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Transient Hypothyroidism at 3-Year Follow-Up among Cases of Congenital Hypothyroidism Detected by Newborn Screening

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Abstract

Objective—To investigate the rate of transient thyroid deficiency and treatment compliance among cases with congenital hypothyroidism diagnosed and followed-up after age 3 years by newborn screening (NBS).

Study design—Cases detected by Michigan NBS between October 1, 2003, and December 31, 2007, and followed-up after age 3 years were included. The χ^2 and Fisher exact tests were used to test differences among followed and lost cases. Logistic regression models were used to investigate predictors of treatment cessation.

Results—Roughly 45% of eligible cases were lost to follow-up, and disease state (transient or permanent congenital hypothyroidism) could not be determined for 12 cases (7.9%). Of the 72 followed cases, 34 (47%) were considered permanent congenital hypothyroidism based on thyroid imaging findings ($n = 7$) or an increase in medication dosage over time ($n = 27$). One-quarter of followed cases with congenital hypothyroidism were no longer being treated, and of these, just over 83% stopped treatment without medical supervision. Of 23 cases that underwent a medically supervised trial without thyroid hormone medication, treatment was reinstated in 20. Laboratory confirmation of euthyroidism was available for 6 of 18 cases clinically deemed transient. After adjustment, black race was the strongest predictor of treatment cessation (OR, 9.86; 95% CI, 1.82–53.31). Treatment cessation was also more common among low birth weight infants and those admitted to the neonatal intensive care unit at birth.

Conclusion—We recommend that NBS programs include long-term follow-up through at least age 3 years to determine treatment compliance and disease permanence. Further research is needed to determine ideal follow-up program operations and reassessment methods for congenital hypothyroidism disease permanence. Guidelines that provide evidence-based reassessment methods would be beneficial for the healthcare providers of children with congenital hypothyroidism.

INTRODUCTION

Long-term follow-up of children diagnosed with diseases detected by newborn screening (NBS) has received increasing attention over the past decade. The *Eunice Kennedy Shriver*

National Institute of Child Health and Human Development, Health Resources and Services Administration Maternal and Child Health Bureau, and Centers for Disease Control and Prevention are each in the process of developing initiatives to promote the development of effective follow-up systems.¹ Although much attention has been given to necessary components of long-term follow-up, including data monitoring systems, quality health indicators, and evaluation metrics,^{2,3} few NBS programs have attempted routine follow-up of detected cases beyond diagnosis, owing to financial constraints and other barriers.⁴

Long-term follow-up of congenital hypothyroidism is of particular interest. Congenital hypothyroidism is an umbrella term for several congenital thyroid disorders usually characterized by pathologically low concentrations of thyroxine that may or may not be accompanied by elevated concentrations of thyroid-stimulating hormone (thyrotropin; TSH). Thyroid hormones act on such processes as neuronal migration and differentiation, myelination, and synaptogenesis, which are essential for proper neurodevelopment and are also involved in maintenance of normal physiological functions, such as bone maturation.^{5,6} Pathologically low concentrations of thyroid hormone experienced during critical stages of development may cause severe mental retardation and skeletal growth abnormalities.^{5,7–15} The deleterious outcomes of untreated congenital hypothyroidism are well known^{9,16–18}; however, recent evidence suggests that many diagnosed children are no longer treated after age 3 years.

Kemper et al¹⁹ analyzed multistate data from 2001–2006 and found that 38% of more than 700 cases of congenital hypothyroidism no longer exhibited claims for thyroid replacement therapy after 36 months. Their data did not allow them to determine whether treatment cessation was medically indicated, however. Although the American Academy of Pediatrics recommends that a trial off therapy be conducted to determine whether treatment remains necessary at around age 3 years for all children with suspected congenital hypothyroidism other than those with thyroid aplasia, few US NBS programs reliably obtain follow-up information beyond diagnosis.^{16,20–22} Accordingly, the percentage of diagnosed cases in the US that are later determined to have transient disease after carrying the diagnosis of congenital hypothyroidism is currently unknown, owing to the lack of long-term follow-up. According to Mitchell et al,²³ 19%–28% of diagnosed cases detected by the New England Regional Newborn Screening Program during 2 birth periods (1991–1994, 2001–2004) were later found to have had transient hypothyroidism, although whether these findings are generalizable to other states is unclear. Here we report the experience of the Michigan Department of Community Health (MDCH) in expanding its NBS Follow-Up Program to include routine follow-up of cases of congenital hypothyroidism detected by NBS after age 3 years to determine disease permanence and treatment compliance.

