Published in final edited form as:

Endocr Pract. 2017 September ; 23(9): 1067–1071. doi:10.4158/EP171881.OR.

TARGETED LEVOTHYROXINE THERAPY FOR TREATMENT OF CONGENITAL HYPOTHYROIDISM

Melissa J. Schoelwer, MD¹, Wanzhu Tu, PhD², Junyi Zhou, MS³, and Erica A. Eugster, MD¹

¹Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, Indiana

²Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana

³Department of Biostatistics, Indiana University-Purdue University Indianapolis, Indiana

Abstract

Objective—The purpose of this study was to determine if infants with congenital hypothyroidism (CH) whose initial dose of levothyroxine (LT4) is based on thyroid gland anatomy require fewer dose adjustments in the first 6 months of life than those who were started empirically on LT4.

Methods—Newborns with CH who had a thyroid ultrasound performed at diagnosis were eligible for this prospective, historical case-controlled study. The daily LT4 dose prescribed was based on results on the thyroid ultra-sound as follows: 15 mcg/kg for athyreosis, 12 mcg/kg for a dysgenetic thyroid, and 10 mcg/kg for an anatomically normal gland. Routine labs according to standard guide-lines were obtained, and the number of dose adjustments over the first 6 months of therapy was recorded. Each study participant was matched with 2 historical controls with CH based on sex and thyroid anatomy.

Results—Twenty-two subjects (10 with athyreosis, 4 with dysgenetic glands, and 8 with anatomically normal glands) were matched to 44 controls. There was no significant difference in the overall number of adjustments in the study group compared to controls ($P = .74$). However, there were significantly fewer adjustments made for undertreatment ($P = .03$) and significantly more adjustments made for overtreatment ($P = .006$) in subjects with athyreosis compared to controls.

Conclusion—Targeted LT4 therapy does not appear to decrease the overall frequency of dose adjustments for infants with CH. However, 15 mcg/kg/day appears to exceed thyroid hormone requirements in infants with CH due to athyreosis.

INTRODUCTION

Thyroid hormone is essential for normal brain growth and development. In children with congenital hypothyroidism (CH), early identification and treatment with high-dose

Address correspondence to Dr. Melissa Schoelwer, 705 Riley Hospital Drive Room 5960, Indianapolis, IN 46202.: MJS3PG@virginia.edu.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

levothyroxine (LT4) at 10 to 15 mcg/kg daily has been shown to rapidly normalize thyroid-stimulating hormone (TSH) levels and improve neurodevelopmental outcomes (1,2). However, the risk of inducing supraphysiologic thyroxine levels increases with higher initial doses of LT4 (3,4). Several studies have suggested that this might also be harmful to the developing brain, and episodes of over-treatment (OT) have been linked to a difficult temperament in infancy, as well as lowered intellectual functioning and decreased attention span later in childhood (3,5,6). While the optimal testing interval remains uncertain, frequent laboratory testing is recommended to prevent prolonged periods of OT and undertreatment (UT) in infants with CH. The American Academy of Pediatrics (AAP) recommends thyroid function testing 2 to 4 weeks after initiation of LT4 therapy and every 1 to 2 months during the first 6 months of life (7), whereas the European Society for Pediatric Endocrinology (ESPE) recommends testing every 2 weeks until the TSH normalizes followed by testing every 1 to 3 months thereafter during the first year (8).

The vast majority of cases of permanent CH are due to thyroid agenesis or dysgenesis in which the gland fails to develop properly leading to complete absence or dysgenetic thyroid tissue (9). A eutopic gland is seen in the setting of dysmorphogenesis due to an inborn error in thyroid hormone synthesis, as well as in transient CH that may be due to maternal antithyroid drug use or blocking antibodies. Thyroid gland anatomy can be determined by multiple modalities including radionuclide uptake scan, scintiscan, or ultrasonography. However, this is widely considered optional as the results do not alter the initial medical management of affected infants.

Conversely, if thyroid anatomy is known at the time of diagnosis, it would seem reasonable that infants with CH due to athyreosis might require more LT4 than those with dysgenetic thyroids or anatomically normal glands that are present in the normal location. Limited information is available about how a targeted dosing strategy compares to empiric dosing within the recommended range along with conventional laboratory monitoring. We hypothesized that targeted dosing based on thyroid anatomy would result in fewer dose adjustments during the first 6 months of treatment and thus fewer periods of OT and UT.

