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Hypothyroidism in Infants With Congenital Heart Disease Exposed to Excess Iodine

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Thyroid hormone is critical for neonatal brain development, and even transient hypothyroidism can cause adverse neurocognitive outcomes. Infants exposed to excess iodine are at risk of developing hypothyroidism, especially those with congenital heart disease (CHD), because they are routinely exposed to excess iodine from intravenous iodinated contrast media and topical antiseptics. The aim of the present study was to identify the proportion of neonates with CHD exposed to iodine who developed hypothyroidism and to identify the associated risk factors. This was a retrospective study of neonates undergoing cardiac catheterization at Boston Children's Hospital during a 3-year period, some of whom also underwent cardiac surgery. Hypothyroidism was defined as an elevated thyroid-stimulating hormone level (>20 mIU/L at 24 to 96 hours of age and >15 mIU/L at >96 hours of age by heel-stick sampling and >9.1 mIU/L at 1 to 20 weeks of age by serum testing). Multivariate logistic regression was performed to predict the odds of developing hypothyroidism. Hypothyroidism was diagnosed incidentally in 46 of 183 infants (25%) with CHD after iodine exposure. Controlling for baseline cardiac risk, postnatal age, and gestational age, we found a fourfold increase in odds of developing hypothyroidism in neonates with serum creatinine >0.9 mg/dL and a fourfold increase in those who underwent more than three procedures. Hypothyroidism in neonates with CHD exposed to excess iodine is associated with multiple procedures and impaired renal function. Routine serial monitoring of thyroid function in these neonates is warranted. Future studies should examine the association between hypothyroidism and neurocognitive function in this population.

Freeform/Key Words: hypothyroidism, congenital heart disease, iodine, cardiac catheterization

Thyroid hormone plays an essential role in brain development in fetal and neonatal life [1], and hypothyroidism during this critical period of early life can lead to adverse neurodevelopmental sequelae [2]. Premature infants and neonates might be particularly susceptible to the development of hypothyroidism after exposure to excess iodine [3]. Typically, in the setting of high iodine levels, the synthesis of thyroid hormone is transiently inhibited via the Wolff-Chaikoff effect [4]. With continued exposure to high iodine, the thyroid is able to "escape" from the Wolff-Chaikoff effect, thereby permitting resumption of normal thyroid hormone synthesis [5, 6]. However, in the immature fetal and neonatal gland, this escape can be delayed, leading to the development of hypothyroidism [7, 8].

Abbreviations: BCH, Boston Children's Hospital; CHD, congenital heart disease; CI, confidence interval; DSC, delayed sternal closure; ICM, iodinated contrast media; IQR, interquartile range; NENSP, New England Newborn Screening Program; RACHS-1, risk adjustment for surgery for congenital heart disease; T4, thyroxine; TSH, thyroid-stimulating hormone; TT4, total thyroxine.

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Neonates with congenital heart disease (CHD) represent an especially vulnerable group, because they have a higher frequency of congenital morphological defects of the thyroid gland [9,10], are routinely exposed to excess iodine, and are at risk of neurodevelopmental disabilities [11, 12]. Sources of excess iodine exposure in infants with CHD include iodinated contrast media (ICM) administered during radiological procedures and topical iodine-containing antiseptics and iodine-impregnated dressings applied to chest wounds in the setting of delayed sternal closure (DSC) after cardiac surgery [13–17]. An injection of 3 to 5 mL/kg of Optiray 350 during cardiac catheterization, for example, contains 350 mg/mL of organically bound iodine and provides an iodine load far greater than the tolerable upper limit of 200 μg/day for infants 1 to 3 years of age [18].

The severity and duration of hypothyroidism in infants with frequent exposure to excess iodine from multiple sources has not been well-characterized. Furthermore, impaired renal function during the postoperative period in infants requiring intervention for CHD might hamper urinary clearance of iodine and further increase the risk of hypothyroidism, and the association between impaired renal function and hypothyroidism in infants with CHD has also not been well-studied.

We previously reported a series of neonates with CHD who had developed iodine-induced hypothyroidism after cardiac catheterization and surgery [19]. From this and other reports, the Food and Drug Administration issued an advisory on the risk of hypothyroidism in infants exposed to ICM [20]. A recent case-control study of children exposed to ICM showed an increased risk of incident hypothyroidism and called for the identification of comorbidities that predispose to thyroid dysfunction in vulnerable subgroups of children [21].

We thus aimed to identify the proportion of neonates with CHD who develop hypothyroidism after iodine exposure from cardiac catheterization and cardiac surgery and to analyze risk factors for the development of hypothyroidism in these infants.

1. Methods

A. Participants and Study Setting

We retrospectively studied all neonates <1 month of age with CHD who had undergone cardiac catheterization at Boston Children's Hospital (BCH) from 1 December 2009 to 1 December 2012 and who had at least one thyroid-stimulating hormone (TSH) value available for analysis, obtained by routine heel-stick sampling during the newborn period, as mandated by the New England Newborn Screening Program (NENSP). Neonates in whom hypothyroidism was diagnosed before iodine exposure were excluded. The institutional review board at BCH approved the study.

B. Study Design

We defined the date of entry into the cohort for each neonate as the date of the neonate's first procedure with exposure to excess iodine—either the date of the first cardiac catheterization or the date of the first cardiac surgery, whichever was first. The exposure period for the neonates who developed hypothyroidism was defined as the period between the date of entry into the cohort and the date of diagnosis of hypothyroidism. Because the median time to diagnosis of hypothyroidism in the neonates who developed hypothyroidism in the present study was 8.5 days, we defined the end of the exposure period for those neonates who remained euthyroid as 8 calendar days after the date of entry into the cohort.

