Risk Factors for the Development of Delayed TSH Elevation in Neonatal Intensive Care Unit Newborns

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Context: Delayed thyrotropin (TSH) elevation (dTSH) is defined as elevated TSH at the second neonatal screening (after normal TSH levels at the initial screening) in premature, low-birth-weight, and ill newborns, mostly in the neonatal intensive care unit (NICU) setting. The pathogenesis of dTSH is elusive.

Objective: To identify the risk factors for dTSH development among newborns in the NICU.

Design, Setting, and Patients: A retrospective medical record review of neonates with dTSH was conducted in eight university-affiliated NICUs. Two controls were selected for each patient, matched for sex and birth weight. The risk factors for dTSH were identified by univariate analysis, followed by multivariate analysis.

Main Outcome Measures: Maternal variables, types of NICU treatments and procedures, syndromes, and various medical conditions were compared between dTSH patients and their matched controls.

Results: We enrolled 100 dTSH patients and 200 matched controls and 46 variables were compared between the two groups. Twelve risk factors for dTSH were identified on univariate analysis: cesarean section, mechanical ventilation, patent ductus arteriosus (PDA), pneumothorax, and administration of cefotaxime, vancomycin, fluconazole, dopamine, ibuprofen, furosemide, insulin, and packed red blood cells. On multivariate analysis, four risk factors were identified: PDA and vancomycin, insulin, and furosemide administration. In 26 twin pairs, in which one twin had dTSH, all variables presented similarly in both twins.

Conclusions: Although some variables had direct effects on pituitary–thyroid axis dysfunction, these variables, altogether, reflect the severity of the clinical conditions in the NICU, which is the common basis for dTSH. (***J Clin Endocrinol Metab*** **102: 3050–3055, 2017)**

Delayed thyrotropin (TSH) elevation (dTSH) is defined as elevated TSH at the second neonatal screening after normal TSH levels at the initial screening, irrespective of thyroxine (T4) levels. A second screening is currently recommended by both the European and the American Pediatric and Endocrinology societies for

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Abbreviations: dTSH, delayed thyrotropin elevation; GA, gestational age; HPT, hypothalamic–pituitary–thyroid; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PRBC, packed red blood cell; T4, thyroxine; TSH, thyrotropin; TT4, total thyroxine.

low-birth-weight (weight, 1500 to 2499 g) and very-low-birth-weight (weight, 1000 to 1499 g) neonates, preterm neonates with a gestational age (GA) of <37 weeks, and ill neonates admitted to the neonatal intensive care unit (NICU) (1, 2). These recommendations are based on the findings from several largescale, population-based retrospective studies (3–7) that showed that dTSH is rare among normal-birth-weight newborns (>2500 g), increases by an order of magnitude in subgroups of low-birth-weight and very-low-birth-weight newborns (3, 4), and is greatest among extremely-low-birth-weight (<1000 g) newborns (7). In addition, a disproportionate number of infants with dTSH are premature (5).

In contrast to these studies, we have recently reported that dTSH is much more common than previously reported (1 of every 40 NICU newborns with low T4), especially among newborns with a birth weight >1500 g (66% of our entire series) (8).

The precise etiology of dTSH is still unknown. Postulated causes include immaturity of the hypothalamic–pituitary–thyroid (HPT) axis (9); administration of medications with suppressive effects on the HPT axis, such as glucocorticoids (10) and dopamine (7, 11); exposure to the thyroid-suppressive effect of iodine-containing topical antiseptic agents (4, 12); and recovery from euthyroid sick syndrome in association with severe stressful events, such as sepsis, surgical intervention, and congenital heart disease (4, 13). In a recent study (8), we refuted some of the suggested risk factors for dTSH. The high incidence of dTSH observed among full-term and normal-birth-weight newborns did not support the postulated explanation of delayed maturation of the HPT axis, which is typical of premature newborns. In addition, our observation that the TSH levels were already mildly elevated soon after birth (*i.e.,* weeks before the late elevation of TSH) refuted the hypothesis that dTSH reflects a recovery from euthyroid sick syndrome. In an editorial published in 2011, Lafranchi (14) also raised doubts about the role of immaturity of the HPT axis in the evolution of dTSH and emphasized that the etiological role of drugs such as dopamine was not well established.

