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A retrospective review of newborn screening for congenital hypothyroidism and newborn thyroid disease at a major medical center

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Abstract

Objective—To study the frequency of congenital hypothyroidism (CH)/ thyroid disorders at a major, urban medical center.

Methods—We conducted a retrospective review of a preexisting database for 2007 to 2011. Infants were classified as having CH, secondary/ tertiary hypothyroidism, thyroid-binding globulin (TBG) deficiency, and other types of newborn thyroid dysfunctions.

Results—353 (50%) abnormal newborn screens were found to be normal and 42% were abnormal upon repeat. Of the latter, 14% had true CH, 1% had TBG deficiency, and 27% had other causes of thyroid dysfunction. The five year incidence of CH at NYP Morgan Stanley Children's Hospital (CHONY) was significantly greater than in New York City, New York State, and Upstate-NY.

Conclusion—The incidence of CH and other thyroid dysfunctions were greater in our population for 2007 to 2010, after which there was an unexplained decline. The study underlines the importance of continued newborn screening for thyroid dysfunction.

Keywords

Congenital hypothyroidism; newborn screening; newborn thyroid disease

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Introduction

The overall incidence of congenital hypothyroidism (CH) in the United States is around 1:3,000 newborns, with a slightly higher frequency in Asian and Hispanic individuals, and a slightly lower frequency in the African- American and Caucasian populations (1). Since mandated in the United States in 1978, newborn screening for CH has become a major public health initiative and has virtually eliminated associated cases of intellectual disability.

Prior studies suggest that a child with undiagnosed CH will have a 5-10-point decline in IQ, delays in speech and language development, and decreased attention and memory skills (2). More recent studies have shown that the potential benefit of screening newborns for CH results in the prevention of 160 cases of intellectual disability annually (3). Indeed it has been stated that children with CH who are started on supplemental thyroid therapy within the first few weeks of life “have a normal or near-normal neurodevelopmental outcome” (1).

In 1965 the first newborn screen was mandated into law with New York State's Public Health Law 2500a (4). Today, New York State tests for 46 different diseases, including congenital hypothyroidism (4). Specialty Care Centers throughout the state are mandated to track all abnormal thyroid function tests; New York Presbyterian's Division of Pediatric Endocrinology, Diabetes, and Metabolism provides evaluation and follow-up to all newborns with suspected CH born within its catchment area, which includes children born at NYP Morgan Stanley Children's Hospital (CHONY) and The Allen Pavilion—a secondary care community hospital affiliated with CHONY—, as well as those children referred to our Center with abnormal newborn screening test results.

The purpose of this study is to examine the geographic distribution and the frequency of the diagnoses of CH as well as other etiologies accounting for abnormal newborn thyroid screens, in newborns at a major urban medical center, over a period of five years (2007-2011). In addition, we will compare our finding to New York State's annual reports to better determine if the diagnoses documented in our Newborn Screen database differ within our sub-population.

Methods

Data Retrieval

Data was retrieved from the Department of Pediatric Endocrinology, Diabetes, and Metabolism (PEDM) at New York Presbyterian- Morgan Stanley Children's Hospital's internal Newborn Screen log, established in 2003 for ongoing tally, review and patient care purposes. Clinical information for each patient is entered into the log at the time of referral, and throughout the patient's follow-up. For the analysis reported here, subjects were subsequently de-identified by the co-authors, and data were extracted from the newborn screening log and entered into a secure study database approved by our Institutional Review Board. A waiver of consent was approved by the IRB, since there was no appreciable risk to the patients.

Patients were classified by NYS as having congenital hypothyroidism, secondary and tertiary hypothyroidism, thyroid-binding globulin (TBG) deficiency, and “other” types of newborn thyroid dysfunctions including sick euthyroid syndrome, transient hypothyrotropinemia and hypothyroxinemia of prematurity. As of May 3, 2010 New York State changed its thyroid stimulation- hormone (TSH) cut-off value from $>50\text{uU/mL}$ to $>100\text{uU/mL}$, thus reducing a high false positive rate for primary congenital hypothyroidism (5).

We also compared our database to New York State's Department of Health Newborn Screening Program's annual reports between the years 2007 to 2011 (6). These annual reports reflect abnormal newborn screen specimens received throughout the years in question. However, of note, abnormal newborn screens may take up to 1-2 years to confirm a diagnosis according to New York State's Department of Health, and may reflect an abnormal screen from a prior year. Thus, it is our understanding that these annual reports reflect the data available at the time of posting and may change on a day-to-day basis.