We extracted data on baseline sociodemographic, clinical, and laboratory variables for each neonate from the electronic medical records. We tracked the number of all surgical and radiological procedures requiring ICM during the exposure period for each infant. The cumulative dose of ICM for each infant was calculated by summing all doses of ICM administered during the exposure period for each infant.

Procedure-type risk categories [22] in infants who underwent cardiac catheterization and Risk Adjustment for Surgery for Congenital Heart Disease (RACHS-1) scores [23] for infants

who underwent cardiac surgery were used to classify the baseline risk at the first procedure. We assigned each infant a cardiac summary risk score as follows. For infants who underwent cardiac surgery, a summary score of 1 was assigned for RACHS-1 scores of 1 to 3; a summary score of 2 for a RACHS-1 score of 4; and a summary score of 3 for RACHS-1 scores of 5 to 6. For patients who underwent cardiac catheterization, a summary score of 1 was assigned for a procedure-type risk category of 1 to 2; a summary score of 2 for a risk category of 3; and a summary score of 3 for a risk category of 4. For patients who underwent both cardiac surgery and catheterization during the exposure period, the higher summary score was used to classify the risk.

We extracted the results of the thyroid function tests from two sources: routine heel-stick blood sampling during the newborn period and serum thyroid function tests obtained by venipuncture during the course of routine clinical care of the infants. The NENSP uses a primary thyroxine (T4) strategy, with follow-up TSH measurements performed for newborns whose blood T4 values are in the lowest 10th percentile and for all infants hospitalized in special care nurseries or neonatal intensive care units at the time of sampling [24]. Repeat filter-paper specimens were routinely obtained for all infants hospitalized in special care nurseries or neonatal intensive care units at 2 weeks, 1 month, and monthly thereafter, until discharge or transfer to another facility. Both TSH and T4 levels were assayed on all repeat screening tests. The results of heel-stick testing were pooled with the results of serum thyroid function tests obtained by venipuncture at BCH. For infants born out of state, we extracted the results of the available thyroid function tests from the medical records.

Total T4 (TT4) and TSH were assayed on filter-paper blood specimens using a time-resolved fluoroimmunoassay procedure (AutoDELFIA System; Perkin-Elmer, Waltham, MA; normal range for TSH, $<$20 mIU/L at 24 to 96 hours of age and $<$15 mIU/L at $>$96 hours of age). Serum TSH was measured using a third-generation chemiluminescent immunoassay (Access hypersensitive human TSH; Beckman Coulter, Waltham, MA; normal range for infants 1 to 20 weeks of age, 1.7 to 9.1 mIU/L) [25]. Serum TT4 and free T4 were measured using an electrochemiluminescent immunoassay (Roche Diagnostics, Indianapolis, IN; normal range for TT4, 9.8 to 16.6 μg/dL at 1 to 5 weeks of age and 7.2 to 15.7 μg/dL at 5 to 20 weeks; normal range for free T4, 0.9 to 2.3 ng/dL). The NENSP laboratory reports the validation of results of filter-paper assays when compared with serum laboratory testing of thyroid function.

C. Outcome

The primary outcome was the diagnosis of hypothyroidism, as determined by an elevated TSH level for age ($\geq$20 mIU/L at 24 to 96 hours of age and $\geq$15 mIU/L at $>$96 hours of age by heel-stick sampling and $>$9.1 mIU/L at 1 to 20 weeks of age by serum testing). Data on the treatment and outcomes of infants with a diagnosis of hypothyroidism were ascertained by review of the electronic medical records through 1 June 2017.

D. Statistical Analysis

The Wilcoxon rank-sum test and χ^2 test were used to compare the continuous and categorical variables, respectively, between the neonates who developed hypothyroidism and those who remained euthyroid after iodine exposure. Continuous variables with strongly skewed distributions were transformed into categorical variables based on quartiles or clinically meaningful cutpoints.

Univariate logistic regression analyses were performed to examine the risk factors for the development of hypothyroidism. We explored whether the cumulative dose of iodinated contrast administered during cardiac catheterization was associated with an increase in odds of developing hypothyroidism. We separately analyzed whether the total number of surgical and radiological procedures during the exposure period was associated with the odds of developing hypothyroidism and whether an association was present between a history of DSC and hypothyroidism.

In the next stage of the model-building process, we postulated that renal dysfunction would be an independent predictor of hypothyroidism in infants with CHD exposed to excess iodine. We extracted the maximum serum creatinine value during the exposure period for each infant as a marker of renal function; this variable was transformed into a categorical predictor using quartile cutpoints and entered into the model. We considered other statistically significant univariate predictors of hypothyroidism ($P < 0.1$) as candidates for entry into the model. In the final stage of the multivariable model development, we controlled for baseline risk and other potential confounders.

Model goodness of fit was ascertained using the Hosmer-Lemeshow test [26], and the C statistic (area under the receiver operating characteristic curve) was used to evaluate the discriminatory performance of the model. We used an *a priori* significance level of 0.05 for all statistical tests. Data analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC).