In the present study, we aimed to identify risk factors for the development of dTSH by comparing a large group of newborns with dTSH to a matched control group in an NICU environment.

Subjects and Methods

Study population

We conducted a retrospective medical record review of all neonates with a diagnosis of dTSH from 1 January 2008 to 31 October 2014 in eight university-affiliated NICUs in Israel. The neonates with dTSH were gathered from a cohort of 333 neonates (from 27 NICUs) with dTSH diagnosed through the Israeli National Newborn Screening program from 1 January 2008 to 31 October 2014 and reported in our previous study (8). In the present study, however, only eight NICUs with a relatively high number of neonates with dTSH were included. dTSH was defined as a TSH level >20 IU/L at the second screening, which excluded 97 neonates with mildly elevated TSH levels (range, 15.1 to 20 IU/L) from the original cohort. The exclusion criteria were hypothyroidism at the first screening and discharge or transfer of the neonate to another NICU before the second screening.

For each neonate with dTSH, we selected two neonates from the NICU without dTSH, who had been born in the same year and were matched for sex and birth weight (control group). In most cases, the controls were matched from the same NICU. In a few cases, controls from another NICU were matched for sex and birth weight. Another comparison was performed with twin pairs, for which only one of the twins had dTSH. According to the Israeli National Newborn Screening protocol for neonates in the NICU, all neonates underwent the first screening for TSH at 48 to 72 hours of age, followed by a second screening for total T4 (TT4) at 10 to 30 days of age. Only neonates with a low TT4 at the second screening (*i.e.,* TT4 level in the lowest 10th percentile of the entire TT4 measurements each day) underwent TSH measurement. Those with TSH >20 IU/L were defined as having dTSH. All newborns included in the present study were tested as part of the routine screening program and not because of clinical signs compatible with hypothyroidism.

The ethics committees of each of the eight participating hospitals approved the study protocol.

Data collection

A comprehensive review of the medical records of the dTSH and control neonates was conducted at all eight NICUs, and the following data were recorded for each participant: maternal parameters (*i.e., in vitro* fertilization, autoimmune thyroid disease, smoking, medications used during pregnancy, and mode of delivery), treatment in the NICU (*i.e.,* antibiotic and antifungal drugs, glucocorticoids, vasoactive and diuretic drugs, nonsteroidal anti-inflammatory drugs, morphine, caffeine, surfactants, insulin, and iodine-containing topical antiseptic agents), procedures in the NICU (*i.e.,* blood transfusion, total parenteral nutrition, mechanical ventilation, phototherapy, and surgery), and syndromes, malformations, and several clinical emergencies. The individual variables are listed in Table 1. All data were collected from the date of birth to the second screening for both dTSH patients and the control group.

Statistical analysis

Univariate analysis was conducted to identify the risk factors for dTSH by comparing the variables in the dTSH and control neonates. A similar approach was used for a comparison of the variables in the twin pairs in which only one of the twins had dTSH. In most comparisons of categorical variables, the Pearson $\chi 2$ test was used. The Fisher exact test was used when a variable was reported for only a small number of neonates. A comparison between continuous variables was performed using the Mann-Whitney *U* test for nonparametric data or *t* test. A comparison of variables between twins was performed using McNemar's test. Variables reported for <5 neonates (patients

Table 1. Comparison of Risk Factors for dTSH Between Patients and Controls by Univariate Analysis