METHODS

Newborn infants diagnosed with CH were prospectively recruited from the pediatric endocrine clinic at Riley Hospital for Children at Indiana University Health in Indianapolis, Indiana. The study was approved by the Indiana University School of Medicine Institutional Review Board and written informed consent was obtained from parents or guardians. The clinical trial was registered as “Targeted Levothyroxine Dosing in Infants with Congenital Hypothyroidism” (NCT02374593 at [https:// www.clinicaltrials.gov](https://www.clinicaltrials.gov)). Per our standard protocol, all subjects were started on LT4 10 to 15 mcg/kg/day by their primary care provider in consultation with the coordinator for the Indiana Newborn Screening Follow-up Program (EAE) as soon as confirmatory serum testing was drawn or had resulted (10). LT4 was prescribed as oral tablets, and parents were instructed to crush the tablet; mix it with a small amount of water, breastmilk, or formula; and give it to the infant using an oral medication syringe. Infants were seen in our clinic within 5 days of diagnosis, and a thyroid ultrasound was performed. Based on the thyroid anatomy as visualized on ultrasound, the

LT4 dose was adjusted if necessary as follows: 10 mcg/kg/day for an anatomically normal gland, 12 mcg/kg/day for a dysgenetic gland, and 15 mcg/kg/day for athyreosis. At times, alternating pill sizes were required to achieve doses within 0.5 mcg/kg of the desired amount. Routine bloodwork (TSH along with a total or free thyroxine [T4]) was recommended per AAP guidelines to be drawn 2 weeks following LT4 initiation and then monthly during the first 6 months. Parents were given standing orders to have their infant's thyroid levels drawn at a laboratory of their choice close to home. The LT4 dose was adjusted per the discretion of the primary pediatric endocrinologist based on the laboratory results. The total number of adjustments was recorded over the first 6 months of treatment and whether the adjustment was made due to OT (dose decreased) or UT (dose increased) was also determined.

Each study participant was matched with two historical controls with CH based on sex and thyroid anatomy. The matched controls had been dosed empirically at diagnosis with starting doses between 10 to 15 mcg/kg/day without prior knowledge of thyroid anatomy. The same data regarding dose adjustments during the first 6 months of treatment was collected for all controls.

Statistical Analysis

We performed χ^2 tests to assess differences in the sex distribution among the 3 anatomical groups. Differences in serum TSH level at the time of diagnosis and the initial LT4 dose were explored using independent *t* tests. A Poisson regression analysis was performed to evaluate for differences in the number of adjustments between the study and control subjects. $P < .05$ was considered statistically significant. Analyses were performed using SAS (SAS Inc, Cary, NC) or SPSS 23 (IBM Corp, Armonk, NY).

RESULTS

Twenty-four subjects were enrolled, of whom 22 had sufficient data for inclusion in the analysis and were matched with 44 controls. The 2 subjects who were not analyzed were known to be extremely noncompliant with the medication and recommended laboratory testing (1 necessitating involvement of Child Protective Services). Of the 22 subjects analyzed, thyroid ultrasonography revealed anatomically normal glands in 8 (36%), dysgenetic glands in 4 (18%) of which the majority were sublingual, and athyreosis in 10 (45%). The majority of participants were Caucasian (91%) and female (64%). There were significantly more females in the athyreosis group ($P = .01$). Serum TSH at the time of diagnosis was significantly higher in subjects with athyreosis compared to those with anatomically normal glands ($P < .001$) and those with ectopic or dysgenetic glands ($P = .006$). Overall, the mean initial LT4 doses were comparable between study participants receiving targeted dosing and controls who were dosed empirically. However, the mean initial LT4 dose was significantly lower in study participants with normal glands compared to empiric controls with normal glands ($P < .001$) and was significantly higher in study participants with athyreosis compared to empiric controls with athyreosis ($P < .001$). There was no difference in initial dose among those who had ectopic or dysgenetic glands. Subject characteristics and initial LT4 dosing are outlined in Table 1.