Data Analysis

For statistical analysis, we calculated overall and yearly means, frequency distributions and specific unduplicated incidence rates of each diagnosis for individual locations available for comparison from the New York State Newborn Screening Program (this included CHONY, New York City, Upstate New York State, and New York State total from 2007 to 2011). Statistical differences in the proportion of incident cases between collection locations were assessed using the Cochran-Mantel-Haenszel method based on table scores. Differences in relative risk of disease between locations are presented as Mantel-Haenszel rate ratios with 95% confidence intervals. To assess the impact of yearly fluctuations in incidence rates of disease, and thus examine specific modifying effects on our results, we performed Cochran-Armitage Trend Tests for individual years from 2007- 2011 for each disease category. We used the Breslow-Day Test to assess the homogeneity of the rate ratios after controlling for yearly fluctuations. All statistical analyses were performed using SAS software. A P -value <0.05 was considered statistically significant.

Results

Three hundred and fifty three (353) abnormal newborn screens were referred to our center between 2007 and 2011. Of these, 177 were interpreted as normal after a repeat screening (50%), 21 expired (6%), 7 were transferred to an outside facility (2%), and 148 (42%) were still abnormal upon repeat screening. (Figure 1).

Of these abnormal thyroid screens, a total of 50 cases (14%) of true primary congenital hypothyroidism were identified at CHONY over the five-year period included in our study. With 34,363 live births recorded during this period, this translated to an overall incidence rate of 1.46 per 1000 births. Additionally, a total of 4 cases of TBG deficiency (1%) were identified (incidence of 0.12 per 1000 births) and 94 newborns (27%) had other cases of thyroid dysfunction; including hypothyroxinemia of prematurity, transient hypertropinemia, and sick euthyroid syndrome (incidence of 2.74 per 1000 births). No cases of secondary/ tertiary thyroid dysfunction were identified in the aforementioned years.

The five-year CH incidence rate at CHONY appeared to be greater than that reported by New York City as a whole without CHONY (1.46 per 1000 at CHONY vs. 0.58 per 1000 in NYC). We found a statistically significant difference in the overall incidence of CH after performing a Cochran-Mantel-Haenszel test and determination of odds ratio, ($\chi^2=47.6$, $df=1$, $p<0.0001$. [(OR)= 2.75, 95% CI =2.04-3.71, $p<0.0001$].). Of note, similar incidences of CH were observed for New York State, Upstate New York State, and New York City.

Stratification of the data by year over the five years that were studied revealed that the incidence of CH at CHONY was quite variable over the five years. We also determined that the regional variation between NYC (without CHONY) and CHONY in the incidence per 1000 births of CH was significant only in years 2008 (0.59 vs 2.00, $z=-5.04$, $p<0.0001$), 2009 (0.67 vs. 1.75, $z=-3.54$, $p=.0004$) and 2010 (0.52 vs. 1.90, $z=-5.20$, $p<0.0001$). After 2010, there was a dramatic decrease in the incidence of CH at CHONY and the 2011 rate of 0.44 per 1000 births was not significantly different than the incidence rate in New York City (0.42 of 1000 births). (Table 1, Figure 2).

Statistically significant regional variation in the overall prevalence of “other” thyroid diagnoses (0.37 per 1000 in NYC vs. 2.74 per 1000 at CHONY, $\chi^2=553.9$, $df=1$, $p<0.0001$. OR= 12.09, 95% CI= 9.28-15.78, $p<0.0001$) were observed. (Table 2).

For TBG deficiency and secondary/tertiary hypothyroidism there was no statistically significant difference in overall or yearly incidences of either diagnosis between New York City, Upstate New York State, New York State (total) and CHONY (data available upon request).

Discussion

Our retrospective review illustrates that the incidence of CH and other thyroid dysfunctions were significantly greater for part of the period of review at CHONY, a large urban tertiary care center compared to that of New York City, Upstate New York State, and New York State (total). Based on previously published data of a national incidence rate of CH, we expected to find that about 0.42 of every 1000 births resulted in CH (1). NYC, Upstate NYS, and NYS had overall incidence rates close to this level, while our overall incidence was almost three times higher. This overall incidence represented the higher rates for years 2007-2010. Of interest is that the number of CH cases and incidence rate did drop significantly after the cutoff value for TSH was increased from 50 uU/ml to 100 uU/ml in mid 2010. This may be a coincidental finding since decreasing the false positive rate should not have affected our overall rate of identification of true CH. Of further interest is that review of New York City, Upstate New York State, and New York State (total) data also revealed a decline in total cases and incidence rate after 2010. Furthermore, because we are a large tertiary care center, we also receive a larger number of case referrals of newborns with significant concurrent complex disorders which may include actual cases of neonatal hypothyroidism.

