Efficacy of Supplemental Liothyronine for Patients with Congenital Hypothyroidism and Pituitary Resistance to Thyroid Hormone

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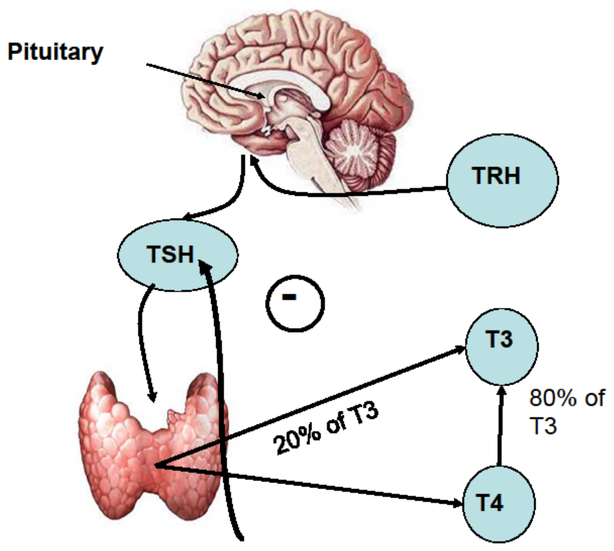
Background

- Thyroid hormone replacement is mandatory for infants with congenital hypothyroidism (CH) to optmize neurodevelopmental outcomes[1]
- Guidelines recommend levothyroxine (LT4) monotherapy[1]
- BUT in up to 1/3 of patients, elevated TSH fails to normalize despite LT4 treatment sufficient to achieve normal or even elevated circulating levels of free T4, termed "pituitary resistance to thyroid hormone"[2]
- To normalize their TSH, these patients require supranormal circulating levels of T4, which may be harmful for neurocognitive development[3]
- Liothyronine (T3) has been proposed as a supplemental therapy for such patients, but data on its use and efficacy are limited[4]



Objectives

Through a retrospective chart review, we sought to test the hypothesis that supplemental T3 treatment will decrease both TSH and T4 in patients with CH and pituitary resistance to thyroid hormone.

Methods

Study Population

•We electronically searched **Boston Children's Hospital records from 1999-2014** for patients with CH based on ICD9 code and serum TSH > 20 mIU/L at diagnosis

•We identified **6 patients treated initially with LT4 monotherapy, in whom supplemental T3 was added** because of failure to normalize the TSH

Statistical Analysis

•We used t-tests to compare thyroid function and anthropometrics measured during the two years before versus two years after starting T3 treatment.

•Data obtained prior to 1 month of age were excluded to avoid inclusion of laboratories prior to LT4 treatment.

•We compared the following within each participant:

➢TSH: mean, % >5 mIU/L, % >10 mIU/L, area under the curve (AUC)

➢FT4 or T4: % > normal for age , AUC

➢T3: mean, AUC

➢Anthropometrics: weight, height, and BMI z-scores

Results

Table 1. Baseline characteristics (n=6)

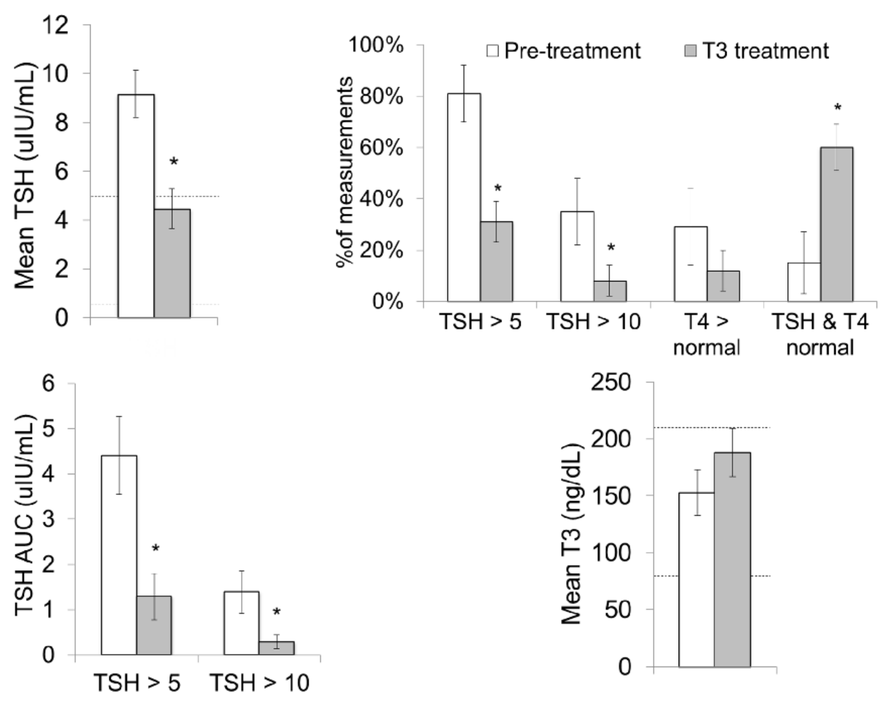
	Median (range)
Birth	
Sex	4M / 2F
Gestational age, wks	41 (30-41)
Birth weight, kg	4.0 (1.8-4.2)
Diagnosis	
TSH at diagnosis, mIU/L	220 (34-460)
Free T4 at diagnosis, ng/dL	0.3 (0.3-1.1)
Thyroid anatomy	Normal eutopic (1) Ectopic (1) Agenesis (1) Unknown (3)
LT4 treatment	
Age at LT4 initiation, wks	1.1 (0.7-5.3)
Initial LT4 dose, mcg	50 (12.5-50)
T3 treatment	
Age at T3 initiation, yrs	3.5 (0.5-11.7)
Before T3	
Follow-up, yrs	2.0 (0.4-2.0)
Thyroid function tests, #	5.5 (5-10)
After T3	
Follow-up, yrs	1.5 (0.4-2.0)
Thyroid function tests, #	4 (1-7)

