

Potentially excessive levothyroxine doses in cases of congenital hypothyroidism with eutopic thyroid gland

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Introduction

The intelligence prognosis of congenital hypothyroidism (CH) is remarkably improved by early detection and optimal levothyroxine (LT4) treatment. It has been reported that initial LT4 overtreatment results in a subsequent decrease of cognitive function. In universal guidelines, an initial dose of 10-15 µg/kg/day of LT4 is recommended. However, we have recognized that in many CH cases that is started with the recommended LT4 dose, some CH cases become LT4 overtreatment.

Aim

The purpose of this study is to investigate the influence of the initial LT4 dosage on the frequency of LT4 overdosing during infancy. We studied frequency of the LT4 overdose in respective groups classified by LT4 dose in eutopic thyroid CH cases.

Materials and Methods

395 infants who became targeted for a detailed examination by CH screening test (Niigata, June 1989~September 2013)

- Exclusion criteria
1. within 36 weeks for gestational ages or less than 2,000 g of birth weight
 2. born from maternal Basedow's disease
 3. with the chromosomal aberration or congenital anomaly syndrome (e.g. Down's syndrome, etc.)
 4. with significant thyroid dysplasia (hypoplasia, aplasia, or ectopic thyroid gland)

227 cases with the eutopic thyroid gland except exclusion cases and cases with data failure

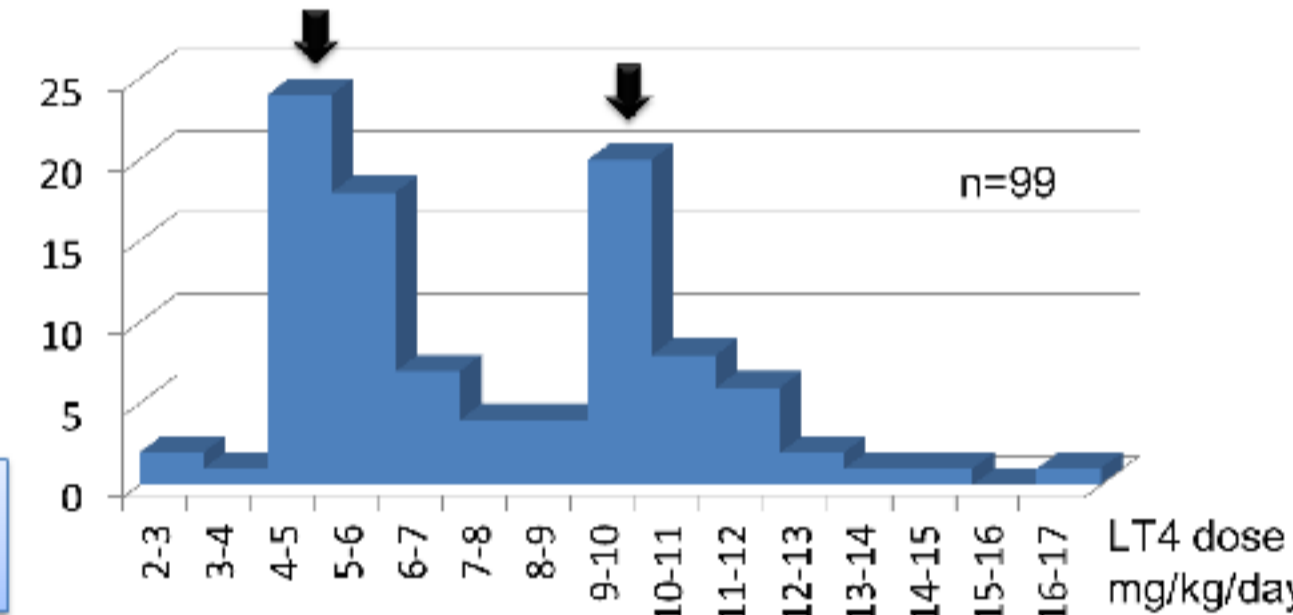
72 cases without initial LT4 treatment

155 cases with initial LT4 treatment

56 cases with the normal TSH level (TSH<15 µIU/ml)

TSH ≥ 15 µIU/ml n=99

initial LT4 dose



The dose of LT4 (µg/kg/day) at the initial diagnosis of 99 cases is shown in the figure. There are two peaks shown in the arrow.

