Liothyronine Improves Biochemical Control of Congenital Hypothyroidism in Patients with Central Resistance to Thyroid Hormone

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Objective To assess whether adding liothyronine (LT3) to levothyroxine (LT4) monotherapy normalizes serum thyrotropin (TSH) and thyroxine (T4) concentrations in children with congenital hypothyroidism and central resistance to thyroid hormone.

Study design We retrospectively studied 12 patients with congenital hypothyroidism and central resistance to thyroid hormone (6 treated with LT3+LT4 combined therapy and 6 treated with LT4 monotherapy). In patients receiving combined therapy, we compared serum concentrations of TSH, T4, and triiodothyronine before and after addition of LT3. We used repeated measures analysis to compare thyroid function in participants receiving combined therapy vs monotherapy, while accounting for age and intrasubject correlation.

Results In patients receiving combined therapy, the addition of LT3 was associated with normalization of mean TSH (9.2 vs 4.5 mIU/L, $P = .002$), a lower proportion of TSH values greater than 10 mIU/L (35% vs 8%, $P = .03$), and a decrease in mean serum T4 by 23 ± 9% ($P < .001$). Compared with patients receiving LT4 monotherapy, patients receiving combined therapy had lower mean TSH (8.5 ± 0.9 vs 4.3 ± 0.4, $P < .001$), lower odds of TSH elevation greater than 10 mIU/L (OR 0.20, 95% CI 0.10-0.41, $P < .001$), and lower odds of T4 elevation (OR 0.21, 95% CI 0.04-1.09, $P = .06$). LT3 treatment did not increase serum T3 levels significantly.

Conclusion The addition of LT3 to LT4 monotherapy facilitates normalization of both serum TSH and T4 in patients with congenital hypothyroidism and central resistance to thyroid hormone. Larger prospective studies are needed to confirm these findings and to determine the effect of combined therapy on neurodevelopmental outcomes. *(J Pediatr 2016;175:167-72)*.

Primary congenital hypothyroidism affects up to 1:2000 infants and leads to poor neurodevelopmental outcomes in the absence of early and adequate thyroid hormone replacement. Current guidelines recommend treatment with levothyroxine (LT4) to restore and maintain normal serum levels of thyrotropin (TSH) and thyroxine (T4).[1,2] In up to 43% of infants and 10% of older children with congenital hypothyroidism, however, TSH elevation fails to normalize despite appropriate LT4 treatment.[3-5] This failure of normal thyroid hormone negative feedback on pituitary TSH secretion is a form of central resistance to thyroid hormone, although the mechanisms underlying this phenomenon in congenital hypothyroidism are poorly understood.

Treatment of these patients requires the clinician to choose between maintaining normal serum T4 levels while permitting modest TSH elevation or normalizing TSH at the expense of elevated serum T4. Studies of children with congenital hypothyroidism, however, have demonstrated that neurocognitive impairment is associated with both undertreatment (reflected by low T4 associated with elevated TSH)[6-10] and overtreatment (reflected by elevated T4).[11-14] Thus, on the basis of current data, neither approach to the treatment of infants who have central resistance to thyroid hormone (high T4 and high TSH) is optimal, and existing consensus recommendations offer no evidence-based guidance.[1,2]

Given the potential risks associated with elevation of either TSH or T4, some have suggested adding liothyronine (LT3) to LT4 monotherapy in patients with congenital hypothyroidism and central resistance to thyroid hormone. Two previous case series of such patients have shown that combined therapy with LT3 and LT4 may help normalize TSH while keeping triiodothyronine (T3) and T4 in the normal range,[15,16] but these studies were limited by several factors, most notably their failure to control for the natural history of central resistance to thyroid hormone to resolve over time in patients with congenital hypothyroidism.[3]

Therefore, we sought to assess the efficacy of adding LT3 treatment to LT4 monotherapy in patients with congenital hypothyroidism and central resistance to thyroid hormone by comparing thyroid function and auxologic variables in

AUC	Area under the curve
LT3	Liothyronine
LT4	Levothyroxine
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyrotropin

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individual patients before and during LT3+LT4 combined therapy and in patients treated with LT3+LT4 combined therapy vs patients treated with LT4 monotherapy. We hypothesized that combined therapy would normalize both serum TSH and T4 in these patients, whereas LT4 monotherapy would not.