2. Results

A total of 217 neonates with CHD presented for cardiac catheterization during the 3-year period, of which 187 had at least one screening TSH level assayed. In four neonates, hypothyroidism was diagnosed before any known iodine exposure. These infants were excluded from the present analysis. Hence, 183 infants were included in the study cohort, of whom 73 (40%) had undergone cardiac catheterization only during the exposure period and 89 (49%) had undergone both cardiac catheterization and cardiac surgery (Fig. 1). Also, 21 infants (11%) underwent cardiac surgery only during the exposure period; these were infants whose cardiac catheterizations had occurred subsequent to their iodine exposure period.

Serial thyroid function tests for the 183 infants were available for analysis up to a median of 14 days from the time of the first iodine exposure (range, 1 day to 42 months). Forty-six infants

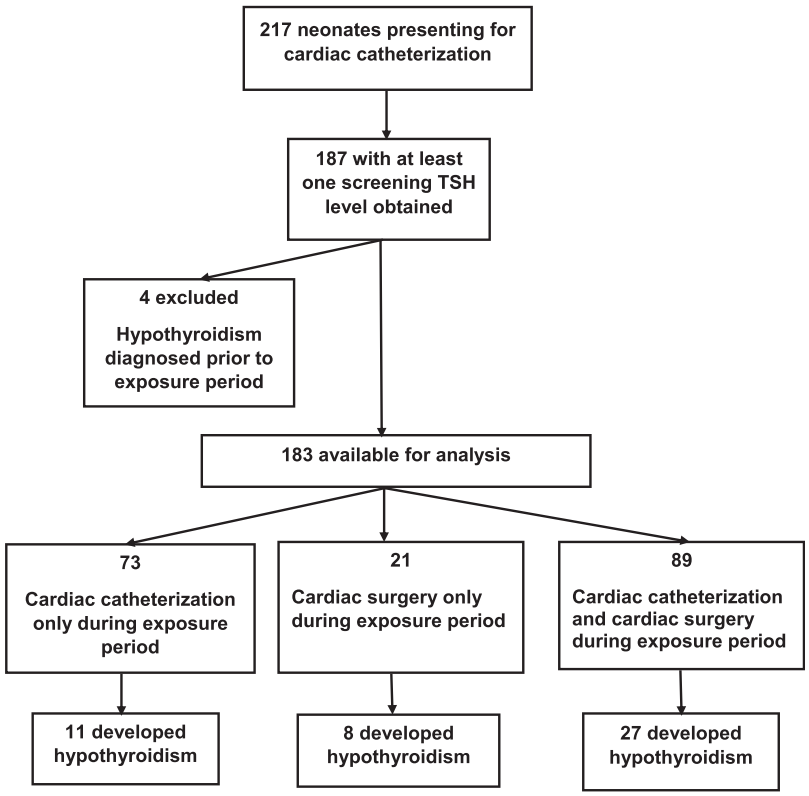

Figure 1. Study cohort flow diagram.

(25%) were diagnosed with hypothyroidism at a median of 8.5 days after exposure (range, 1 day to 25 months).

The sociodemographic and clinical characteristics of the infants are listed in Table 1. The median postnatal age of the infants on the day of their first procedure was 3 days [interquartile range (IQR), 2 to 7], and the median gestational age was 38.7 weeks (IQR, 37.6

Table 1. Baseline Characteristics of Neonates With CHD

Characteristic	Patients, n	Median (IQR) or n (%)
Postnatal age, days	183	3 (2–7)
Birth weight, g	183	3048 (2805–3390)
Gestational age, wk	183	38.7 (37.6–39.1)
Male sex	183	108 (59)
White race	183	123 (67)
Classification of CHD[a]	183	
Septal defects		69 (38)
Obstructive defects		77 (42)
Cyanotic defects		106 (58)
Any congenital anomaly or genetic syndrome[b]	183	46 (25)
Baseline TSH, mIU/L	169	4.1 (2.5–7.3)
Baseline TT4, μg/dL	161	9.5 (6.5–12.9)
Baseline BUN, mg/dL	155	8 (7–11)
Baseline creatinine, mg/dL	155	0.7 (0.6–0.8)
Maximum BUN during exposure period, mg/dL	179	24 (13–38)
Maximum creatinine during exposure period, mg/dL	179	0.7 (0.6–0.9)
Cumulative iodinated contrast load, mL/kg	183	3.5 (1.1–7.2)
Procedures during exposure period (all surgical and radiological with ICM), n	183	2 (2–3)
Surgical complications during exposure period	110	
Any surgical complication		56 (51)
Required ECMO		21 (19)
Arrhythmia		15 (14)
Required CPR		10 (9)
Delayed sternal closure after cardiac surgery	110	49 (45)
Cardiac summary risk score[c]	160	
Summary risk score 1		7 (4)
Summary risk score 2		116 (73)
Summary risk score 3		37 (23)
Medications during exposure period	183	
Any pressor		106 (58)
Dopamine		96 (52)
Amiodarone		3 (2)
Glucocorticoids		97 (53)

Abbreviations: BUN, blood urea nitrogen; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.

To convert creatinine to μmol/L, multiply values by 88.4; to convert TT4 to nmol/L, multiply values by 12.87.

[a]Septal defects included atrial septal defects and ventricular septal defects; obstructive defects included aortic stenosis, pulmonic stenosis, and coarctation of the aorta; cyanotic defects included tetralogy of Fallot, transposition of the great arteries, pulmonary atresia, truncus arteriosus, total anomalous pulmonary venous circulation, and hypoplastic left heart syndrome—the categories were not mutually exclusive.

