Treatment Discontinuation within 3 Years of Levothyroxine Initiation among Children Diagnosed with Congenital Hypothyroidism

Alex R. Kemper, MD, MPH, MS[1], Scott D. Grosse, PhD[2], Mei Baker, MD[3], Allison J. Pollock, MD[3], Cynthia F. Hinton, PhD[4], and Stuart K. Shapira, MD, PhD[2]

Objectives To measure the rates of thyroid gland imaging and levothyroxine ($L\text{-}T_4$) discontinuation and to assess whether discontinuation was monitored with thyroid-stimulating hormone testing in subjects with congenital hypothyroidism.

Study design This is a retrospective analysis of claims data from the IBM MarketScan Databases for children born between 2010 and 2016 and continuously enrolled in a noncapitated employer-sponsored private health insurance plan or in Medicaid for ≥36 months from the date of the first filled $L\text{-}T_4$ prescription.

Results There were 263 privately insured and 241 Medicaid-enrolled children who met the inclusion criteria. More privately insured than Medicaid-enrolled children had imaging between the first filled prescription and 180 days after the last filled prescription (24.3% vs 12.9%; $P = .001$). By 36 months, 35.7% discontinued $L\text{-}T_4$, with no difference by insurance status ($P = .48$). Among those who discontinued, 29.1% of privately insured children and 47.7% of Medicaid-enrolled children had no claims for thyroid-stimulating hormone testing within the next 180 days ($P = .01$).

Conclusions Nearly one-third of children with suspected congenital hypothyroidism discontinued $L\text{-}T_4$ by 3 years and fewer Medicaid-enrolled than privately insured children received timely follow-up thyroid-stimulating hormone testing. Future studies are indicated to understand the quality of care and developmental outcomes for children with congenital hypothyroidism and barriers to guideline adherence in evaluating for transient congenital hypothyroidism. *(J Pediatr 2020;223:136-40)*.

Congenital hypothyroidism is a preventable cause of intellectual disability that is detected by newborn screening programs in the US and around the world. Before the introduction of newborn screening, about 1 in 7000 children in high-income countries experienced clinical congenital hypothyroidism, ~30% of whom (1 in 20 000) developed intellectual disability as a result of late-diagnosed or undiagnosed congenital hypothyroidism.[1] Newborn screening identifies ~1 in 2000 infants with congenital hypothyroidism in the US who, as a result of timely treatment, are not at increased risk of intellectual disability.[1] According to recommendations from the American Academy of Pediatrics, the American Thyroid Association, and the Lawson Wilkins Pediatric Endocrine Society, infants with congenital hypothyroidism should be treated as soon as possible with thyroid hormone replacement (ie, levothyroxine [$L\text{-}T_4$]), ideally within 2 weeks after birth, with frequent monitoring to adjust dosing and to evaluate growth and development.[2-4] To minimize delays to treatment, guidelines recommend that infants begin care before it is known whether the congenital hypothyroidism is permanent, which requires long-term treatment, or transient, in which case $L\text{-}T_4$ can be discontinued. Most often, this determination is based on laboratory testing, but in certain circumstances it can be based on thyroid gland imaging.[5,6] Causes of permanent congenital hypothyroidism include thyroid dysgenesis, defects in thyroid hormone synthesis, thyroid hormone receptor mutations, and disorders causing hypopituitarism.[7]

Congenital hypothyroidism is usually confirmed through laboratory testing that shows the thyroid-stimulating hormone (TSH) concentration is elevated and the free thyroxine concentration is low. Infants with elevated TSH but normal free thyroxine concentrations on confirmatory testing are also typically considered to have congenital hypothyroidism and begun on $L\text{-}T_4$, although these infants are more likely to have transient congenital hypothyroidism.[8-11]

The determination of permanent vs transient congenital hypothyroidism is generally not possible at the time of diagnosis in the newborn.[3] Thyroid imaging (eg, thyroid ultrasound examination, uptake scans with iodine 123 or sodium technetium 99m pertechnetate) can be definitive; if the thyroid gland is ectopic or absent, congenital hypothyroidism is permanent.[3] Longitudinal TSH concentration monitoring provides an indirect approach to determining whether congenital hypothyroidism is permanent. Generally, with normal growth of the child, the $L\text{-}T_4$

