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 (LTI4) treatment. It has been reported that initial LTI4 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 2000—September 2013)

1. within 36 weeks of pernatal age or less than 2,000 g of birth weight
2. were born maternal thyroid disease
3. with the neonatal detection in congenital hypothyroidism (TSH of >20 mU/L, T4 of <4 μg/dL, etc.)
4. with significant thyroid hypothyroidism (hypoplastic, aplasia, or ectopic thyroid gland)

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

72 cases without initial LT4 treatment

135 cases with initial LT4 treatment

56 cases with the normal TSH level (TSH<2.5 μIU/mL)

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

<table>
<thead>
<tr>
<th>LT4 overdosage ratios</th>
<th>A: low initial dose</th>
<th>B: high initial dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild CH</td>
<td>1/40</td>
<td>5/14</td>
<td>6/54</td>
</tr>
<tr>
<td>(TSH=15-30 μIU/mL)</td>
<td>2.5%</td>
<td>37.5%</td>
<td>11.1%</td>
</tr>
<tr>
<td>moderate/severe CH</td>
<td>3/20</td>
<td>12/25</td>
<td>15/45</td>
</tr>
<tr>
<td>(TSH&gt;30 μIU/mL)</td>
<td>15.0%</td>
<td>48.0%</td>
<td>33.3%</td>
</tr>
<tr>
<td>total</td>
<td>4/60</td>
<td>17/39</td>
<td>21/99</td>
</tr>
<tr>
<td>6.7%</td>
<td>43.6%</td>
<td>21.2%</td>
<td></td>
</tr>
</tbody>
</table>

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 no-over-treatment

| 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 |
| (ratio)               | 0.28±0.11           | 0.20±0.12           | 0.9290 |
| Size of thyroid gland | 30.2±3.9            | 26.5±3.0            | 0.0996 |
| (maximal diameter mm) | (n=5)               | (n=6)               |       |
| LT4 dosage (μg/kg/day)| 11.7±2.1            | 10.1±0.8            | 0.0049 |

DEF=digital 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

J Pediatr 2000 (n=61)
Severe: FT4 0.21±0.16 ng/dL (n=31)
Mild: FT4 0.67±0.29 ng/dL (n=20)
TSH=0.5 μU/L

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 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)
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.