[b]Congenital anomalies and genetic syndromes included heterotaxy with intestinal malrotation in 7 (4%), Down syndrome in 6 (3%), hydronephrosis in 4 (2%), chromosome anomaly in 4 (2%), omphalocele in 2 (1%), cleft palate in 2 (1%), and 1 each with Hirschsprung disease, Turner syndrome, choanal atresia, CHARGE syndrome, Alagille syndrome, severe combined immunodeficiency, Smith-Lemli-Opitz syndrome, and Kabuki syndrome; another 18 infants (10%) had other minor isolated congenital anomalies.

[c]Summary risk score was assigned as follows: for infants who underwent cardiac surgery, a summary score of 1 was assigned for RACHS-1 scores 1 to 3; a summary score of 2 for RACHS-1 score of 4; and a summary score of 3 for RACHS-1 scores 5 to 6. For patients who underwent cardiac catheterization, a summary score of 1 was assigned for a procedure-type risk category of 1 to 2; a summary score of 2 for a risk category of 3; and a summary score of 3 for a risk category of 4. For patients who underwent both cardiac surgery and catheterization during the exposure period, the higher summary score was used to classify risk.

to 39.1). Overall, 58% of infants had cyanotic heart defects, and congenital anomalies or genetic syndromes had been diagnosed in 25% (Table 1). Thirty-eight infants (21%) had died by the end of the follow-up period, of whom 14 (30%) had developed hypothyroidism and 24 (18%) had remained euthyroid ($P = 0.06$).

Figure 2 shows the distribution of TSH and TT4 values in the 46 infants with hypothyroidism. In 18 neonates (39%), the TSH concentration was >20 mIU/L, a level warranting treatment according to the recent consensus guidelines for management of congenital hypothyroidism [27]. Hypothyroidism had been diagnosed in the infants at a median age of 12 days of life (range, 2 days to 26 months). Hypothyroidism had been diagnosed at a median of 8.5 days (range, 1 day to 25 months) after exposure to excess iodine from cardiac catheterization or cardiac surgery.

Levothyroxine was initiated in 20 of the 46 infants (43%) with hypothyroidism, of which nine continued to receive therapy until the date of death (median duration of treatment, 45 days; range, 6 to 316). Of the 20 infants who received levothyroxine therapy, seven were successfully withdrawn from therapy at 3 years of age and remained euthyroid without therapy. Two of these seven infants have Down syndrome. One infant was treated with levothyroxine for 26 days and then successfully discontinued therapy. Three infants continued to receive long-term levothyroxine therapy through June 2017 (aged 4 years, 2 months; 4 years, 1 month; and 6 years, 8 months).

Of the 26 infants who did not receive treatment with levothyroxine after the diagnosis of hypothyroidism, 15 experienced spontaneous resolution of hypothyroidism (median time to resolution, 15 days; range, 4-367). Of these 26 infants, nine had transferred care to another center and were lost to follow-up and two had died before the initiation of levothyroxine therapy.

In unadjusted analyses (Table 2), infants in whom hypothyroidism was ultimately diagnosed had impaired renal function, had undergone a greater number of procedures, had a lower baseline TT4 level, and had higher cardiac summary risk scores. The cumulative iodinated contrast dose was not a statistically significant predictor of hypothyroidism [median dose, 3.6 mL/kg (IQR, 0.3 to 6.9) vs 3.3 mL/kg (IQR, 1.3-7.2), in those with hypothyroidism vs euthyroid infants, respectively; $P = 0.74$]. Although DSC and baseline TT4 levels were

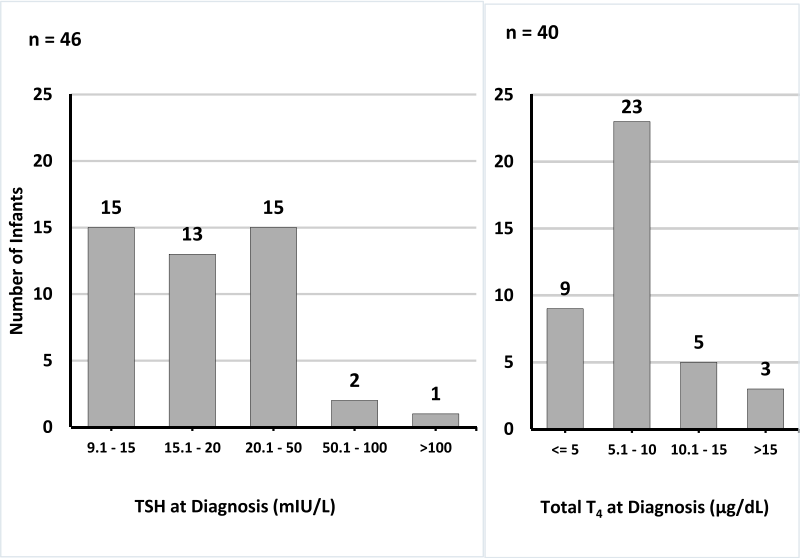

Figure 2. Thyroid function in infants with CHD at diagnosis of hypothyroidism. Normal range for TSH on filter-paper blood specimens: <20 mIU/L at 24 to 96 hours of age and <15 mIU/L at >96 hours of age. Normal laboratory range for serum TSH: 1.7 to 9.1 mIU/L for infants 1 to 20 weeks of age. Normal laboratory range for serum TT4: 9.8 to 16.6 µg/dL at 1 to 5 weeks of age and 7.2 to 15.7 µg/dL at 5 to 20 weeks of age.