Methods

We searched the electronic medical record by *International Classification of Diseases, Ninth Revision* code and medication prescriptions to identify all patients with congenital hypothyroidism seen at Boston Children's Hospital from 1999 to 2014 who had been treated with LT3 for central resistance to thyroid hormone (n = 8). All patients were treated initially with LT4 monotherapy, with LT3 added later at the discretion of the treating clinician because of failure to normalize serum TSH in the face of high-normal or elevated serum T4. These patients are referred to as the combined therapy group.

To account for the tendency of central resistance to thyroid hormone in congenital hypothyroidism to resolve spontaneously over time, we also analyzed a group of patients with congenital hypothyroidism and central resistance to thyroid hormone who were managed exclusively with LT4 monotherapy and never received LT3. These patients were identified in the electronic medical record by the *International Classification of Diseases, Ninth Revision* diagnostic code for congenital hypothyroidism and the finding of concurrent supranormal TSH and supranormal T4 on at least 2 occasions. Manual record review of identified patients was conducted independently by 2 authors, and patients were included if they met clinical criteria for central resistance to thyroid hormone based on a pattern of failure to suppress TSH in face of elevated T4 levels. Discrepancies in assignment were resolved by discussion after review by a third author (R.B.). These patients are referred to as the monotherapy group (n = 6).

For all patients, data were abstracted from the medical record, including demographic information, birth history, results of laboratory and thyroid imaging studies, heart rate, auxologic variables, and doses of LT4 and LT3. We excluded from analysis any patient with documented nonadherence to therapy at any point (n = 2 in the combined therapy group). Patients received various formulations of LT4 and LT3 tablets at the discretion of the treating provider. Because of the retrospective nature of this study, the timing of thyroid function measurements relative to ingested doses of LT4 and LT3 could not be determined. The study was approved by the Boston Children's Hospital Institutional Review Board.

Statistical Analyses

Within the combined therapy group, we used paired *t* tests to compare measurements of thyroid function, heart rate, and auxologic variables in each patient before vs after initiating combined therapy. This analysis included data obtained up to 2 years before and 2 years after initiation of LT3, except for the a priori exclusion of data obtained before 1 month of age (to avoid inclusion of abnormal thyroid function measurements shortly after diagnosis). Because free T4 was measured in some patients and total T4 in others, we could not calculate mean serum T4 levels across the cohort. Therefore, we analyzed only within-patient changes in free T4 or total T4 before vs after initiating combined therapy, and in our analysis the term "T4" denotes free T4 or total T4, as measured in each patient. Mean values of serum TSH, T4, and T3 over the study period were calculated for each patient by use of the area under the curve (AUC) to account for variation among patients in timing of measurements and duration of follow-up. To measure accumulated exposure to states of abnormal TSH, T4, and T3 elevation, we also calculated: (1) the AUC of TSH that exceeded 5 and 10 mIU/L thresholds; and (2) the proportion of T4 and T3 measurements that exceeded the age-specific normal range.

We compared baseline characteristics of patients in the combined therapy vs monotherapy groups by using the Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables owing to their skewed distribution. We fit linear and logistic repeated measures regression models to compare the time course of thyroid function in patients receiving combined therapy vs monotherapy. We adjusted each model for age as a time-varying covariate. Further adjustment for sex and gestational age had negligible impact. Data on other baseline covariates (eg, birth weight, TSH, and free T4 at diagnosis) were missing for too many patients in this small sample to be included without introducing selection bias.

From variables of the fitted model, we constructed pairwise contrasts for mean TSH, odds of TSH exceeding 5 or 10 mIU/L, and odds of supranormal T4 between the following patient groups: (1) combined therapy group pre-LT3 vs monotherapy group; (2) combined therapy group pre-LT3 vs combined therapy group on LT3; and (3) combined therapy group on LT3 vs monotherapy group. The principle of closed testing allowed us to make all 3 pairwise comparisons as well as the overall comparison (3 groups) with a critical *P* value of .05 for statistical significance while preserving a familywise Type I error rate of 5%.[17] We obtained SEs for the contrasts by the generalized estimating equation method. Models that compared thyroid function in the combined therapy and monotherapy groups were fit by the use of all available thyroid function measurements for each patient. A sensitivity analysis limited to data obtained within 2 years before or after initiation of LT3 in the combined therapy group did not significantly alter the results. We used SPSS version 21.0 (IBM Corp, Armonk, New York) and SAS version 9.4 (SAS Institute, Cary, North Carolina) for statistical computations.

Results

Baseline characteristics of subjects in the combined therapy and monotherapy groups are shown in **Table I**. To assess