$L\text{-}T_4$	Levothyroxine
TSH	Thyroid-stimulating hormone

From the [1]Division of Primary Care Pediatrics, Nationwide Children's Hospital, Columbus, OH; [2]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA; [3]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI; and [4]National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA

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requirement will increase, leading to an increase in the TSH concentration if the dose is not adjusted, which is suggestive of permanent congenital hypothyroidism.[3] Alternatively, if after age 3 years, there is still a question of whether congenital hypothyroidism might be transient (eg, the L-T_4 requirement has not increased with growth as expected), a clinically supervised trial of phasing out or decreasing the dose of L-T_4 over a 4- to 6-week period that is monitored with TSH testing is recommended.[3,4]

We previously found that, between 2001 and 2006, approximately 38% of children with congenital hypothyroidism no longer had prescriptions for L-T_4 filled by 3 years after initiating treatment based on administrative claims data for privately insured and Medicaid-enrolled children.[12] This rate of discontinuation raised questions about the degree to which some children did not receive appropriate care, families were not adherent with L-T_4 treatment, or transient congenital hypothyroidism was more common than suspected.[12] Subsequently, the Michigan Department of Health surveyed endocrinologists regarding the 3-year follow-up of 152 newborns with congenital hypothyroidism detected between 2003 and 2007 and reported that nearly one-half (45%) of the children were lost to follow-up.[13] Of the 84 cases with follow-up, 4 had not been evaluated to determine whether they had transient or permanent congenital hypothyroidism and 8 were in the process of a trial of L-T_4. Among the remaining 72 children, 34 had suspected permanent congenital hypothyroidism based on either the need for greater doses of L-T_4 or thyroid imaging findings. Among the other 38 children, 23 (61%) had a medically supervised trial of L-T_4 dose reduction or discontinuation, 20 of whom were subsequently classified as having permanent congenital hypothyroidism. In 15 (39%), the family stopped L-T_4 without a medically supervised trial. The researchers reported that all 15 were clinically deemed as transient cases, with documented laboratory reports for 3 and physician reports of normal TSH concentrations for the other 12.

The objective of our study was to evaluate the rate of discontinuation of thyroid hormone treatment in a relatively recent cohort of US children treated for congenital hypothyroidism. In our previous study of discontinuation,[12] we could only describe when children were no longer filling prescriptions for L-T_4, but could not evaluate the proportion of children who had thyroid gland imaging or who had follow-up TSH testing. These data are now available to us in the more current claims databases, allowing for a significantly better understanding of thyroid hormone discontinuation. Although the importance of long-term follow-up after newborn screening[14] has been expounded upon since our previous study, we are not aware of any specific efforts targeted specifically to congenital hypothyroidism.

Methods

We conducted a retrospective analysis of health insurance claims for children with congenital hypothyroidism to determine the duration of thyroid hormone replacement with L-T_4 based on prescription refills. For those individuals who no longer had L-T_4 prescriptions after the first 3 years of L-T_4 treatment, we evaluated whether there were claims for relevant imaging tests or laboratory tests for TSH concentration.

Data Sources

We analyzed claims data from the IBM MarketScan Commercial Database (MarketScan is a registered trademark of IBM Corporation in the United States, other countries, or both) from January 1, 2010, through April 30, 2019 and the MarketScan Multi-State Medicaid Database from January 1, 2009, through December 31, 2018. Both databases include inpatient and outpatient encounters with diagnosis and procedure codes and outpatient pharmacy claims. Both include an encrypted enrollee identification number that can be used for longitudinal analysis. The commercial claims database is a nationwide convenience sample of employer-sponsored private health insurance plans. The Medicaid claims database includes claims data from 8 to 11 unidentified states, varying by year. We accessed both databases via IBM MarketScan Treatment Pathways 4.0, an online analytic platform using a dynamic version of the data that is stored on IBM Watson Health servers and includes plans that report outpatient pharmacy claims.

To have complete claims data for each privately insured subject, we accessed 2 overlapping Treatment Pathways Commercial samples, one for claims from January 1, 2010, through July 31, 2017, and one with claims from January 1, 2012, through April 30, 2019. We used data from the first sample on births from 2010 to 2014 and from the second sample on births from 2012 to 2016, to allow for 3 years of follow-up. Many, but not all, enrollees were included in both samples. The Medicaid database included all years in 1 file.