Table 2. Univariate Predictors of Hypothyroidism

Variable	Infants With Hypothyroidism	Euthyroid Infants	*P* Value
Renal function during exposure period, n (%)	n = 46	n = 133	0.005
Maximum creatinine ≤0.6 mg/dL	10 (22)	53 (40)	
Maximum creatinine >0.6 but ≤0.7 mg/dL	9 (19)	29 (22)	
Maximum creatinine >0.7 but ≤0.9 mg/dL	10 (22)	37 (28)	
Maximum creatinine >0.9 mg/dL	17 (37)	17 (37)	
Total procedures during exposure period (all surgical and radiological with ICM), n (%)	n = 46	n = 137	0.01
1 Procedure	6 (13)	32 (23)	
2 Procedures	14 (30)	47 (34)	
3 Procedures	7 (15)	33 (24)	
>3 Procedures	19 (41)	25 (18)	
Baseline TT4, μg/dL	n = 30	n = 131	0.02
Median (IQR)	7.8 (5.0–10.9)	10.2 (6.6–13.2)	
Cardiac summary risk score, n (%)	n = 40	n = 120	0.04
Summary risk score 1	1 (3)	6 (5)	
Summary risk score 2	24 (60)	92 (77)	
Summary risk score 3	15 (37)	22 (18)	
DSC, n (%)	20 (57)	29 (39)	0.07

statistically significant univariate predictors of hypothyroidism, these variables were no longer statistically significant when controlling for other covariates in the multivariate models.

The multivariate logistic regression models are presented in Table 3. The final model (multivariate model 2) included 160 infants with data available for all relevant variables. Of these 160 infants, 40 had developed hypothyroidism. Controlling for baseline risk, postnatal age, and gestational age, an increase was found in the odds of hypothyroidism in neonates with the highest quartile of serum creatinine [creatinine >0.9 mg/dL; odds ratio, 4.22; 95% confidence interval (CI), 1.61 to 11.05], and those who underwent more than three procedures (odds ratio, 3.65; 95% CI, 1.48 to 9.02). The multivariate model demonstrated goodness of fit as assessed by the Hosmer-Lemeshow test ($P = 0.38$) and good discriminatory ability to predict hypothyroidism (C statistic, 0.80).

Table 3. Multivariate Logistic Regression Models Predicting Odds of Developing Hypothyroidism in Neonates With CHD

	Univariate Analysis			Multivariate Model 1[a]			Multivariate Model 2[b]		
Predictor	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Highest quartile of serum creatinine (>0.9 mg/dL)	5.15	2.28–11.63	<0.0001	5.02	1.92–13.11	0.001	4.22	1.61–11.05	0.003
>3 Procedures (surgical/radiological with ICM)	3.15	1.52–6.54	0.002	3.18	1.31–7.70	0.01	3.65	1.48–9.02	0.005
Highest cardiac summary risk score (3)[c]	2.67	1.21–5.89	0.015	1.96	0.78–4.93	0.15	1.87	0.72–4.81	0.20

Abbreviation: OR, odds ratio.

[a]Three-predictor model.

[b]Multivariate model 1 adjusted for postnatal age and gestational age.

[c]Summary risk score of 3 included patients with RACHS-1 score of 6 and/or catheterization charge category of 4; for patients who underwent both cardiac catheterization and surgery during the exposure period and for whom both RACHS-1 scores and catheterization charge categories were available, the higher summary risk score was used to classify the risk category.

3. Discussion

To the best of our knowledge, the present study is the largest cohort study to date to analyze the risk factors for development of hypothyroidism in an iodine-exposed population of neonates with CHD undergoing cardiac catheterization and cardiac surgery. Hypothyroidism was diagnosed in 25% the infants in our study after iodine exposure—a finding consistent with previous estimates of an incidence of 8% to 33% of iodine-induced hypothyroidism in infants with CHD [15, 16, 28].

It is important to note that the diagnosis of hypothyroidism in the infants in our study was incidental and a result of the mandated state screening of acutely ill infants with extended hospital stays. In the absence of a policy of repeat thyroid screening, the diagnosis would have been missed in those with transient hypothyroidism or delayed in cases of severe hypothyroidism until the emergence of overt signs, which are difficult to recognize in critically ill infants. Serial monitoring of thyroid function is not routinely performed in infants undergoing surgical procedures and radiological procedures with ICM; hence, the true incidence of hypothyroidism in this cohort of infants is likely to be greater than that estimated in our study. Because even transient hypothyroxinemia can increase the risk of adverse neurodevelopmental outcomes in neonates [29], detection of iodine-induced hypothyroidism, even of short duration, is vital in infants with CHD who are already at increased risk of neurocognitive deficits.

We found a strong association between the number of procedures with exposure to iodine and the subsequent development of hypothyroidism. A similar finding was noted by Linder *et al.* [15] in their prospective study of iodine-induced hypothyroidism in infants with CHD, although statistical significance could not be demonstrated in their small study. In a recent large case-control study of adults exposed to ICM followed up for a 6-year period in Taiwan, Kornelius *et al.* [30] noted a significantly greater risk of hypothyroidism in subjects with two or more exposures to ICM (hazard ratio, 2.22; 95% CI, 1.55 to 3.16; $P < 0.01$)]. The investigators attributed this finding to failure to escape from the Wolff-Chaikoff effect with repeated exposure to excess iodine, a phenomenon that is likely exaggerated in neonates with immature thyroid glands [7].