METHODS

In 2007, 3-year follow-up of cases with congenital hypothyroidism in Michigan was initiated by mailing a brief survey to the endocrinologist recorded in NBS Follow-Up Program data. Materials were shared with the Region 4 Genetics Collaborative and are available at http://region4genetics.org/region4/_docs/advisory_group/HO4_CH_Pilot.pdf. The survey was developed by the lead author and the NBS Follow-Up Program manager in collaboration with the Michigan Pediatric Endocrinology Advisory Committee and pilot-tested by several pediatric endocrinologists. Surveyed endocrinologists not currently providing care to the child were asked to provide contact information for the last known care provider (endocrinologist or primary care provider), and another survey was mailed to the identified provider. If the child's current care provider was unknown or misspecified, then NBS Follow-Up Program staff extracted current physician contact information from the Michigan Care Improvement Registry, a register of childhood immunization data, and this

physician was surveyed by phone. If a medical care provider could not be reached, then NBS Follow-Up Program staff contacted the parent again, using contact information listed in the Michigan Care Improvement Registry.

This study was approved by the MDCH Institutional Review Board. Demographic and perinatal information collected on the NBS card and NBS follow-up and medical management data were used to identify and characterize cases born between October 1, 2003, and December 31, 2007. Inclusion criteria for the study were: (1) Michigan resident infants born and screened in Michigan who were diagnosed with congenital hypothyroidism between October 1, 2003, and December 31, 2007, by NBS; (2) were followed-up after age 3 years; and (3) whose clinician either conducted a diagnostic reevaluation or reported the reason for not doing so (e.g., thyroid imaging was indicative of permanent disease). Patients followed up who did not undergo diagnostic reevaluation were excluded, because we were unable to determine whether they experienced transient or permanent congenital hypothyroidism. Results of 3-year follow-up of cases with congenital hypothyroidism detected by the MDCH NBS program since October 1, 2003, and recorded by the Michigan NBS Follow-up Program via survey were also used. Survey activities were halted temporarily while transitioning responsibilities from the NBS Follow-Up Program to the Endocrine Follow-up Program housed at the University of Michigan in 2009. On resumption of 3-year follow-up survey activities, the decision was made to start with children born in 2007; consequently, follow-up was attempted for only 3 cases born in 2006.

Demographic and perinatal information extracted to characterize infants included sex, race, gestational age (in weeks), birth weight (in grams), and admission to a neonatal intensive care unit (NICU). NBS information extracted to characterize infants included dried blood spot TSH concentrations, serum TSH and free thyroxine (FT4) concentrations, and ultrasound imaging and/or radioisotope scanning results. Infants who had a positive dried blood spot screening determinations and underwent treatment at the conclusion of confirmatory testing performed by the Endocrine Follow-up Program are considered to have congenital hypothyroidism by the MDCH NBS Follow-Up Program. Infants with laboratory-confirmed normal thyroid function after discontinuation of thyroid hormone medication are considered to have transient hypothyroidism.

Because there is no standardized case definition for congenital hypothyroidism, “normal thyroid function” was defined by the diagnosing clinicians. Infants no longer being treated for congenital hypothyroidism were also considered to have transient hypothyroidism, although only a subset underwent testing of thyroid hormone profiles to confirm their assignment to the transient hypothyroidism group and provided those profiles to the MDCH NBS Follow-Up Program.

Analyses

The 3-year follow-up findings, including the rate of diagnostic reassessment and subsequent determinations, are reported in association with selected newborn characteristics. Followed cases are presented by (1) whether a medically supervised trial off thyroid hormone supplementation was conducted; (2) whether the patient stopped taking medication absent medical supervision; and (3) whether the patient was deemed ineligible for a trial off medication. Among followed cases deemed eligible for a trial off thyroid hormone supplementation, those continuing to receive treatment after age 3 years, (representing permanent cases) were compared with those no longer receiving treatment (representing transient cases), using the χ^2 test for differences in proportions; when 25% or more of the cells had a count <5 , the Fisher exact test was used. Predictive logistic regression models were used to investigate predictors of treatment cessation/transient disease among cases diagnosed and followed up, including those deemed ineligible for a trial off medication.

Covariates included in adjusted models were selected based on clinical knowledge, and model reduction was also performed based on the plausibility of regression coefficients, association with independent variables, and magnitude of change in parameter estimates.²⁴

RESULTS

Follow-up after age 3 years was attempted for 152 children with congenital hypothyroidism detected by the Michigan NBS Follow-Up Program between October 1, 2003, and December 31, 2007. Follow-up was attempted for only 3 cases detected in 2006. Sixty-eight children (44.7%) were lost-to follow-up (LTFU), diagnostic reevaluation was in process for 8 (5.3%), and diagnostic reevaluation was not completed, in-process, or planned for unknown reasons for 4 (2.6%), for a final study population of 72 children who had undergone some degree of diagnostic reevaluation to identify transient or permanent congenital hypothyroidism (Figure).

