[3,4,7]

Postulated causes for dTSH include immaturity of the hypothalamic-pituitary-thyroid (HPT) axis,[9,10] administration of medications with suppressive effects on the HPT axis, such as glucocorticoids[11] and dopamine,[7,12] exposure to the thyroid suppressive effect of iodine-containing topical antiseptics,[4,13] and recovery from euthyroid sick syndrome in association with severe stressful events, such as sepsis, surgical intervention, and congenital heart diseases.[4,14]

The objectives of this study were to determine the incidence, clinical and hormonal characteristics, best timing for the second screen, and short-term outcome of dTSH in a large cohort of newborns admitted to the NICU.

BW	Birth weight
dTSH	Delayed TSH elevation
ELBW	Extremely LBW
GA	Gestational age
HPT	Hypothalamic-pituitary-thyroid
LBW	Low BW
NBW	Normal BW
NICU	Neonatal intensive care unit
nTSH	Normal TSH
TSH	Thyroid stimulating hormone
TT4	Total T4
VLBW	Very LBW

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Methods

The study is based on the Israeli national newborn screening database. During the study period, newborn screening for congenital hypothyroidism was routinely practiced by measuring total T4 (TT4) at 48-72 hours of age, with a subsequent measurement of TSH at low levels of TT4.[15] However, neonates admitted to the NICU were initially tested for TSH, followed by TT4 measurement if TSH was elevated (ie, ≥20 IU/L). It was recommended that TT4 would be tested at 10-30 days of age in newborns who stayed in the NICU, and low TT4 levels triggered TSH testing. Low TT4 levels both in the first and second screen were defined by the lowest 10th percentile of the entire TT4 measurements each day. Because the main aim of our study was to elucidate the characteristics of dTSH, we included only newborns admitted to the NICU tested twice for TSH levels (ie, both on the first screen and a few weeks later) because of low TT4. All newborns included in this study were tested as part of the routine screening program and not because of clinical signs compatible with hypothyroidism.

Between January 1, 2008, and October 31, 2014, a total of 1 172 791 newborns were screened for congenital hypothyroidism on the third day of life, and about 10% of them were newborns admitted to the NICU, as shown in the database flowchart (**Figure 1**; available at www.jpeds.com). Newborns diagnosed with congenital hypothyroidism on the initial screen (n = 342), newborns positive for other diseases diagnosed on newborn screening (n = 3495), and newborns discharged before the second screen (n = 73 958) were excluded. Out of 23 384 newborns admitted to the NICU evaluated, 13 201 (56%) presented with low TT4 and were subsequently tested for TSH (**Figure 1**).

The study protocol was approved by the Ethics Committee of Kaplan Medical Center. We gathered the following clinical and hormonal data from our cohort of 13 201 newborns admitted to the NICU: sex, GA, BW, single vs multiple pregnancy, day of second screen, TT4 (in the second screen), and TSH levels both in the first and second screen.

According to the algorithm of the national newborn screening program, in case of low T4 and high TSH (>20 IU/L), regional health bureaus or local hospitals were informed. Subsequently, repeated tests of serum free T4 and TSH were performed, and a decision was made by the local endocrinologists on treatment initiation and thyroid gland imaging. Data on this short-term follow-up were obtained by phone calls to the local physicians and recorded in the national screening program.

Statistical Analyses

Clinical and hormonal measurements in different groups were compared using Student *t* test and Mann-Whitney rank sum test for nonparametric data. For comparison of measurements between multiple groups, we used 1-way ANOVA and Kruskal-Wallis 1-way ANOVA by ranks in cases of nonparametric data. To isolate which group or groups differ from the others, we performed multiple comparison procedure by Dunn test. Differences in measurements expressed as a percentage were calculated by comparing proportions with Yates correction applied to the calculation. A correlation between TT4 and TSH levels was performed by Pearson correlation. Data are presented as mean ± SD. A P value of <.05 was considered significant. Statistical analysis was performed using Sigmaplot/Sigmastat software (Jandel Corporation, San Rafael, California).

Results

The study population included 13 201 newborns admitted to the NICU (54% males) with low TT4 on the second screen that were subsequently tested for TSH. Out of the entire cohort of 13 201 newborns, 333 (51% males) had TSH level above 15 IU/L (ie, defined as dTSH [1:40]) (**Figure 1**).

The newborns with dTSH were further divided into 3 TSH-based subgroups of low (15.1-20.0 IU/L), medium (20.1-40.0 IU/L), and high (>40 IU/L) TSH level, with a similar number of newborns in each subgroup (**Figure 1**).

Clinical Characteristics of Newborns with dTSH

Two hundred ninety-five out of 333 newborns (89%) with dTSH compared with 12 322 out of 12 868 newborns (96%) with low TT4 but nTSH levels on the second screen (nTSH group) were born premature (ie, at <37 weeks of GA) ($P < .001$ between the groups). Similarly, mean GA was higher in newborns with dTSH than in newborns with nTSH (**Table I**). Although most newborns in our study were born premature, the incidence of dTSH was proportionally higher in full-term (ie, GA 37-39 weeks) than in premature newborns (**Figure 2**). By comparison to the nTSH group, the proportion of newborns born at 37-39 weeks was higher in the group with dTSH (**Table II**); 303 out of 333 newborns (91%) with dTSH compared with 12 153 out of 12 868 newborns (94%) in the nTSH group had BW ≤2500 g ($P = .012$ between the groups). Similarly, mean BW was higher in newborns with dTSH than in newborns with nTSH (**Table I**).

The incidence of dTSH was proportionally higher in the 2 opposite groups of ELBW and NBW than in the other BW-based groups (**Figure 2**). By comparison with the group with nTSH, the proportions of ELBW and NBW newborns were higher, whereas the proportion of LBW newborns was lower in the group with dTSH (**Table III**). Notably, 220 of 333 newborns with dTSH (66%) had BW above 1500 g.

Hormonal Characteristics of Newborns with dTSH

Although the entire cohort of 13 201 newborns had low TT4 on the second screen, those with dTSH had significantly lower TT4 levels than the newborns with nTSH (**Table I**).

Table I. A comparison between newborns admitted to the NICU with dTSH and nTSH on the second screen

	Patients (dTSH)	Newborns with nTSH	*P* value
No.	333	12 868	
Age (d)	19.3 ± 10.6	20.7 ± 10.8	.021
BW (g)	1736 ± 682	1673 ± 534	.040
GA (wk)	32.8 ± 3.3	32.1 ± 3.0	<.0001
TT4 (μg/dL)	5.9 ± 2.8	7.6 ± 1.7	<.0001