Our study also demonstrated a strong association between impaired renal function and hypothyroidism in iodine-exposed neonates with CHD. A prolonged inhibitory effect of iodine on thyroid function in nephrectomized rats was established in the early studies by Wolff and Chaikoff [31]. Sato *et al.* [32] suggested that impaired urinary excretion of iodide might play a role in the delayed escape from the Wolff-Chaikoff effect in patients with renal dysfunction. Iodine-induced hypothyroidism has also been reported in adult and pediatric dialysis patients with high dietary iodine intake [33] and exposure to iodine-containing topical antiseptics [34]. Infants with CHD have an increased risk of developing renal insufficiency; hence, serial monitoring of thyroid function in the setting of increasing creatinine levels might uncover unrecognized cases of hypothyroidism.

The baseline T4 levels were lower in the neonates who ultimately developed hypothyroidism than in those who remained euthyroid, possibly reflecting the effect of critical illness in the former neonates. Alternatively, the neonates with low T4 who became hypothyroid might have had intrinsically abnormal thyroid glands that decompensated under the stress of an iodine load. When controlling for other covariates, including baseline risk score, the baseline T4 level was not a statistically significant predictor of hypothyroidism. Likewise, we did not find an association between DSC and hypothyroidism on multivariate analysis. Although a previous study reported such an association [17], that study did not control for underlying morbidity or renal function.

The elevated TSH levels in the infants in our study were not likely to have resulted from recovery from the "euthyroid sick syndrome." This syndrome, which has been well-documented in infants after cardiopulmonary bypass and cardiac surgery [35, 36], is characterized by a decrease in the serum TSH, free T4, and triiodothyronine concentrations during critical illness, often followed by a subsequent transient increase in serum TSH to greater than normal, but rarely >10 mIU/L [37, 38]. In our study, 93% of the infants who developed

hypothyroidism had a sustained TSH level >10 mIU/L after iodine exposure—a pattern that is not likely explained by recovery from the euthyroid sick syndrome. Furthermore, although congenital hypothyroidism with delayed TSH elevation is a common form of transient thyroid dysfunction among premature infants [39, 40], 90% of the infants in our study were born at ≥36 weeks' gestation. Thus, this phenomenon is not a likely explanation of our findings.

The strength of our study is the large sample size of infants cared for at a single tertiary care medical center where the clinical and laboratory parameters are uniformly documented in the electronic medical records. Moreover, the close relationship between our medical center and the NENSP allowed for excellent adherence to the mandated serial screening of thyroid function in infants with prolonged hospital stays.

Our study was limited by its retrospective design, which necessitated a nonuniform follow-up duration and likely resulted in an underestimation of the true incidence of hypothyroidism in infants discharged from the hospital who were thus exempt from continued monitoring of thyroid function. Because many of the infants in our study were critically ill at the time of diagnosis of hypothyroidism, ultrasound examination of the thyroid was not performed. Thus, it is possible that some infants might have had morphologically abnormal thyroid glands, conferring an increased risk of developing hypothyroidism even in the absence of exposure to excess iodine. Congenital hypothyroidism is more common in infants with CHD [41]; however, we excluded neonates in whom hypothyroidism had been diagnosed before iodine exposure from our study. We used a serum TSH cutoff of 9.1 mIU/L to define hypothyroidism in infants older than 1 week of age [25] according to the laboratory reference ranges. However, recent population-based data have shown that the upper limit of normal (97.5 percentile) for serum TSH might be much lower (4.4 to 4.8 mIU/L) in infants 1 week to <6 months of age [42, 43]. Thus, our higher TSH cutoff value might have resulted in an underestimation of the true incidence of hypothyroidism in this population.

4. Conclusions

Neonates with CHD exposed to excess iodine have an increased risk of hypothyroidism, in particular, those with impaired renal function and those who undergo multiple procedures. Systematic monitoring of thyroid function in all neonates at close intervals after exposure to excess iodine is warranted. Future studies investigating the optimal frequency and timing of screening and the association between the severity and duration of hypothyroidism and neurocognitive function in these infants are needed.

Acknowledgments

Our report is dedicated to the memory of Dr. Marvin Mitchell (1922-2016), who established the pioneering program in 1976 to test newborns for thyroid disease at the Massachusetts State Laboratory Institute. The program has since been replicated across the United States and is responsible for identifying thousands of cases of occult thyroid disease, a preventable cause of mental retardation worldwide. Dr. Mitchell was active in advising and assisting with this project until shortly before his death. We are grateful to his staff at the New England Newborn Screening Program for their assistance in obtaining complete reports of the thyroid screening results for the infants in the present study. We thank the members of the administrative staff in the Division of Cardiology at Boston Children's Hospital for their assistance with our study.

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V.V.T. conceptualized and conceived the study, conceived and supervised the data collection, participated in the analyses, drafted the initial manuscript, and approved the final manuscript as submitted; M.F.G. participated in the study design, performed data extraction, participated in the data analyses, and

approved the final manuscript as submitted; A.C.M. participated in the study design, facilitated identification of cohort and data collection, participated in the data analyses, and approved the final manuscript as submitted; M.C.A. participated in the study design, facilitated data extraction, participated in the analyses, and approved the final manuscript as submitted; H.-W.H. facilitated data collection from New England Newborn Screening Program, provided expertise in the interpretation of the results, and approved the manuscript as submitted; C.J.A. participated in data extraction and approved the manuscript as submitted; H.A.F. participated and guided the data analyses and interpretation of the results, refined the manuscript, and approved the manuscript as submitted; R.S.B. participated in the study design, data analyses, and interpretation of the results, provided input for the manuscript, and approved the manuscript as submitted; and B.-S.L. conceptualized and designed the study, performed the data analyses, revised the manuscript, approved the final manuscript as submitted, and is the guarantor of the results presented in the manuscript.