Patients

We classified infants treated for congenital hypothyroidism based on a first filled outpatient prescription for L-T_4 within 90 days of the first claim associated with a live birth claim and a second filled prescription between 7 and 185 days after the first one. We retained children who were enrolled in the same health plan for at least 36 months in noncapitated plans from the date of the first L-T_4 claim. Records for individuals with presumed congenital hypothyroidism were exported and merged in a spreadsheet file, then deduplicated on the basis of enrollee identification number.

To protect subject confidentiality, birth year, but not exact birth date, is available in MarketScan research databases. No information is available regarding race/ethnicity in the commercial data. No information on the clinicians who established diagnoses, provided prescriptions, or ordered laboratory tests is available in either the commercial or Medicaid data.

Thyroid Imaging, L-T_4 Discontinuation, and Follow-up TSH Testing

Thyroid imaging testing was based on claims at any date with procedure codes 78000-78014 for either thyroid imaging or

thyroid uptake nuclear medicine imaging, along with 76536 for ultrasound imaging of the soft tissues of the neck, including the thyroid gland. We calculated the date of L-T_4 discontinuation as the last day of a filled prescription within the study period plus the days supplied by that prescription. Follow-up TSH testing was based on claims for TSH testing (procedure codes 84443, 80438, and 80439) within 180 days after the date of the last filled prescription.

Data Analyses

We used χ^2 tests of association to evaluate categorical data and the Kruskal-Wallis test was used to evaluate differences in medians for the time to TSH testing. Kaplan-Meier analysis was used to evaluate the rate of continuation of L-T_4 from initiation. All analyses were conducted with Stata statistical software (StataCorp LLC., College Station, Texas). We considered differences with a P value of less than .05 to be statistically significant.

Results

Study Population

In the private insurance database, we identified 667 infants of 1 187 981 live births during 2010-2014 (birth prevalence of 1:1781) who met the case definition for presumed congenital hypothyroidism (ie, ≥2 filled prescriptions for L-T_4). Similarly, we identified 649 infants with presumed congenital hypothyroidism out of 1 034 439 live births during 2012-2016 (birth prevalence of 1:1594). After deduplication, 263 children were enrolled for at least 36 months in noncapitated private health insurance plans. In the Medicaid database, we identified 587 infants out of 728 417 live births (birth prevalence of 1:1241) who met the case definition for presumed congenital hypothyroidism, of whom 241 children were enrolled for at least 36 months in noncapitated Medicaid health insurance plans.

Thyroid Gland Imaging

Privately insured children treated with L-T_4 were about twice as likely to have received imaging at any time as those in the Medicaid database, 24.3% vs 12.9% (P = .001).

Discontinuation Rates

The Figure presents the Kaplan-Meier curve for continuation of L-T_4 treatment. By 3 years after treatment initiation, 32.7% of privately insured children and 35.7% of Medicaid-enrolled children had discontinued thyroid hormone treatment (P = .48). Of those who discontinued