As seen in Figure 1, there was no difference in the mean total number of adjustments made over the first 6 months of treatment between study participants and controls (2.5 vs. 2.4, $P = .74$). However, compared to controls with athyreosis, study participants with athyreosis had significantly fewer adjustments made for UT (0.4 vs. 1.3, $P = .03$) and more adjustments due to OT (2.7 vs. 1.3; $P = .006$). Notably, there was no difference in the overall mean numbers of labs obtained during the first 6 months of treatment between the study group and controls (6 vs. 6.4).

DISCUSSION

While high-dose initial LT4 replacement in the range of 10 to 15 mcg/kg daily is the standard of care in CH management, the optimal dosing strategy and approach to laboratory monitoring remain unclear and differ among institutions. One study suggested that treatment and follow-up algorithms should be tailored to etiology as unique hormonal patterns and different responses to therapy were observed based on thyroid gland anatomy (11). Variable initial LT4 dosing based on CH etiology has been reportedly used at Starship Hospital in New Zealand since 1993 (12). However, thyroid anatomy at that center is determined by thyroid scintiscan (using technetium-99), LT4 is prescribed in the form of a suspension that is prepared weekly at an on-site pharmacy, and more intensive laboratory assessments are performed than during routine clinical care in the U.S. (weekly for 4 weeks, then at 6 weeks, then monthly until 24 months of age) (13). Mathai et al reported that this regimen resulted in normalization of free T4 levels within 7 days in 78% of subjects and within 14 days in 100% of subjects. However, 28% of subjects had supraphysiologic free T4 levels at some point during the first 4 weeks of treatment, the majority of whom were started on higher doses of LT4 (13-15 mcg/kg/day) (12). Moreover, almost 80% of subjects required a dose adjustment in the first 6 weeks of treatment.

The same group in New Zealand has also reported neurocognitive and body composition outcomes of their patients with CH treated with this dosing strategy compared to sibling controls (14). No difference was seen in intelligence quotient (IQ) or motor function at a mean age of 9.6 years, but greater time to normalization of free T4 was associated with worse motor balance. Similarly, no difference in body composition was found between groups. Overall these results are promising, as many studies continue to show mild cognitive and motor deficits in children with CH despite early high-dose replacement (15–20). It is possible that the normal neurocognitive outcomes reported in this study are related to the increased frequency of laboratory monitoring rather than in the choice of initial LT4 doses prescribed.

We found that infants with athyreosis who were dosed initially at the upper end of the recommended range (15 mcg/kg) had significantly more adjustments made for OT than those who were dosed empirically (13.4 mcg/kg). This is consistent with the findings of another study that reported more frequent OT 1 month after starting therapy when >12 mcg/kg was given (4). These authors suggested that initial LT4 doses of 10 to 11.9 mcg/kg for infants with a TSH >100 mcU/L and 8 to 10 mcg/kg for those with a TSH <100 mcU/mL are sufficient. The detrimental effects of CH that is untreated or undertreated are well documented, although concerns regarding the impact of OT are less well understood. A

recent prospective, longitudinal study reported an association between any degree of OT (short or long) and cognitive outcome at age 11 years (3). The authors found that IQ was as much as 17.8 points lower in children who experienced OT than those who did not. Interestingly, those who had UT without OT had normal scores.

While we routinely perform thyroid ultrasounds in infants with CH at the time of diagnosis, this is not universally practiced. A retrospective review of thyroid imaging at our institution compared thyroid ultrasound to technetium-99m-pertechnetate scanning, and the importance of utilizing color Doppler to differentiate ectopic glands from athyreosis was highlighted (21). Despite the fact that imaging does not alter initial management, we feel that it provides useful information regarding prognosis (whether or not the infant can be trialed off therapy at the age of 3 years) and can inform parents of the genetic risk to subsequent pregnancies, which varies based on etiology.