Table 2. Thyroid function and anthropometrics [mean (95% CI)] before versus after T3 treatment

	Before T3	After T3	*p*
TSH, mean (mIU/L)	9.16 (7.26-11.06)	4.46 (2.86-6.06)	0.002
TSH values > 5 mIU/L (%)	81 (58-100)	31 (16-46)	0.001
TSH > 5, AUC (mIU/L)	4.41 (2.73-6.09)	1.29 (0.30-2.29)	0.004
TSH values > 10 mIU/L (%)	35 (10-60)	8 (0-19)	0.03
TSH > 10, AUC (mIU/L)	1.39 (0.46-2.32)	0.29 (0-0.59)	0.04
FT4/TT4 values > normal (%)	29 (0-60)	12 (0-28)	0.32
Change in FT4/TT4, AUC with T3 treatment (%)		24 (17-31)	0.002
Both TSH & FT4/TT4 normal (%)	15 (0-38)	60 (42-78)	<0.001
T3 values > normal (%)*	0 (0-0)	17 (0-38)	0.16
T3, mean (ng/dL) (%)	153 (122-185)	188 (155-221)	0.33
Weight z-score	0.71 (-0.51-1.92)	0.76 (-0.31-1.83)	0.65
Height/length z-score	0.36 (-1.07-1.80)	0.25 (-1.07-1.57)	0.35
BMI z-score	0.54 (-0.42-1.50)	0.97 (0.25-1.69)	0.23

AUC = area under curve, normalized for time. FT4 = free T4. TT4 = total T4.
* n=4 (mean of 2.7 checks prior and 4.5 checks after T3 treatment)

Figure. Effect of T3 treatment (---- denotes normal range)



Conclusions

- Addition of T3 to LT4 monotherapy is associated with lower serum TSH and T4 in CH patients with pituitary resistance to thyroid hormone.
- Future studies will include a control group of untreated patients with CH and pituitary resistance from the same hospital and time period to account for improvement in pituitary resistance over time.
- Larger prospective studies are also needed to validate these findings and to investigate whether the addition of T3 improves cognitive development.

References

1. Leger, J, Oliviera, A, Donaldson, M, et al. European Society for Pediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism. *J Clin Endocrinol Metab.* 2014; 99(2):363-84.
2. Fisher, DA, Schoen EJ, LaFranchi S, et al. The Hypothalamic Pituitary Thyroid Negative Feedback Control Axis in Children with Treated Congenital Hypothyroidism. *J Clin Endocrinol Metab.* 2000; 85(8): 2722-7.
3. Bongers-Schokking JJ, Resing WC, deRijke YB, et al. Congnitive Development in Congenital Hypothyroidism: Is Overtreatment a Greater Threat than Undertreatment? *J Clin Endocrinol Metab.* 2013; 98(11): 4499-506.
4. Akcay, T, Turan S, Guran T, et al. T4 Plus T3 Treatment in Children with Hypothyroidism and Inappropriately Elevated Thyroid-Stimulating Hormone Despite Euthyroidism on T4 Treatment. *Horm Res Paediatr.* 2010;73:108-114.

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Thyroid

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