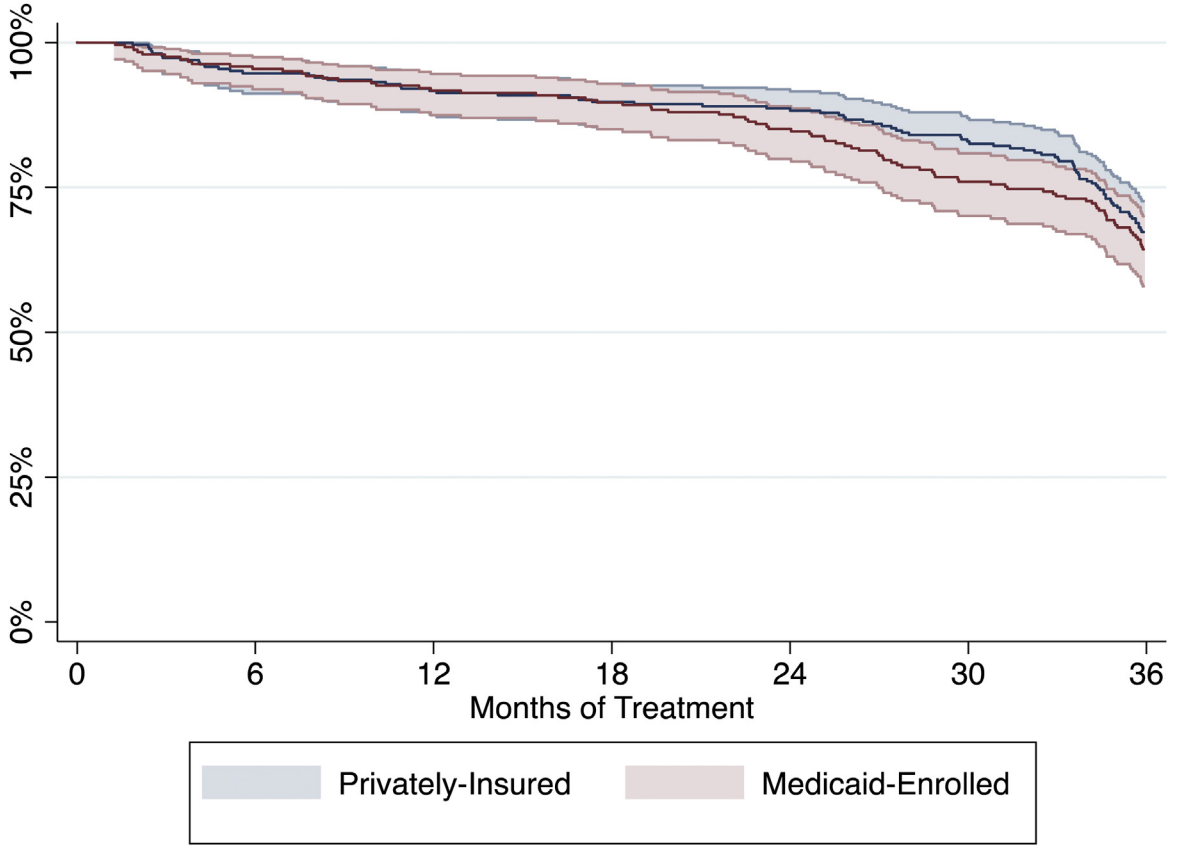

Figure. Proportion of patients receiving thyroid hormone treatment over time stratified by insurance status. The shaded area is the 95% CI.

L-T_4, more than one-half of the privately insured and Medicaid-enrolled children did so between 2 and 3 years after initiating treatment (65.1% vs 58.1%; $P = .21$).

Discontinuation and Follow-up TSH Testing

Among those who discontinued L-T_4 before 3 years, 29.1% of those with private insurance and 47.7% enrolled in Medicaid did not have a TSH test in the 180 days after the date of the last filled prescription ($P = .01$). For those who did have a TSH test in the next 180 days, the median number of days and IQR did not differ ($P = .51$) for those with private insurance (63 days; IQR, 38-89 days) and those enrolled in Medicaid (59 days; IQR, 41-89 days). The likelihood of having follow-up TSH testing within 180 days did not vary by the age of discontinuation (privately insured, $P = .68$; Medicaid enrolled, $P = .74$). For privately insured children, having a TSH test within 180 days was associated with an increased likelihood of receiving thyroid gland imaging (29.5% vs 8%; $P = .03$) but not for Medicaid-enrolled children (8.9% vs 7.3%; $P = .79$).

Discussion

Clinical guidelines for the management of congenital hypothyroidism after newborn screening underscore the importance of close medical management, including TSH assessment soon after discontinuation of L-T_4. Similar to our previous study of claims data from 2001-2006, we found that about one-third of children with congenital hypothyroidism discontinued thyroid hormone treatment by 3 years.[12] This rate is higher than the generally expected rate of transient congenital hypothyroidism, although consistent with some clinical observations.[5,6] Of children in the present study who stopped treatment, nearly one-third of privately insured children and one-half of Medicaid-enrolled children did not have TSH testing within the subsequent 180 days. For all children with congenital hypothyroidism, the rate of thyroid gland imaging was fairly low, which is consistent with the US clinical guidelines that do not call for routine imaging.[3] The proportion with thyroid imaging claims was about twice as high for privately insured children compared with those enrolled in Medicaid.