The percentage of cases born low birth weight or premature, admitted to the NICU at birth, and having a pretreatment serum FT4 value <1 pmol/L were nonsignificantly greater among the children LTFU (Table I). Few followedup children underwent thyroid imaging (n = 11; 13%), although this percentage was consistent with the overall rate of thyroid imaging in cases detected in Michigan (data not shown) and did not differ from that in the cases LTFU. Nine of the 11 children who underwent thyroid imaging had a thyroid abnormality. A minority of followed children had an initial TSH concentration <50 µIU/mL (27%) or a pretreatment serum TSH concentration <20 mU/L (36%). Nearly half of the followed-up children had a pretreatment serum FT4 concentration <1 pmol/L.

Of the 72 cases followed up and known to have undergone some form of diagnostic reevaluation, 34 (47%) were deemed ineligible for a trial off thyroid hormone supplements (Figure). Reasons for ineligibility reported by clinicians included permanent congenital hypothyroidism depicted on thyroid imaging (n = 7; 21%) and required increases in thyroid hormone supplement dosage over time (n = 27; 79%), representing a permanent need for treatment. Characteristics of cases considered permanent based on thyroid imaging and increasing medication dosage are listed in Table II. Of note, 3 of the 27 children whose diagnosis was considered permanent based on an increase in thyroid hormone supplement dosage had their dosage increased at age 5 weeks, age 6 months, and age 9 months. Age at the time of supplement dosage increase was not reported for the remaining 24 children deemed to have permanent congenital hypothyroidism by this criterion.

A trial during which patients were either not receiving thyroid hormone supplements or receiving lower doses of supplements was conducted under medical supervision. Among 23 patients (32%), only 3 were determined to have transient congenital hypothyroidism and did not resume treatment. Some 20% of the patients followed-up stopped taking thyroid hormone supplements without medical supervision; among these, only 3 had normal thyroid hormone profiles transmitted to MDCH. The remainder were considered to have transient congenital hypothyroidism by their primary care physicians, but laboratory confirmation was not provided. Unsupervised cessation of thyroid hormone supplementation was more common among nonwhite children ($P = .004$) and infants admitted to an NICU at birth ($P = .047$) compared with white children and newborns not transferred to an NICU.

Of the 38 cases deemed eligible for a trial off medication, 47% are no longer receiving treatment. However, confirmation of transient hypothyroidism in the form of normal laboratory values was provided for only 6 cases no longer receiving medication for congenital hypothyroidism. Children no longer receiving thyroid hormone supplementation were statistically indistinguishable from those continuing to receive treatment in terms of

initial TSH concentrations ($P = .21$), and confirmatory testing results (pretreatment serum TSH <20 mU/L, $P = .88$; serum FT4 <1 pmol/L, $P = .92$). However, among them, the percentage of children with an initial TSH concentration <50 μ IU/mL (61.5%) was appreciably elevated compared with those who resumed treatment (38.5%), and the difference likely would have been significant with a larger sample size.

Table III reports the relative odds of treatment cessation/transient disease among all followed cases, including those deemed ineligible for a trial off treatment based on a medication dosage increase or abnormal thyroid imaging results. The unadjusted odds of treatment cessation at follow-up were significantly elevated in nonwhite children, those born low birth weight, and those admitted to the NICU after birth. After adjustment, the only factor significantly predictive of treatment cessation was black race (OR, 9.86; CI, 1.82–53.31).

DISCUSSION

Our study found that 25% of children with congenital hypothyroidism followed-up after age 3 years are no longer receiving thyroid hormone supplementation, and that black race was the strongest predictor of treatment cessation. It is particularly noteworthy that 20% of the children followed up in this study had stopped treatment without medical supervision. This finding could indicate the presence of an important public health problem, inasmuch as poor treatment compliance is a predictor of adverse neurodevelopmental outcomes in congenital hypothyroidism.^{9,16–18} In addition, although clinicians frequently reported normal thyroid function in children who stopped taking their medication without medical supervision, confirmation of this by laboratory testing was rarely available. Because we were unable to follow up 44% of our cohort, the burden of unsupervised treatment cessation in congenital hypothyroidism that we uncovered is may be an underestimate of the magnitude of the problem. NBS programs might follow the lead of the follow-up services in place in many states for contagious diseases, such as tuberculosis, that make use of public health nurses to maintain regular contact with affected persons to address this problem.