Risk Factor	dTSH Group	Control Group	*P* Value
Participants, n	100	200	
Sex			
Male	52 (52)	104 (52)	1.000
Female	48 (48)	96 (48)	
IVF	23 (31.5)	36 (21.8)	0.110
Multiple pregnancy	40 (40)	80 (40)	1.000
Maternal smoking	3 (5.1)	9 (6.4)	1.000
IUGR	27 (27.3)	44 (22.3)	0.348
Delivery method			
Vaginal	22 (23.9)	72 (36.7)	0.030[a]
Cesarean section	70 (76)	124 (63.3)	
Medication during pregnancy			
Betamethasone (Celestone)	34 (34)	82 (41.4)	0.215
Nifedipine (Pressolat)	9 (9)	8 (4)	0.081
Levothyroxine	4 (4)	4 (2)	0.449
Antibiotics			
Ampicillin	66 (66)	114 (57.9)	0.175
Gentamycin	63 (63)	111 (56.3)	0.271
Piperacillin/tazobactam (Tazocin)	32 (32)	57 (28.9)	0.586
Amikacin	27 (27)	55 (27.9)	0.867
Cefotaxime	10 (10)	4 (2)	0.006[a]
Vancomycin	12 (12)	6 (3)	0.002[a]
Carbapenem	4 (4)	7 (3.6)	1.000
Any	22 (22)	44 (22)	1.000
Antifungal drug (fluconazole)	13 (13)	12 (6.1)	0.043[a]
Other drugs			
Dopamine	10 (10)	6 (3)	0.012[a]
Caffeine	40 (40)	69 (35)	0.401
Morphine	8 (8)	6 (3)	0.080
Theophylline	13 (13)	19 (9.6)	0.378
Fentanyl	4 (4)	8 (4.1)	1.000
Dexamethasone	0 (0)	6 (3)	0.101
Ibuprofen	17 (17)	13 (6.6)	0.005[a]
Spironolactone (Aldactone)	5 (5)	3 (1.5)	0.124
Furosemide	13 (13)	6 (3)	0.001[a]
Insulin	5 (5)	2 (1)	0.045[a]
Sepsis	8 (8)	6 (3)	0.080
Other treatment			
PRBCs	24 (24)	27 (13.7)	0.026[a]
FFP	7 (7)	9 (4.6)	0.380
TPN	63 (63)	132 (67)	0.492
Surfactant	31 (31)	55 (27.8)	0.562
Ventilation	38 (38)	46 (23.4)	0.008[a]
CPAP	35 (35)	61 (31.1)	0.500
Phototherapy	59 (59)	131 (66.8)	0.183
Surgery	6 (6)	10 (5.1)	0.747
Syndrome	2 (2)	4 (2)	1.000
Heart disease			
PDA	21 (21)	16 (8.1)	0.001[a]
ASD/VSD	10 (10)	13 (6.6)	0.300
PPHTN	4 (4)	2 (1)	0.184
GI disease			
Inguinal hernia	13 (13)	19 (9.6)	0.378
NEC	3 (3)	4 (2)	0.691
CNS disease (IVH)	8 (8)	8 (4.1)	0.155
Respiratory system disease			
BPD	12 (12)	16 (8.1)	0.280
Pneumothorax	4 (4)	1 (0.5)	0.046[a]
ROP	8 (8)	8 (4.1)	0.155
Hypoglycemia	20 (20)	41 (20.8)	0.870

Data presented as n (%); data for risk factors reported for five or fewer participants were not included.

Abbreviations: ASD, atrium septal defect; BPD, bronchopulmonary dysplasia; CNS, central nervous system; CPAP, continuous positive airway pressure; FFP, fresh frozen plasma; GI, gastrointestinal; IUGR, intrauterine growth retardation; IVF, *in vitro* fertilization; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PPHTN, primary pulmonary hypertension; ROP, retinopathy of prematurity; TPN, total parenteral nutrition; VSD, ventricular septal defect.

[a]Statistically significant.

and controls combined) were excluded from the analysis. Multivariate analysis was conducted using stepwise logistic regression to include variables with statistical significance on univariate analysis.

Data are presented as the mean ± standard deviation. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SSPS Statistics software (IBM Corp., Armonk, NY).

Results

The study population included 100 neonates with dTSH (52 males) and 200 control neonates (104 males). The dTSH and control patients had similar birth weights (1611 ± 520 vs 1617 ± 469 g, respectively) and GA (32.1 ± 3.3 vs 32.2 ± 3.1 weeks, respectively).