For this analysis, we relied on a large administrative claims database because there is no US registry of patients with congenital hypothyroidism. Although claims data have inherent limitations, a retrospective study within individual clinics is not feasible because children with congenital hypothyroidism can be taken care of by a variety of clinician types (eg, pediatric endocrinologists, adult endocrinologists, pediatricians, family physicians).[15] Survey studies of outcomes after newborn screening have been limited by low response rates.[13] In particular, families of patients who no longer receive active congenital hypothyroidism management might be less likely to respond or to provide valid information.

While conducting this analysis, we observed that the rate of thyroid imaging varied by census divisions from 2012 to 2016, with the highest rate in the Mountain states and the lowest rate in the Pacific states (40% vs 8%). We chose not to include this finding in the formal analysis because of incomplete data across all subjects and the overall small sample size. This finding may reflect regional variation in the approach to congenital hypothyroidism management and further emphasizes the need to understand care delivery at the local level.

One possible future opportunity to better understand care delivery for children with congenital hypothyroidism is to analyze linked administrative health, education, and newborn screening records for multiple years of births. For example, 1 report described 2 separate analyses based on linking newborn screening records on 362 390 births in metropolitan Atlanta, Georgia, during 1981-1991 with surveillance data on developmental disabilities and linking data on 520 625 children born in 1981-1995 to special education records.[16] Another study linked newborn screening records for 354 137 children born in New South Wales, Australia during 1994-2002 to education records and records for 149 569 children born during 2002-2008 to developmental assessments.[17] However, neither study was able to assess the impact of treatment patterns on outcomes. The metropolitan Atlanta study reported that 1 of the 2 children with confirmed congenital hypothyroidism who accessed speech and language therapy services was nonadherent to treatment, but the investigators were unable to access clinical data for the majority of children with congenital hypothyroidism.[16]

We cannot directly determine the degree to which each case of discontinuation of treatment before 3 years was appropriate or whether there was any harm associated with stopping L-T_4. Newborn screening is highly sensitive and, therefore, by design should identify some infants with transient congenital hypothyroidism for whom stopping treatment is appropriate. In 14 states, infants are routinely screened a second time at around 2 weeks of age.[18-20] Most infants (75%-80%) identified only on the second screen have transient congenital hypothyroidism, suggesting this subpopulation may be more likely to discontinue L-T_4 and have subsequent reassuring TSH concentrations.[6,18] We are unable to determine in this analysis whether an infant was identified with a first or second newborn screening test.

Newborn screening also identifies many infants with subclinical congenital hypothyroidism.[1] Whether stopping treatment for children with subclinical congenital hypothyroidism might be appropriate is unclear, particularly because 1 study from Australia reported that children with TSH concentrations that fell slightly below the newborn screening cutoff had higher risk of poorer educational and developmental outcomes than those with TSH concentrations above the screening cutoff, who were presumably treated.[17,21]

There are limitations to the use of claims data; we do not have laboratory or imaging results or clinical notes, so we cannot comment on whether laboratory or imaging results were appropriately acted upon or whether those who

discontinued treatment were more likely to have transient or subclinical congenital hypothyroidism. even when TSH testing occurred after L-T_4 discontinuation, we cannot determine whether this was in the context of a medically supervised trial of treatment discontinuation. This study cannot predict the degree to which inappropriate discontinuation occurs or the number of children who might be adversely affected. We have limited demographic information and no specific information about the healthcare providers. Health plan enrollment attrition also limited the total number of children who could be followed for 3 years. However, we set a low standard for evidence of follow-up testing to identify the minimum potential magnitude of problems related to unmonitored discontinuation, and nearly all children continued to be enrolled in their insurance plans for 180 days after discontinuation of L-T_4.

Despite these limitations, these results signal that a substantial number of children, with more enrolled in Medicaid than privately insured, may not receive recommended care, potentially putting them at risk for intellectual impairment. This study underscores the need for new approaches to monitor long-term outcomes after newborn screening, such as integrated electronic health record systems with such monitoring capabilities.[22] Newborn screening for congenital hypothyroidism can achieve its goal of optimizing child health and development if clinicians and families work together to ensure that those children who need it continue to receive medical management for the condition. ■

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Reprint requests: Alex R. Kemper, MD, MPH, MS, 700 Children's Drive, LAC5411, Columbus, OH 43205-2664. E-mail: alex.kemper@nationwidechildrens.org

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