The striking difference in the determination of disease permanence by whether or not treatment cessation was conducted under medical supervision is also noteworthy, because it may indicate a need for evidence-based guidelines on assessing disease permanence. Although unlikely, some children who underwent a medically supervised trial off medication might have had insufficient time for their thyroid hormones to normalize and thus could have been prematurely categorized as permanent congenital hypothyroidism. Similarly, some cases considered to have permanent congenital hypothyroidism based on an increase in thyroid hormone medication dosage might also have been prematurely categorized as having permanent congenital hypothyroidism. American Academy of Pediatrics guidelines¹⁶ could be updated to specify which blood tests to obtain and what constitutes important changes in thyroid hormones warranting continuation and/or reinstatement of treatment in terms of both degree and timing. Updated guidelines also could specify the desired time of treatment cessation and appropriate monitoring strategies thereafter, considering that both vary significantly among the few published studies.^{20,25,26}

Although limited by LTFU, our findings on prevalence of transient hypothyroidism in children with congenital hypothyroidism diagnosed by NBS are consistent with those of Mitchell et al,²³ who reported a transient form of the disease in 28% of cases with congenital hypothyroidism detected by the New England Regional NBS Program in 2001–2004. We found a nonsignificantly smaller percentage of cases no longer receiving treatment after a medically supervised trial off therapy at age 3 years (13%) than that reported by Eugster et al²⁰ in a clinic-based follow-up study of 33 cases with euthyroid congenital

hypothyroidism (36%). Our overall rate of treatment cessation among all cases of congenital hypothyroidism detected by NBS (25%) is lower than that found in the claims-based analysis of Kemper et al,²⁵ which estimated that 38% of children were no longer receiving medication after age 3 years. However, it is possible that because the children LTFU in this study were also more likely to have stopped treatment given their demographic characteristics, our rate might be an underestimate. Our findings related to race should be interpreted with caution, given our lack of sufficient data to measure other potential confounders, such as education or socioeconomic status, which might have explained the observed association with treatment compliance. The dearth of thyroid imaging among study participants also limited our ability to determine eligibility for a trial off treatment, although the rate of thyroid imaging in study participants was equivalent to that of the children LTFU, making it unlikely to have biased our findings. Because thyroid imaging provides useful information relevant to the distinction between potentially transient and clearly permanent congenital hypothyroidism, further work is needed to obtain thyroid imaging for all children referred for confirmatory testing after a positive dried blood spot screening determination.²⁷

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Glossary

FT4	Free thyroxine
LTFU	Lost-to-follow-up
MDCH	Michigan Department of Community Health
NBS	Newborn screening
NICU	Neonatal intensive care unit
TSH	Thyroid-stimulating hormone

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Figure 1.

Figure Flow diagram of the 3-year follow-up study. *TX*, treatment.

Transient Hypothyroidism at 3-Year Follow-Up among Cases of Congenital Hypothyroidism Detected by Newborn Screening

Table I

Proportion of cases with congenital hypothyroidism detected by Michigan NBS October 1, 2003, through December 31, 2007, and followed-up at or beyond age 3 years by selected demographic/perinatal characteristics

Population segment	Lost to follow-up, n (%)	Followed-up, n (%)	P value
Race			
White	46 (67.7)	56 (66.7)	.34
Black	9 (13.2)	17 (20.2)	
Other	13 (19.1)	11 (13.1)	
Sex			
Female	37 (55.2)	40 (47.6)	.35
Male	30 (44.8)	44 (52.4)	
Multiple birth			
No	66 (97.1)	80 (95.2)	.69*
Yes	2 (2.9)	4 (4.8)	
Birth weight			
<2500 g	17 (25.4)	8 (9.9)	.06*
>2500 g	50 (74.6)	73 (90.1)	
Gestational age			
<37 weeks	23 (33.8)	15 (17.9)	.08
>37 weeks	45 (66.2)	69 (82.1)	
NICU admission			
No	48 (70.6)	70 (83.3)	.06
Yes	20 (29.4)	14 (16.7)	
Dried blood spot TSH, mIU/mL			
#50	24 (35.3)	23 (27.4)	.29
\$50	44 (64.7)	61 (72.6)	
Serum TSH, mU/L			
<20	22 (32.8)	29 (36.0)	.66
\$20	45 (67.2)	51 (63.8)	
Serum FT4, pmol/L			
<1	39 (63.9)	37 (47.4)	.053
\$1	22 (32.4)	41 (48.8)	
Thyroid imaging results			
Normal	1 (1.5)	2 (2.4)	.47
Abnormal	12 (17.7)	9 (10.7)	
None	55 (80.9)	73 (86.9)	
Total	68 (100)	84 (100)	