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References and Notes

1. Nunez J, Celi FS, Ng L, Forrest D. Multigenic control of thyroid hormone functions in the nervous system. *Mol Cell Endocrinol*. 2008;**287**(1-2):1–12.
2. Van Vliet G. Neonatal hypothyroidism: treatment and outcome. *Thyroid*. 1999;**9**(1):79–84.
3. Leung AM, Braverman LE. Iodine-induced thyroid dysfunction. *Curr Opin Endocrinol Diabetes Obes*. 2012;**19**(5):414–419.
4. Wolff J, Chaikoff IL. The inhibitory action of excessive iodide upon the synthesis of diiodotyrosine and of thyroxine in the thyroid gland of the normal rat. *Endocrinology*. 1948;**43**(3):174–179.
5. Eng PH, Cardona GR, Fang SL, Previti M, Alex S, Carrasco N, Chin WW, Braverman LE. Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. *Endocrinology*. 1999;**140**(8):3404–3410.
6. Braverman LE, Ingbar SH. Changes in thyroidal function during adaptation to large doses of iodide. *J Clin Invest*. 1963;**42**(8):1216–1231.
7. Theodoropoulos T, Braverman LE, Vagenakis AG. Iodide-induced hypothyroidism: a potential hazard during perinatal life. *Science*. 1979;**205**(4405):502–503.
8. Connelly KJ, Boston BA, Pearce EN, Sesser D, Snyder D, Braverman LE, Pino S, LaFranchi SH. Congenital hypothyroidism caused by excess prenatal maternal iodine ingestion. *J Pediatr*. 2012; **161**(4):760–762.
9. Passeri E, Frigerio M, De Filippis T, Valaperta R, Capelli P, Costa E, Fugazzola L, Marelli F, Porazzi P, Arcidiacono C, Carminati M, Ambrosi B, Persani L, Corbetta S. Increased risk for non-autoimmune hypothyroidism in young patients with congenital heart defects. *J Clin Endocrinol Metab*. 2011;**96**(7): E1115–E1119.
10. Kempers MJE, Ozgen HM, Vulsma T, Merks JH, Zwinderman KH, de Vijlder JJ, Hennekam RC. Morphological abnormalities in children with thyroidal congenital hypothyroidism. *Am J Med Genet A*. 2009;**149A**(5):943–951.
11. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, Beca J, Donofrio MT, Duncan K, Ghanayem NS, Goldberg CS, Hövels-Gürich H, Ichida F, Jacobs JP, Justo R, Latal B, Li JS, Mahle WT, McQuillen PS, Menon SC, Pemberton VL, Pike NA, Pizarro C, Shekerdemian LS, Synnes A, Williams I, Bellinger DC, Newburger JW; International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics*. 2015;**135**(5): 816–825.
12. Sterken C, Lemiere J, Van den Berghe G, Mesotten D. Neurocognitive development after pediatric heart surgery. *Pediatrics*. 2016;**137**(6):e20154675.
13. Aitken J, Williams FLR. A systematic review of thyroid dysfunction in preterm neonates exposed to topical iodine. *Arch Dis Child Fetal Neonatal Ed*. 2014;**99**(1):F21–F28.
14. l'Allemand D, Grüters A, Beyer P, Weber B. Iodine in contrast agents and skin disinfectants is the major cause for hypothyroidism in premature infants during intensive care. *Horm Res*. 1987;**28**(1):42–49.
15. Linder N, Sela B, German B, Davidovitch N, Kuint J, Hegesh J, Lubin D, Sack J. Iodine and hypothyroidism in neonates with congenital heart disease. *Arch Dis Child Fetal Neonatal Ed*. 1997;**77**(3): F239–F240.
16. Fernández Ruiz A, García-Guereta L, Benito Bartolomé F, Burgueros M, Ares Segura S, Moreno F, Gracia Bouthelier R. Alteraciones de la función tiroidea en niños con cardiopatía congénita tras la realización de cateterismo con contrastes yodados. *Rev Esp Cardiol*. 2000;**53**(4):517–524.