On univariate analysis, 12 of 46 variables were significantly more common in the dTSH group than in the control group and hence could be considered risk factors for dTSH: cesarean section, mechanical ventilation, patent ductus arteriosus (PDA), pneumothorax, and the administration of cefotaxime, vancomycin, fluconazole, dopamine, ibuprofen, furosemide, insulin, and packed red blood cells (PRBCs) (Table 1). Six dTSH patients (6%) had undergone surgery or other invasive procedure, including Blalock–Taussig shunt in one, catheterization in one, esophageal atresia correction in two, and chest tube insertion in two. Ten controls (5.1%) had undergone surgery or other invasive procedure, including laparotomy, intestinal resection and ileostomy, and correction of intestinal perforation in one each, correction of imperforate anus in two, correction of diaphragmatic hernia in one, correction of inguinal hernia in one, chest tube insertion in two, and gastrostomy in one. Six neonates had a syndrome: two patients (2%) with dTSH (hypoplastic right heart syndrome and Scimitar syndrome in one each) and four controls (2%) without dTSH (Dandy-Walker syndrome, Bartter syndrome, Klinefelter syndrome, and Cornelia de Lange syndrome). Administration of iodine-containing topical antiseptic agents was reported in only 1 of 300 participants in the present study.

For nine variables (out of 12) that were substantially different between the dTSH and control groups on univariate analysis, the dosage of medication, number of PRBC units, and duration of drug administration and ventilation were similar between the two groups using the Mann-Whitney *U* test (Table 2). On multivariate analysis, four variables were sufficient to explain the difference between the neonates with dTSH and their matched controls: PDA and the administration of vancomycin, insulin, and furosemide (Table 3).

Forty-three neonates with dTSH were twins. In three twin pairs, both twins presented with dTSH, and in 11 pairs, the healthy twin had not been admitted to the NICU; thus, the data for those twins were limited. Therefore, a comparison of the risk factors was performed for 26 twin pairs for which only one twin had dTSH. The healthy and dTSH twins had similar birth weights (1618 ± 488 vs 1595 ± 502 g, respectively). Nine variables that were present in at least five twins were also present in the healthy twins and those with dTSH: PDA, continuous positive airway pressure, phototherapy, mechanical ventilation, and administration of total parenteral nutrition, surfactants, ampicillin, gentamycin, and/or caffeine. Only two of the variables (PDA and mechanical ventilation) were risk factors on univariate analysis between the dTSH and control neonates in the entire cohort of patients and controls.

Table 2. Comparison of Duration of Administration and Dosage of Medications and Procedures Between dTSH Patients and Controls

Variable	dTSH Group	Control Group	*P* Value[a]
Dopamine			
Maximum dose, μg/kg min	7.0 ± 3.5	10.8 ± 6.1	0.181
Duration, d	3.2 ± 1.9	2.7 ± 2.2	0.263
Cefotaxime duration, d	4.8 ± 2.7	2.3 ± 0.5	0.142
Vancomycin duration, d	6.0 ± 4.2	5.5 ± 2.6	0.892
Fluconazole duration, wk	1.1 ± 0.4	0. 8 ± 0.3	0.114
Ibuprofen doses, n	2.2 ± 0.8	2.2 ± 1.2	0.837
Furosemide			
Dose, mg/d	2.0 ± 0.7	2.0 ± 0.6	0.884
Duration, d	7.6 ± 8.7	11.3 ± 15.3	0.966
Insulin duration, d	5.3 ± 3.2	3.0 ± 0.0	0.500
PRBC units, n	1.8 ± 1.0	1.7 ± 0.9	0.530
Ventilation duration, d	5.6 ± 6.2	4.4 ± 4.9	0.332

Data presented as mean ± standard deviation.

All the medications and procedures were significantly different between the patients and controls on univariate analysis (Table 1).

[a] *P* value calculated using *t* test with Mann-Whitney *U* test for nonparametric data.