◆ Definition: LT4 overdosing: About four weeks after start of LT4 therapy, TSH levels <0.5 µIU/mL and FT4 levels >2.5 ng/dL

◆ Classification

- Severity (classified with only initial TSH levels)
 - TSH 15-30 µIU/mL: mild CH groups (n=54)
 - TSH ≥30 µIU/mL: moderate-severe CH groups(n=45)
- Initial LT4 dose
 - High initial dose (≥9 µg/kg/day, n=39)
 - Low initial dose (<9 µg/kg/day, n=60)

We investigated the LT4 overtreatment ratio in each group by calculating the odds ratio. To compare median values of two groups, we used the Mann-Whitney U test or, if there were more than two groups, Kruskal-Wallis test.

Results

99 cases stratified into four treatment groups

	Mild /low dose n=40	Moderate-severe /low dose n=20	Mild /high dose n=14	Moderate-severe /high dose n=25
Gestational age (week)	39.0 ± 1.2	39.1 ± 1.4	39.6 ± 1.1	39.0 ± 1.2
Birth weight (g)	3057 ± 470	3091 ± 530	3051 ± 399	3143 ± 391
Age (days) *	28.9 ± 6.0	23.7 ± 7.3	27.9 ± 11.5	21.9 ± 8.0
Body weight (g)	4030 ± 604	3738 ± 601	3831 ± 452	3801 ± 684
TSH (mIU/ml) *	21.2 ± 4.0	59.3 ± 22.5	22.1 ± 4.9	197.8 ± 261.9
ft4 (ng/dl) *	1.37 ± 0.21	1.21 ± 0.41	1.42 ± 0.25	0.76 ± 0.39
Initial LT4 dose * (mg/kg/日)	4.9 ± 0.9	6.5 ± 1.5	9.9 ± 0.8	10.9 ± 1.7

- In moderate-severe CH groups, the high-dose group had significantly higher TSH level and lower ft4 level than a low-dose group had.

LT4 overdosing ratios

	A : low initial dose	B : high initial dose	total
mild CH (TSH15-30 µIU/ml)	1/40 2.5%	5/14 37.5%	6/54 11.1%
moderate/severe CH (TSH ≥ 30 µIU/ml)	3/20 15.0%	12/25 48.0%	15/45 33.3%
total	4/60 6.7%	17/39 43.6%	21/99 21.2%

- The odds ratio between mild/low-dose and mild/high-dose were 14.29 (p<0.05) and between moderate-severe/low-dose and moderate-severe/high-dose were 3.20 (p<0.05), while the LT4 overtreatment ratio was significantly higher in each high-dose groups.

Discussion

13 cases of LT4 overtreatment VS 12 cases of not-overtreatment

	Overtreatment n=12	Not overtreatment n=13	P value
Body weight(g)	4052±770	3570±520	0.1277
TSH(µIU/ml)	228.9±312.2	169.0±214.3	0.6438
FT4(ng/dl)	0.68±0.43	0.83±0.35	0.3116
DEF (ratio)	0.28±0.11 (n=9)	0.28±0.12 (n=9)	0.9290
Size of thyroid gland (maximal diameter mm)	30.2±3.9 (n=5)	26.5±3.0 (n=6)	0.0996
LT4 dosage (µg/kg/day)	11.7±2.1	10.1±0.8	*0.0496

DEF=distal epiphyses / femoral metaphysis * Mann-Whitney's U test

- It is difficult to predict later LT4 overtreatment from data at the initial diagnosis.
- Only an initial LT4 dose showed a significant difference between two groups.

Previous report about LT4 overdosing

	Severity of the patients	Definition of the overtreatment
Jacobson J. Bongers-Schokking et al	Severe: ft4 0.21±0.16 ng/dl Mild: ft4 0.67±0.29 ng/dl	ft4>+2SD ng/dl TSH<0.5 mU/L
J Pediatr 2000 (n=61)		<ul style="list-style-type: none"> ➤ The results of the Bayley test at the age of 10 to 30 months ➤ The optimal treatment includes achievement of euthyroidism before the third week of life by initiation of therapy before 13 days with a LT4 dose above 9.5 µg/kg/d and maintenance of FT4 concentrations in the upper normal range during the first year ➤ Early enough treatment helps the development of the CH patients
J Clin Endocrinol Metab 2013 (n=61)		<ul style="list-style-type: none"> ➤ About the development of CH patients at 11 years old ➤ The early TSH normalization does not affect the IQ of the patients at 11 years old ➤ The initial two years overtreatment caused the decrease of the later cognitive function

- Our study targets a milder case as compared with these reports. Thus, about the evaluation whether or not LT4 surplus has a similar influence, we require further examination.

Conclusion

The initial dosage of LT4 of 10-15 µg/kg/day for neonatal-screening-positive CH cases with eutopic thyroid gland may raise the risk of LT4 overtreatment.

We should conduct the confirmation of TSH level repeatedly and regulate LT4 dose appropriately in reference to the value, when high dose LT4 treatment is started.