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Screening for Congenital Hypothyroidism in Newborns Transferred to Neonatal Intensive Care

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Abstract

Objective—To evaluate the effectiveness of four screening protocols for congenital hypothyroidism (CH) in newborns transferred to the NICU. Determine an evidence base for the Center for Laboratory Standards Institute's Newborn Screening for Preterm, Low Birth Weight, and Sick Newborns Approved Guideline by evaluating a nearly identical protocol.

Design, Setting & Patients—Michigan newborns transferred to the NICU from 1998–2011 and screened for CH are included in this population-based retrospective cohort study.

Main Outcome Measures—Screening performance metrics are computed and logistic regression is used to test for differences in the likelihood of detection across four periods characterized by different testing protocols.

Results—Primary TSH plus retest at 30 days of life or discharge achieved the greatest detection rate (2.6: 1,000 births screened). The odds of detection was also significantly greater in this period compared to the tandem T4 and TSH testing period and separately compared to TSH testing alone, adjusted for birth weight, sex and race (aOR 1.5; CI 1.0–2.2; p=0.046, and aOR 2.2; CI 1.5–3.4, respectively). Approximately half of the cases detected during primary TSH plus serial testing periods were identified by retest.

Conclusion—Primary TSH testing programs that do not incorporate serial screening may fail to identify approximately half of newborns with congenital thyroid hormone deficiency transferred to the NICU. Tandem T4 and TSH testing programs also likely miss cases who otherwise would receive treatment if serial testing were conducted. Further research is necessary to determine the

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optimal NBS protocol for CH; strategies combining tandem T4 and TSH with serial testing conditional on birthweight may be useful.

Keywords

Newborn Screening; Performance Evaluation; Congenital Hypothyroidism; Repeat Testing

Introduction

Thyroid hormones are involved in neuronal migration and differentiation, myelination and synaptogenesis and are essential for proper neurodevelopment.[1, 2] Pathological concentrations of thyroid hormones at birth (congenital hypothyroidism -CH) cause severe mental retardation if left untreated.[3–5] Newborn screening (NBS) for CH began nearly 40 years ago in response to reports that few cases were treated within the appropriate three months of birth to avoid intellectual deficit.[6] Many NBS programs operate by measuring thyrotropin (TSH) in dried blood spots collected during the first several days of life when most newborns experience a surge reaching greater than 50 mU/L as a physiological response to cold environment followed by a decrease to below ~10 mU/L after several weeks[7]; newborns who do not exhibit the characteristic decline are referred for confirmatory testing.

NBS programs that make referrals for confirmatory testing based on TSH concentrations measured in dried blood spots collected before some children are able to mount the typical surge risk rendering false negative determinations. Later rising TSH is common among preterm infants (gestation < 37 weeks) and/or sick newborns presumably due to immaturity of the hypothalamic-pituitary-thyroid (HPT) axis.[8–12] Van Wassenae et al. report that TSH increases from day of life 3–7 onward and stabilizes after the 28th day among children born prior to 30 weeks of gestation.[11] Thus, as NBS programs strive for earlier specimen collection (<3rd day of life) to facilitate prompt identification of rare metabolic disorders, the likelihood of false negative determination for CH increases.

To offset the impact of later rising TSH on NBS, serial testing approaches have emerged.[12] Serial NBS involves retesting selected infants later in life to avoid false negative determination. Past studies of such protocols have applied varying inclusion criteria and testing procedures.[10, 12–15] In 2009, the Clinical and Laboratory Standards Institute (CLSI) published a guideline for NBS for preterm, low birthweight (LBW) and sick newborns recommending a first screen upon admission to a sick child birthing unit (SCBU), again at 48–72 hours of life, and once more at discharge or day 28 of life.[16] While the CLSI states that their recommendations “..provide the most reliable screening for the infant requiring the fewest specimens possible..(pg.19)”, it is based on expert opinion and has yet to be formally evaluated. Further, according to recent surveys, few physicians are aware of the guideline and nearly 75% of US NBS programs do not adhere to them.[17]

In this study we contribute to an evidence base for the CLSI guideline by evaluating the performance of a nearly identical protocol now used in Michigan to three prior protocols used in NBS for CH.

Methods

Study Design & Participants

This population-based retrospective cohort study includes Michigan resident infants transferred to the NICU after birth from 1998–2011.