It is also possible that our findings may be due to minor demographic differences between collection locations. CHONY has a large number of Hispanic patients. Prior studies have

suggested that CH is more common among Hispanic newborns. Hinton et al. (7) showed a 100% higher incidence rate in Hispanic newborns compared with white newborns across the United States from 1991 to 2000. However due to the retrospective nature of our review we were unable to obtain demographic data and the magnitude of the effect of ethnicity can only be speculated.

Finally, of note, was the high relative risk (almost 12 times higher risk in our catchment area than that of New York City as a whole) of other thyroid dysfunction such as hypothyroxinemia of prematurity, transient hypertropinemia, sick euthyroid syndrome. It is well established that premature infants are “relatively hypothyroxinemic with normal to low levels of serum TSH and T3 concentration” due to the “stresses of extrauterine transition superimposed on an immature thyroid axis” (8). Children born at extremely low gestational ages (<28 weeks gestation) are more greatly affected by transient hypothyroxinemia. Due to the fact that CHONY is a tertiary care center with a large high risk nursery, there may have been a disproportionately large number of very low birth weight (VLBW) infants who contributed to the larger number of reported cases of thyroid disorders in our population. We are also a popular referral center for complicated cases so our incidence rate may also include cases from outside our catchment area that are transferred to our tertiary care center for specialized care. Due to the nature of this retrospective review we cannot confirm these suggestions. We intend to continue to analyze our data from the upcoming years to confirm and compare our future rates compared to New York City, Upstate New York State, and New York State (total).

One of the major limitations of our findings is that, as previously stated, the annual reports provided by the New York State Department of Health may not reflect the exact number of confirmed cases of thyroid diseases at a specific point in time. Thus, although we compared our incidence of CH, secondary and tertiary hypothyroidism, TBG deficiency and other abnormal thyroid diagnoses to New York State's annual reports, we caution over-interpretation due to the above cited limitations.

In summary, we found that across five years CHONY has had consistently higher incidence rates of CH but showed an unexplained dramatic decline from 2010 to 2011 after the cutoff value for TSH was changed and the false positive rate decreased for CH. We also found a much greater relative risk of other newborn thyroid disorders at our hospital. Both discrepancies can possibly be explained by the selection bias that results from our high risk nursery with a disproportionate amount of premature, VLBW, sick newborns. To our knowledge, only one other publication has examined the incidence of CH from abnormal newborn screens in a similar clinical patient population in New York City (9); and no follow-up reports have since been published.

Finally, a prior published cost-benefit analysis performed thirty years ago found that the detection and treatment of a single child with CH cost \$11,800, while the cost of life- long special education and lost productivity of the affected person would value \$105,000 per case (10). Adjustment for today's monetary value would be exponentially greater. Therefore, our findings underscore the importance of continuing newborn screening for thyroid disorders to

prevent adverse outcomes such as mental retardation and developmental delays in our population.

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Figure 1. Study Population Results

Figure 2. Incidence per 1000 births of CH

Table 1

Total Cases and Incidence of Congenital Hypothyroidism, by site of collection

	2007		2008		2009		2010		2011		Overall	
	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)
New York State (NYS)	200	0.78	129	0.51	141	0.57	113	0.46	94	0.39	677	0.54
Upstate New York State	103	0.81	55	0.44	53	0.43	47	0.39	42	0.36	300	0.49
New York City (NYC)	88	0.71	72	0.59	82	0.67	62	0.52	50	0.42	354	0.58
Children's Hospital of New York (CHONY)	8	1.16	14	2.00	12	1.75	13	1.90	3	0.44	50	1.46

Table 2

Total Cases and Incidence of other newborn thyroid disorders, by site of collection

	2007		2008		2009		2010		2011		Overall	
	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)	Total Cases	Incidence (per 1000)
New York State (NYS)	17	0.07	51	0.20	51	0.20	107	0.43	176	0.73	402	0.32
Upstate New York State	7	0.06	23	0.18	22	0.18	42	0.35	72	0.61	166	0.27
New York City (NYC)	9	0.07	28	0.23	28	0.22	61	0.51	98	0.82	224	0.37
Children's Hospital of New York (CHONY)	24	3.47	30	4.30	21	3.06	9	1.32	10	1.48	94	2.74