There are a number of limitations that warrant consideration when interpreting the results of this clinical study. First, given our sample size, power was low to detect anything but large effects. Second, we could not control for compliance both with taking the medication and with obtaining laboratory testing per the recommended schedule. Poor adherence could certainly impact results, which is why the 2 subjects who were known to be extremely noncompliant were not included in the analysis. Reassuringly, study participants and controls did not significantly differ in the number of labs obtained over the first 6 months of treatment, and the mean number of labs obtained in each group reflected good compliance with the recommended laboratory testing. Third, our subjects were treated by a large group of pediatric endocrinologists and precisely how and when dose adjustments were performed was not standardized. However, this was also true for both study participants and controls and allows for clinical judgment to take precedent, which is reflective of standard clinical practice. Fourth, it is possible that ultrasonography incorrectly categorized infants with ectopic glands as having athyreosis though color Doppler was always used to maximize sensitivity. Finally, we know that LT4 dose requirements increase as children grow; thus, some episodes of UT, particularly at the end of the study period, might reflect growth rather than inadequate initial replacement.

CONCLUSION

To our knowledge, this is the first study to investigate targeted LT4 therapy based on thyroid anatomy in infants with CH who are being treated according to standard AAP guidelines. This strategy does not appear to decrease the overall number of dose adjustments needed during the first 6 months of treatment. However, initial doses of 15 mcg/kg/day exceeds the thyroid hormone replacement requirement in infants with CH due to athyreosis, which has important implications for clinical care. Large-scale, long-term studies are needed to determine if targeted LT4 therapy with routine laboratory monitoring has any impact on the neurocognitive outcomes of children with CH.

Acknowledgments

Dr. Schoelwer was supported by NIH 2 T32DK065549.

Abbreviations

CH	congenital hypothyroidism
LT4	levothyroxine
OT	overtreatment
T4	thyroxine
TSH	thyroid-stimulating hormone
UT	undertreatment

References

1. Selva KA, Harper A, Downs A, Blasco PA, Lafranchi SH. Neurodevelopmental outcomes in congenital hypothyroidism: comparison of initial T4 dose and time to reach target T4 and TSH. *J Pediatr*. 2005; 147:775–780. [PubMed: 16356430]
2. Salerno M, Militerni R, Bravaccio C, et al. Effect of different starting doses of levothyroxine on growth and intellectual outcome at four years of age in congenital hypothyroidism. *Thyroid*. 2002; 12:45–52. [PubMed: 11838730]
3. Bongers-Schokking JJ, Resing WC, de Rijke YB, de Ridder MA, de Muinck Keizer-Schrama SM. Cognitive development in congenital hypothyroidism: is overtreatment a greater threat than undertreatment? *J Clin Endocrinol Metab*. 2013; 98:4499–4506. [PubMed: 23979950]
4. Vaidyanathan P, Pathak M, Kaplowitz PB. In congenital hypothyroidism, an initial L-thyroxine dose of 10–12 mg/kg/day is sufficient and sometimes excessive based on thyroid tests 1 month later. *J Pediatr Endocrinol Metab*. 2012; 25:849–852. [PubMed: 23426811]
5. Alvarez M, Iglesias Fernández C, Rodríguez Sánchez A, Dulin Lñiguez E, Rodríguez Arnao MD. Episodes of overtreatment during the first six months in children with congenital hypothyroidism and their relationships with sustained attention and inhibitory control at school age. *Horm Res Paediatr*. 2010; 74:114–120. [PubMed: 20395659]
6. Rovet JF, Ehrlich RM, Sorbara DL. Effect of thyroid hormone level on temperament in infants with congenital hypothyroidism detected by screening of neonates. *J Pediatr*. 1989; 114:63–68. [PubMed: 2909709]
7. Rose SR, Brown RS, Foley T, et al. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics*. 2006; 117:2290–2303. [PubMed: 16740880]
8. Léger J, Olivieri A, Donaldson M, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. *J Clin Endocrinol Metab*. 2014; 99:363–384. [PubMed: 24446653]
9. LaFranchi SH. Approach to the diagnosis and treatment of neonatal hypothyroidism. *J Clin Endocrinol Metab*. 2011; 96:2959–2967. [PubMed: 21976744]
10. Eugster EA, Pescovitz OH, Quigley CA, Johnson N, Rivkees SA. Development of a congenital hypothyroidism follow-up program-The Indiana experience. *Endocrinologist*. 2000; 10:9.
11. Hanukoglu A, Perlman K, Shamis I, Brnjac L, Rovet J, Daneman D. Relationship of etiology to treatment in congenital hypothyroidism. *J Clin Endocrinol Metab*. 2001; 86:186–191. [PubMed: 11231999]
12. Mathai S, Cutfield WS, Gunn AJ, et al. A novel therapeutic paradigm to treat congenital hypothyroidism. *Clin Endocrinol (Oxf)*. 2008; 69:142–147. [PubMed: 18598275]
13. LaFranchi SH. Should the levothyroxine starting dose be tailored to disease severity in neonates with congenital hypothyroidism? *Nat Clin Pract Endocrinol Metab*. 2008; 4:658–659. [PubMed: 18825139]