Newborn Screening Protocols

In 1998, Michigan used a tandem T4 and TSH testing protocol to detect CH. (Table 1) Tandem T4 and TSH testing involved making referrals for confirmatory testing based on either low T4 or elevated TSH concentration. T4 was removed from the NBS panel after 10/1/2003. Starting 3/1/2007, a repeat testing element was added to the primary TSH protocol in which infants born weighing < 1,800g were re-screened at two and four weeks of life. Additionally, if the final specimen was affected by blood transfusions and/or total parenteral (TPN) nutrition, then repeat NBS was conducted after 72 hours from discontinuation of TPN and/or transfusion. Repeat NBS was also conducted again 90 days after the last transfusion if there was no documented pre-transfusion negative screen for hemoglobinopathies. In July of 2010, the serial testing protocol was revised to include a re-screen at 30 days of life or discharge for all newborns transferred to the NICU. The latter protocol nearly matches the CLSI guideline. Confirmatory testing was performed by the Endocrine Follow-up Program located at the University of Michigan Medical Center. Confirmatory testing involved serum tests of venipuncture blood samples combined with some measure of binding proteins (i.e., T3 resin uptake) used to differentiate free (active) from total T4.[18] Scintigraphy and ultrasound were also used clinically in managing suspected cases of CH.

Statistical Analysis

Perinatal characteristics and screening performance metrics are tabulated by protocol period. Logistic regression models are used to test whether the likelihood of detection differed significantly across protocol periods. Adjusted models include covariates that are both significantly associated with the dependent variable (CH detection) and varied significantly during the four protocol periods. To avoid multicollinearity, birthweight and gestational age were added separately. The final adjusted model includes birthweight instead of gestational age as it is more strongly associated with CH.[19] Effect modification terms are used to test for differences in the magnitude of association between screening protocol and detection as a function of other covariates (birthweight, gestational age, and sex). Differences in categorical and arithmetic variables are assessed using the chi-square test and Mann-Whitney U test, respectively. A 5% threshold is used for determining statistical significance. Statistical analyses were performed using SAS version 9.3 (Cary, NC, U.S.A).

Results

Nearly 145,000 resident infants born and screened in Michigan were transferred to the NICU after birth from 1998–2011. The distribution of selected perinatal characteristics did not meaningfully differ across protocol periods (Table 2); although, differences were statistically significant due to the large sample size.

Table 3 reports performance metrics for each protocol period. The detection rate was the greatest during the primary TSH plus retest at 30 days of life or discharge period (2.6/1,000); this protocol also achieved the greatest positive predictive value (14%). The false positive rate was far greater during the tandem T4 and TSH testing period (11%) than in primary TSH testing periods (<2%). The lowest detection rate was observed during the primary TSH without serial testing period. Comparatively, implementation of serial testing among births weighing <1,800g at two and four weeks of life increased the rate of detection; however, two normal birthweight infants accordingly excluded from serial testing during this period were later diagnosed with CH after having a negative initial screen. No additional false negative screens were reported after serial testing expanded to all NICU patients at 30 days of life or discharge. The median age at diagnosis did not differ significantly by protocol period (range: 19–36 days of life; $p=0.13$). One case of central hypothyroidism was detected during the tandem T4 and TSH testing period; once T4 testing ceased, no further cases were detected.

The likelihood of detection was significantly increased in both primary TSH plus repeat screen periods and in the tandem T4 and TSH testing period each compared to primary TSH testing alone (Table 4); these associations persisted after adjustment for birthweight, sex and race. The adjusted odds of detection were also greater during the primary TSH plus retest at 30 days of life than in the tandem T4 and TSH period (aOR 1.5; CI 1.0–2.2; $p=0.046$). The likelihood of detection differed further by screening protocol as a function of birthweight ($p=0.01$). Figure 1 shows the number of screens performed for each case detected stratified by birthweight and screening protocol. Tandem T4 and TSH testing achieved the greatest detection rate among normal birthweight infants, although the detection rate among moderately low birthweight infants (1,500g–2,499g) was less than observed in other periods. Primary TSH plus serial testing achieved the greatest detection rates among low birthweight infants.