Table 3. Comparison of Risk Factors for dTSH Between Patients and Controls Using Stepwise Logistic Regression Multivariate Analysis

Parameter	*P* Value	Adjusted OR	95% CI
Vancomycin	0.027	3.4	1.1–9.9
Furosemide	0.044	3.0	1.0–8.9
Insulin	0.068	4.9	0.9–26.8
PDA	0.021	2.4	1.1–5.2

Abbreviations: CI, confidence interval; OR, odds ratio.

Discussion

The occurrence of dTSH weeks after a normal TSH measurement at the first neonatal screening is enigmatic. The TSH levels at the second screening might be only mildly elevated; however, as we showed in our previous study (8), in many neonates, the TSH levels will reach ≥100 IU/mL. Considering the importance of normal thyroid function to neurocognitive development, especially during the early years of life, a second thyroid screening is currently recommended for certain at-risk populations (1, 2). We aimed to elucidate the risk factors for dTSH in the neonatal period. In the present case-control study, univariate analysis revealed 12 variables that were associated with dTSH, 4 of which were confirmed by multivariate analysis.

These variables have no common pathogenic pathway, and they seem to reflect the severity of the clinical condition of the newborns in the NICU. Some of the variables (PDA and ibuprofen) are associated with the same medical condition. For example, ibuprofen is used for closure of clinically important PDA (15). Several types of antibiotics [ampicillin, gentamycin, amikacin, and piperacillin/tazobactam (Tazocin)] were similarly reported in many dTSH and control neonates alike. These antibiotics are routinely administered when neonatal sepsis is suspected from the clinical signs and laboratory results. Unlike these antibiotics, cefotaxime and vancomycin were reported for only a few neonates, because they are mostly used to treat culture-proven septicemia, an important condition in the neonatal period. The administration of these agents reflects severe infection, and they were more commonly used in neonates with dTSH than in controls. Other medications associated with dTSH were insulin, which is used for stress-induced hyperglycemia, furosemide, which is used for fluid overload and various types of edema, and dopamine, which is used for low blood pressure. Similarly, PRBC transfusion, mechanical ventilation for respiratory distress syndrome, and the presence of pneumothorax reflect important clinical conditions and were more commonly reported in the neonates with dTSH. It is of interest that delivery by cesarean section was associated with dTSH, which might reflect some contribution of prenatal stress (which led to the cesarean section) to the development of dTSH. Twin pairs who share identical intrauterine conditions showed a similar distribution of postnatal variables between twins with and without dTSH. Maternal levothyroxine consumption during pregnancy was not associated with dTSH, although the numbers were too low to draw solid conclusions. A few studies have suggested that the offspring of mothers treated with levothyroxine during pregnancy should be retested for thyroid function at a few weeks of age to identify the late development of hypothyroidism (16).

Two of the risk factors for dTSH found in the present study, dopamine and PRBC transfusion, were also reported in a previous study by Larson *et al.* (4). It has been suggested that dopamine affects thyroid function in the neonatal period through suppression of the HPT axis (7, 11). Blood transfusion has also been suggested to affect the results of thyroid screening (17). Finally, congenital heart disease has also been associated with dTSH, although the specific heart diseases were not reported (4). Larson *et al.* (4) defined the risk factors merely according to their prevalence in patients with dTSH, with no comparison with a matched control group. In addition, they identified some risk factors using limited data, such that blood transfusion, for example, was captured by notation on a laboratory slip or the detection of high concentrations of hemoglobin A, or both. Unlike that study, we suggest that dopamine, PRBC transfusion, and several other variables are surrogate markers for disease severity during the neonatal period and are not etiologically related to dTSH.

The main strengths of our study were the size of the neonatal population with dTSH (the largest cohort reported to date to the best of our knowledge), the participation of multiple NICUs (reflecting the heterogeneity of the population), and the comparison of variables to those from a matched control group.

In conclusion, the observations from the present study strengthen our previous work in which we reported that dTSH is not associated with GA or birth weight but, rather, is typical of the most severe cases in the NICU (8). The findings from both studies support a paradigm of performing a second thyroid screening for all NICU patients rather than the selective approach for certain at-risk populations (1, 2). Although we found certain risk factors were associated with dTSH, further studies are required to elucidate the common pathway by which these different factors contribute to its evolution.

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