P values represent the test for differences in the proportion of infants in each population segment by follow-up

Table II

Method of trial off thyroid hormone medication or reason for lack of trial, cases of congenital hypothyroidism detected in October 1, 2003 through December 31, 2007 and followed-up after age 3 years, Michigan NBS

Population segment	Cases followed-up, n (%)	Trial off medication, n (%)		Reason for continuing medication without trial, n (%)	
		Medically unsupervised cessation of medication	Medically supervised trial off medication	Abnormal thyroid scan	Medication increase
Race					
White	48 (66.7)	5 (33.3)	17 (73.9)	3 (42.9)	23 (85.2)
Black	15 (20.8)	7 (46.7)	4 (17.4)	2 (28.6)	2 (7.4)
Other	9 (12.5)	3 (20.0)	2 (8.7)	2 (28.6)	2 (7.4)
Sex					
Female	38 (52.8)	10 (66.7)	14 (60.9)	4 (57.1)	10 (37.0)
Male	34 (47.2)	5 (33.3)	9 (39.1)	3 (42.9)	17 (63.0)
Twin					
No	69 (95.8)	14 (93.3)	22 (95.7)	7 (100)	26 (96.3)
Yes	3 (4.2)	1 (6.7)	1 (4.3)	0 (0)	1 (3.7)
Gestational Age					
<28 weeks	5 (6.9)	1 (6.1)	3 (13.0)	0 (0)	1 (3.7)
28-37 weeks	8 (11.1)	2 (13.3)	1 (4.3)	1 (14.3)	4 (14.8)
>37 weeks	59 (81.9)	12 (80.0)	19 (82.6)	6 (85.7)	22 (81.5)
Low birth weight					
No	64 (88.9)	13 (86.7)	20 (90.9)	7 (100)	24 (92.3)
Yes	6 (8.3)	2 (13.3)	2 (9.1)	0 (0)	2 (7.7)
NICU					
No	61 (84.7)	10 (66.7)	20 (87.0)	7 (100)	24 (88.9)
Yes	11 (15.3)	5 (33.3)	3 (13.0)	0 (0)	3 (11.1)
Medication continued					
No	18 (25.0)	15 (100)	3 (13.0)	0 (0)	0 (0)
Yes	54 (75.0)	0 (0)	20 (87.0)	7 (100)	27 (100)
Total	72 (100)	15 (100)	23 (100)	7 (100)	27 (100)

The percentages reported are column-based. Missing data are as follows: birth weight, n = 2

Table III

Predictors of transient determination among children diagnosed with congenital hypothyroidism and followed-up by Michigan NBS after age 3 years, 2004–2007

Population segment	Cases followed, n	Treatment cessation at follow-up					
		Unadjusted			Adjusted		
		OR	LCL	UCL	OR	LCL	UCL
Race							
White*	48	1.0					
Black	15	6.69	1.84	24.39	9.86	1.82	53.31
Other	9	2.93	0.59	14.52	5.10	0.86	30.19
Sex							
Female	38	2.15	0.71	6.57			
Male	34	1.0					
Gestational age							
<28 weeks	5	0.73	0.08	7.09			
28–37 weeks	8	0.98	0.18	5.38			
>37 weeks*	59	1.0					
Low birth weight							
No*	64	1.0					
Yes	6	7.14	1.18	43.11	2.77	0.18	42.26
NICU admission							
No*	61	1.0					
Yes	11	4.70	1.22	18.05	5.20	0.78	34.71
Dried blood spot screen result							
TSH <50 µIU/mL	18	3.36	1.06	10.69	1.35	0.30	6.02
TSH >50 µIU/mL*	54	1.0					
Confirmatory testing results							
Serum TSH <20 mU/L	24	2.50	0.82	7.61			
Serum TSH 20 mU/L*	45	1.0					
Serum FT4 <1 pmol/L*	35	1.0					
Serum FT4 1 pmol/L	37	2.60	0.80	8.48			
Total	72						

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LCL, lower confidence limit; *UCL*, upper confidence limit

These results show the likelihood of treatment cessation after age 3 years in a selected population segment relative to a referent, indicated by *. Blank cells in the adjusted column indicate that sex, gestational age, and confirmatory testing results were removed from the final model. Missing data are as follows: birth weight, n = 2; serum TSH, n = 1; and FT4, n = 1.