Among all children diagnosed with CH by NBS, the proportion born at lower birthweights was far greater among those detected by retest (46% among births <1,500g and 24% among births 1,500g–2,499g compared to 6% among those of normal birthweight, $p<0.0001$). Otherwise, retest detection was not significantly associated with race ($p=0.69$), sex ($p=0.80$) or confirmatory testing result (serum TSH and serum FT4 before treatment; $p=0.72$ and 0.30 , respectively). Five cases detected by retest were born weighing $\geq 2,500$ g and one of four had an initial TSH concentration < 6 mU/l. The proportion of cases detected by retest was non-significantly greater ($p=0.16$) during the TSH plus retest at 30 days of life or discharge period (61%; $n=31/55$) compared to TSH plus retests for births weighing <1,800g (48%; $n=37/77$).

Figure 2 shows the distribution of postmenstrual age (PMA) at final dried blood spot specimen collection (gestational length in weeks + week of life at final retest) during the primary TSH plus retest at 30 days of life or discharge testing period stratified by gestational week at birth. Few (12%) preterm infants were last screened at a term-equivalent PMA (≥ 37 weeks). Three of four extremely low gestational age newborns (gestational age < 28 weeks) were last screened at PMA ≤ 32 weeks. Fewer than 25% of moderately preterm births (34–<37 weeks gestation) were last screened at or beyond 37 weeks PMA. Among

children born very preterm (<32 weeks gestation), 12% and 13% had their final dried blood spot specimen collected prior to 3–7 days of chronological age, respectively.

Discussion

The principle findings of this study are: 1) primary TSH plus retest at 30 days of life or discharge achieved the greatest overall detection rate, the likelihood of detection in this period was significantly greater than in the primary TSH testing alone or tandem T4 and TSH testing periods, primarily due to increased sensitivity among lower birthweight infants; 2) two false negative determinations occurred among normal birthweight newborns transferred to the NICU who were not re-screened due to later rising TSH during the primary TSH plus serial testing for births <1800g period, no additional false negatives were observed after serial testing was expanded to all patients at 30 days of life or discharge; 3) tandem T4 and TSH testing achieved the greatest detection rate among normal birthweight infants, although the false positive rate was increased by seven fold compared to primary TSH plus retest at 30 days of life or discharge; 4), during primary TSH plus serial testing periods, approximately half of the diagnosed cases were detected by retest; and 5) during the primary TSH plus retest at 30 days of life or discharge period, most children born preterm were last screened at a postmenstrual age less than term equivalent.

Our findings support the CLSI guideline as a preferred means of NBS for CH in newborns transferred to specialty care compared to primary TSH testing alone. It remains uncertain whether the CLSI guideline is an optimal approach as additional research is necessary to quantify the residual risk of false negative determination. Existing evidence indicates that TSH rises between days 3–7 of life and declines after 28 days among children born prior to 30 weeks gestation.[11] Thus, false negative screening determinations remain possible particularly among children born very preterm who are last screened prior to 3–7 days of life, although no such false negatives have been reported thus far. Additional research is necessary to better understand the natural history of neonatal thyroid hormones among newborns transferred to specialty care and the implications for NBS.

Our findings do not support the conclusion of Vincent et al.[12], that serial testing may not be necessary in programs that make referrals for confirmatory testing based on T4 or TSH independently. The likelihood of detection was significantly greater during the primary TSH plus retest at 30 days of life or discharge than in the tandem T4 and TSH testing period. The latter protocol was able to detect central hypothyroidism, although only a single case was identified during the several years it was used. Tandem T4 and TSH testing did achieve the greatest detection rate among normal birthweight infants, although it also achieved the lowest detection rate among moderately preterm births. Investigation of approaches combining tandem T4 and TSH screening with serial testing to maximize detection among normal and low birthweight infants, respectively, may be warranted.

The results of this study also do not support those of Korada et al.[20] who proposed a 6 mU/l initial TSH screening threshold instead of serial testing. Had Michigan employed this cutoff, one of four cases detected by retest would have been missed. However, Michigan collects approximately 95% of initial dried blood spot specimens at 24–48 hours of life,

much sooner than on the fifth day of life as in Korada et al.'s study, complicating a meaningful direct comparison of the two approaches. Had Michigan collected initial specimens at five days of life, it is possible that findings similar to those of Korada et al would have been observed.