14. Albert BB, Heather N, Derraik JG, et al. Neurodevelopmental and body composition outcomes in children with congenital hypothyroidism treated with high-dose initial replacement and close monitoring. *J Clin Endocrinol Metab.* 2013; 98:3663–3670. [PubMed: 23861458]
15. Dimitropoulos A, Molinari L, Etter K, et al. Children with congenital hypothyroidism: long-term intellectual outcome after early high-dose treatment. *Pediatr Res.* 2009; 65:242–248. [PubMed: 18787501]
16. Huo K, Zhang Z, Zhao D, et al. Risk factors for neurodevelopmental deficits in congenital hypothyroidism after early substitution treatment. *Endocr J.* 2011; 58:355–361. [PubMed: 21467693]
17. Hauri-Hohl A, Dusoczky N, Dimitropoulos A, et al. Impaired neuromotor outcome in school-age children with congenital hypothyroidism receiving early high-dose substitution treatment. *Pediatr Res.* 2011; 70:614–618. [PubMed: 21857388]
18. Komur M, Ozen S, Okuyaz C, Makharoblidze K, Erdogan S. Neurodevelopment evaluation in children with congenital hypothyroidism by Bayley-III. *Brain Dev.* 2013; 35:392–397. [PubMed: 22858380]
19. van der Sluijs Veer L, Kempers MJ, Wiedijk BM, Last BF, Grootenhuys MA, Vulsma T. Evaluation of cognitive and motor development in toddlers with congenital hypothyroidism diagnosed by neonatal screening. *J Dev Behav Pediatr.* 2012; 33:633–640. [PubMed: 23027136]
20. Simic N, Khan S, Rovet J. Visuospatial, visuoperceptual, and visuoconstructive abilities in congenital hypothyroidism. *J Int Neuropsychol Soc.* 2013; 19:1119–1127. [PubMed: 24124766]
21. Supakul N, Delaney LR, Siddiqui AR, Jennings SG, Eugster EA, Karmazyn B. Ultrasound for primary imaging of congenital hypothyroidism. *AJR Am J Roentgenol.* 2012; 199:W360–W366. [PubMed: 22915427]

Fig. 1. Mean number of adjustments in study participants compared to controls. *A*, Total adjustments; *B*, adjustments for UT (significant difference in the athyreosis group, $P = .03$); *C*, adjustments for OT (significant difference in the athyreosis group, $P = .006$).

Table 1**Subject Characteristics**

	All subjects	Anatomically normal gland	Dysgenetic gland	Athyreosis
n (% total)	22	8 (36%)	4 (18%)	10 (45%)
Sex (% female)	64%	25%	75%	90%
Mean serum TSH (mIU/mL) at diagnosis (SD)	296 (180)	158 (89)	202 (95)	444 (147) ^a
Mean initial LT4 dose (mcg/kg/d) (SD) <i>vs. controls</i>	12.8 (2.3) <i>13.0 (1.4)</i>	10.3 (0.3) ^b <i>12.5 (1.3)</i>	12.3 (0.5) <i>12.9 (1.5)</i>	15.1 (0.3) ^c <i>13.4 (1.4)</i>

Abbreviations: LT4 = levothyroxine; TSH = thyroid stimulating hormone.

^aSignificant difference vs. normal gland ($P<.001$) and vs. dysgenetic gland ($P=.006$)

^bSignificant difference vs. empirically dosed controls with normal glands ($P<.001$)

^cSignificant difference vs. empirically dosed controls with athyreosis ($P<.001$)