17. Kovacikova L, Kunovsky P, Lakomy M, Skrak P, Hraska V, Kostalova L, Tomeckova E. Thyroid function and ioduria in infants after cardiac surgery: comparison of patients with primary and delayed sternal closure. *Pediatr Crit Care Med*. 2005;**6**(2):154–159.
18. Institute of Medicine, Academy of Sciences, USA. *Dietary Reference Intakes for Vitamin D, Vitamin K, Arsenic, Boron, Chromium, Copper Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press; 2001.
19. Thaker VV, Leung AM, Braverman LE, Brown RS, Levine B. Iodine-induced hypothyroidism in full-term infants with congenital heart disease: more common than currently appreciated? *J Clin Endocrinol Metab*. 2014;**99**(10):3521–3526.
20. Drug Safety Communication. FDA Drug Safety Communication: FDA advises of rare cases of underactive thyroid in infants given iodine-containing contrast agents for medical imaging. 2015. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm472782.htm. Accessed 22 November 2015.
21. Barr ML, Chiu HK, Li N, Yeh MW, Rhee CM, Casillas J, Iskander PJ, Leung AM. Thyroid dysfunction in children exposed to iodinated contrast media. *J Clin Endocrinol Metab*. 2016;**101**(6):2366–2370.
22. Bergersen L, Gauvreau K, Marshall A, Kreutzer J, Beekman R, Hirsch R, Foerster S, Balzer D, Vincent J, Hellenbrand W, Holzer R, Cheatham J, Moore J, Lock J, Jenkins K. Procedure-type risk categories for pediatric and congenital cardiac catheterization. *Circ Cardiovasc Interv*. 2011;**4**(2):188–194.
23. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg*. 2002;**123**(1): 110–118.
24. Mitchell ML, Hsu H-W, Sahai I; Massachusetts Pediatric Endocrine Work Group. The increased incidence of congenital hypothyroidism: fact or fancy? *Clin Endocrinol (Oxf)*. 2011;**75**(6):806–810.
25. Elmlinger MW, Kühnel W, Lambrecht HG, Ranke MB. Reference intervals from birth to adulthood for serum thyroxine (T4), triiodothyronine (T3), free T3, free T4, thyroxine binding globulin (TBG) and thyrotropin (TSH). *Clin Chem Lab Med*. 2001;**39**(10):973–979.
26. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. Hoboken, NJ: John Wiley & Sons; 2000.
27. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, Polak M, Butler G; ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAE; Congenital Hypothyroidism Consensus Conference Group. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. *Horm Res Paediatr*. 2014;**81**(2):80–103.
28. Ahmet A, Lawson ML, Babyn P, Tricco AC. Hypothyroidism in neonates post-iodinated contrast media: a systematic review. *Acta Paediatr*. 2009;**98**(10):1568–1574.
29. Heyerdahl S, Oerbeck B. Congenital hypothyroidism: developmental outcome in relation to levothyroxine treatment variables. *Thyroid*. 2003;**13**(11):1029–1038.
30. Kornelius E, Chiou J-Y, Yang Y-S, Peng C-H, Lai Y-R, Huang C-N. Iodinated contrast media increased the risk of thyroid dysfunction: a 6-year retrospective cohort study. *J Clin Endocrinol Metab*. 2015; **100**(9):3372–3379.
31. Wolff J, Chaikoff IL. Plasma inorganic iodide, a chemical regulator of normal thyroid function. *Endocrinology*. 1948;**42**(6):468–471.
32. Sato K, Okamura K, Yoshinari M, Kuroda T, Ikenoue H, Okazawa K, Mizokami T, Onoyama K, Fujishima M. Reversible primary hypothyroidism and elevated serum iodine level in patients with renal dysfunction. *Acta Endocrinol (Copenh)*. 1992;**126**(3):253–259.
33. Takeda S, Michigishi T, Takazakura E. Iodine-induced hypothyroidism in patients on regular dialysis treatment. *Nephron*. 1993;**65**(1):51–55.
34. Brough R, Jones C. Iatrogenic iodine as a cause of hypothyroidism in infants with end-stage renal failure. *Pediatr Nephrol*. 2006;**21**(3):400–402.
35. Dagan O, Vidne B, Josefsberg Z, Phillip M, Strich D, Erez E. Relationship between changes in thyroid hormone level and severity of the postoperative course in neonates undergoing open-heart surgery. *Paediatr Anaesth*. 2006;**16**(5):538–542.
36. Murzi B, Iervasi G, Masini S, Moschetti R, Vanini V, Zucchelli G, Biagini A. Thyroid hormones homeostasis in pediatric patients during and after cardiopulmonary bypass. *Ann Thorac Surg*. 1995;**59**(2): 481–485.
37. Hamblin PS, Dyer SA, Mohr VS, Le Grand BA, Lim CF, Tuxen DV, Topliss DJ, Stockigt JR. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. *J Clin Endocrinol Metab*. 1986;**62**(4):717–722.
38. Franklin R, O'Grady C. Neonatal thyroid function: effects of nonthyroidal illness. *J Pediatr*. 1985; **107**(4):599–602.
39. Hyman SJ, Greig F, Holzman I, Patel A, Wallach E, Rapaport R. Late rise of thyroid stimulating hormone in ill newborns. *J Pediatr Endocrinol Metab*. 2007;**20**(4):501–510.

40. Kaluarachchi DC, Colaizy TT, Pesce LM, Tansey M, Klein JM. Congenital hypothyroidism with delayed thyroid-stimulating hormone elevation in premature infants born at less than 30 weeks gestation. *J Perinatol*. 2017;**37**(3):277–282.
41. Olivieri A, Stazi MA, Mastroiacovo P, Fazzini C, Medda E, Spagnolo A, De Angelis S, Grandolfo ME, Taruscio D, Cordeddu V, Sorcini M; Study Group for Congenital Hypothyroidism. A population-based study on the frequency of additional congenital malformations in infants with congenital hypothyroidism: data from the Italian Registry for Congenital Hypothyroidism (1991-1998). *J Clin Endocrinol Metab*. 2002;**87**(2):557–562.
42. Chaler EA, Fiorenzano R, Chilelli C, Llinares V, Areny G, Herzovich V, Maceiras M, Lazzati JM, Mendioroz M, Rivarola MA, Belgorosky A. Age-specific thyroid hormone and thyrotropin reference intervals for a pediatric and adolescent population. *Clin Chem Lab Med*. 2012;**50**(5):885–890.
43. Bailey D, Colantonio D, Kyriakopoulou L, Cohen AH, Chan MK, Armbruster D, Adeli K. Marked biological variance in endocrine and biochemical markers in childhood: establishment of pediatric reference intervals using healthy community children from the CALIPER cohort. *Clin Chem*. 2013; **59**(9):1393–1405.