The detection rate observed in this study among very low birthweight newborns during primary TSH plus serial testing periods (~1:130) is greater than reported in Larson et al.'s analysis of repeated tandem T4 and TSH testing in New England at 2, 6 and 10 weeks of age or until reaching a weight of 1,500g (1:250).[14] Our findings are more similar to those of Silva et al., who evaluated primary TSH testing plus retest at 5, 10 and 30 days of life in very low birthweight newborns and/or those born at gestational ages < 32 weeks, and Tylek-Lemanska et al.'s analysis of primary TSH plus retest for low birthweight infants at four weeks of life.[10, 15] Unlike in their studies, by re-testing all newborns transferred to the NICU at 30 days of life or discharge rather than restricting serial testing by birthweight or gestational age, Michigan was able to identify several term-born and/or normal birthweight cases by retest.

Further research is necessary to determine whether cases detected by retest who otherwise would have fit the definition of subclinical hypothyroidism benefit from early identification and treatment. Few studies have investigated the cognitive outcomes of subclinical hypothyroidism [21–23] and results of small investigations regarding benefit of treatment have been mixed.[24–28] Accordingly, there is little evidence that expanded sensitivity in NBS for CH improves patient outcomes. Our observation that serum TSH and FT4 concentrations used for confirmatory testing are statistically indistinguishable among cases detected by retest compared to those detected by an initial screen is suggestive of equivalent disease severity meaning these children may benefit equally from treatment.

Our findings per false negative determinations should be interpreted with caution as Michigan relies on passive reporting. Potentially missed cases may be detected clinically later in life. Diagnosed cases may later be found to have had transient hypothyroidism, although our findings are representative of NBS during the first several months of life. Changes in diagnostic practices over time may also have impacted our findings; until a standardized case definition is developed, we are unable to quantify such impact. Missing data may also have influenced our findings, although 'missingness' did not vary significantly by protocol making it unlikely to meaningfully bias our study. Our calculation of PMA is also limited in that gestational age at birth was measured in weeks leaving a margin of error of +/- six days. Finally, our estimated proportion of very preterm newborns last screened prior to 3–7 days of life is perhaps overestimated as some of these children may have expired prior to a scheduled retest and we were unable to evaluate this.

Conclusion

Primary TSH testing programs that do not incorporate serial screening for CH may fail to identify approximately half of newborns with congenital thyroid hormone deficiency transferred to the NICU. Programs referring newborns for confirmatory testing based on T4 instead of performing serial screening may also fail to identify some cases, particularly those

born low birthweight and/or preterm. Further research is necessary to determine the optimal NBS for CH protocol for newborns transferred to specialty care; strategies combining tandem T4 and TSH with serial testing conditional on birthweight may be useful. Further investigation is also necessary to evaluate the benefit of expanded sensitivity in NBS for CH.

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Abbreviations

CH	Congenital Hypothyroidism
g	Grams
LCL	Lower 95% Confidence Limit
NBS	Newborn Screening
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
PMA	postmenstrual age
T4	Thyroxine
TSH	Thyrotropin
UCL	Upper 95% Confidence Limit
US	United States

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What is already known on this topic

- Preterm and sick newborns are at increased risk of false negative screening determinations for congenital hypothyroidism due to later rising thyrotropin.
- Guidelines recommend repeat testing at 30 days of life or at discharge from special care but these are based on expert opinion and have yet to undergo formal evaluation.

What this study adds

- Primary TSH testing that does not incorporate serial screens may fail to identify approximately half of newborns with congenital thyroid hormone deficiency in the NICU.
- Programs relying on confirmatory testing based on T4 concentrations instead of serial TSH may also fail to identify some cases.
- Further research is necessary to determine the optimal screening protocol for newborns transferred to specialty care; strategies combining tandem T4 and TSH with serial testing conditional on birthweight or those designed with specimen collection conditional on postmenstrual age may be appropriate.

Figure 1.

Congenital Hypothyroidism Detection Rate by Screening Protocol Period among Michigan Newborns Transferred to Neonatal Intensive Care in 1998–2011 Stratified by Birthweight (n= 144,241)

Figure 2. Postmenstrual Age in Weeks (+/- 6 days) at Final Dried Blood Spot Specimen Collection by Gestational Age at Birth during the Primary TSH plus retest at 30 Days of life or Discharge Protocol Period (n=19415)

Table 1

Michigan Newborn Screening for Congenital Hypothyroidism Initial Thyroid Stimulating Hormone Concentration Cutoff Values by Age at Specimen Collection

Screening Protocol	Age at Specimen Collection	T4 Cutoff (ng/dl)	TSH Cutoff (uIU/mL)	Result
Tandem T4 and TSH (1/1998–9/2003)	All Ages	< 5	>20	Positive
			23–49	Borderline Positive
			>49	Strong Positive
Primary TSH testing (10/1/2003–12/31/2011)	< 24 hours	Not Applicable	50	Strong Positive
			< 50	Early specimen
	24–36 hours		< 33	Negative
			33–49	Borderline Positive
			50	Strong Positive
	37hours-6days		< 25	Negative
			25–49	Borderline Positive
			50	Strong Positive
	7–31 days		< 13	Negative
			13–49	Borderline Positive
			50	Strong Positive
	> 31 days		10	Negative
			> 10	Positive

Note: *Positive or strong positive determination results in referral for confirmatory testing. Early specimen and borderline positive determinations result in repeat dried blood spot screen; after an initial borderline positive determination, if the repeat dried blood spot screen is also positive then the newborn is referred for confirmatory testing.

Descriptive Characteristics of Michigan Newborns Transferred to Neonatal Intensive Care in 1998–2011 by Screening Protocol Period

Table 2

Population Segment		Tandem T4and TSH (1/1998–9/2003)		TSH, No Serial Testing (10/2003–2/2007)		TSH, Serial Testing <1800g (3/2007–6/2010)		TSH, Serial Testing NICU (7/2010–12/2011)	
		N	%	N	%	N	%	N	%
Race	White	21477	60.4	26336	62.8	23549	60.8	10785	60.0
	Black	11197	31.5	12201	29.1	12023	31.1	5524	30.7
	Other	2898	8.1	3424	8.1	3142	8.1	1662	9.3
Sex	Female	16859	44.4	19869	44.7	18498	44.9	8546	44.3
	Male	21098	55.6	24601	55.3	22669	55.1	10731	55.7
Birth Weight		2340		2649		2640		2695	
(median -IQR)		(1644–3178)		(1974–3340)		(1970–3300)		(2020–3335)	
Gestational Age - median		35		36		36		36	
(Inter-Quartile Range)		(32–38)		(33–39)		(33–39)		(34–39)	
Total		38257		45072		41497		19415	

Note: Missing data are as follows: race, n=10440; sex, n=1479; birth weight, n=2103; gestational age, n=13934; Percentages reported are column based.

Table 3

Performance Metrics by Screening Protocol Period Determined among Michigan Resident Newborns Transferred to Neonatal Intensive Care in 1998–2011 (n= 144,241)

Exposure Period	Detection Rate *	Positive Predictive Value (%)	False Positive Rate (%)	Sensitivity (%)	Specificity (%)
Tandem T4 & TSH testing, no serial test	2.0/1,000	1.7	11.3	100	88.7
Primary TSH, no serial testing	1.2/1,000	7.6	1.5	100	98.5
Primary TSH, serial testing among births <1,800g	1.9/1,000	10.0	1.7	100	98.3
Primary TSH, serial testing among infants transferred to NICU	2.6/1,000	14.5	1.6	100	98.5

Note:

* Detection rate is defined as the number of cases detected per 1,000 newborns screened.

Table 4
Likelihood of Congenital Hypothyroidism Detection Compared to Primary TSH Testing Alone among Michigan Newborns Transferred to Neonatal Intensive Care 1998–2011(n= 144,241)

Screening Protocol	Crude			Adjusted		
	OR	LCL	UCL	OR	LCL	UCL
Primary TSH, plus serial testing among infants transferred to NICU	2.2	1.5	3.2	2.2	1.5	3.2
Primary TSH, plus serial testing among births <1,800g	1.6	1.1	2.3	1.6	1.1	2.3
Tandem T4 & TSH testing, no serial testing	1.8	1.3	2.6	1.5	1.0	2.2
Primary TSH, no serial testing	1			1		

Note: The above table reports the likelihood of congenital hypothyroidism detection by screening protocol compared to primary TSH without serial testing expressed as an odds ratio; Odds ratio confidence intervals that do not encompass '1' are indicative of a significant association compared to the primary TSH without serial testing period. Adjusted models included birth weight (continuous), race & sex; OR= Odds Ratio, LCL=Lower 95% Confidence Limit, UCL=Upper 95% Confidence Limit; Missing data are as follows: race, n=10440; sex, n= 1479; birth weight, n= 2103; gestational age, n= 13934.