Validity of 6th month L-Thyroxine Dose for Differentiation of Transient-Permanent Congenital Hypothyroidism

Short Running Title: Validity of 6th month L-Thyroxine Dose at Congenital Hypothyroidism

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What is already known on this topic?
Setting a lower TSH level as cut-off in neonatal screening program have an increasing trend. This had resulted in diagnosing much more transient CH thereby need for making decision to stop the therapy earlier.

What this study adds?
L-thyroxine doses required at the 6th month of therapy would be a good marker for predicting transient CH patients with an eutopic thyroid gland.

Abstract
Objective: Increase in availability of neonatal screening programs, has resulted in an increase in the incidence of congenital hypothyroidism (CH), particularly transient cases. Therefore, there is a need for developing criteria for differentiation of transient and permanent CH at an early stage to avoid overtreatment. In this study, we evaluate sixth-month L-thyroxine dose as a predictive marker for differentiation of transient and permanent CH.

Method: Data of patients who had been followed with the diagnosis of CH between the year 2010 and 2019 in a tertiary pediatric endocrine centre were examined retrospectively.

Results: In total 226 cases recruited. Of which, 186(82.3%) had eutopic CH, and 40(17.7%) had dysgenetic CH. While there was a statistically non-significant decrease in FT4 levels of dysgenetic CH patients, TSH levels were significantly higher(p:0.44 and p:0.023, respectively). L-thyroxine doses in the beginning and at the 6th month in the patients with thyroid dysgenesis were higher compared to CH patients with eutopic thyroid gland(p:0.001). In ROC analysis, regardless of aetiology, the optimum cut-off value for L-thyroxine dose at the 6th month for transient vs. permanent CH was 2µgr/kg/day(sensitivity 77% and specificity 55%). Similarly, the optimum cut-off value for L-thyroxine dose at the 6th month for eutopic permanent vs. transient CH was 2µgr/kg/day(sensitivity 72% and specificity 54%).

Conclusion: Results of the present study suggest that L-thyroxine doses required at the 6th month of therapy would be a good marker for predicting transient CH patients with eutopic thyroid gland. Hence, would help to make decision for earlier discontinuation of the treatment.

Keywords: Congenital Hypothyroidism, Transient, Permanent, 6th month L-Thyroxine Dose

Introduction
Thyroid hormones play vital roles in brain development during the intrauterine period and early infancy. Therefore, delay in the diagnosis and treatment of congenital hypothyroidism (CH) lead to severe neurological and psychiatric disorders (1,2). Indeed, CH is considered as the most common cause of preventable mental retardation (1,3,4). Neonatal screening for diagnosis of CH has improved the early diagnosis and immediate treatment of CH. In the majority of screening programs, only TSH is being measured, as the secondary hypothyroidism account for only 2-5% of all neonates with CH (4, 5). The cut-off value for TSH in neonatal screening programs has been gradually declined from 20-50 µU/mL to lower values (1,4,6). Determination of lower cut off values has led to an increase in the incidence of CH from 1/3000-4000 (4), to 1/2000-3000(1,7).

Incidence of CH has an increasing trend with neonatal screening, while, incidence of permanent CH has not changed much (8,9). Therefore, developing criteria for differentiation of transient and permanent CH is important from the point of management. In this study, we evaluate the clinical characteristics of the patients diagnosed with CH in a 10-year period and assessed the case characteristics for determination of a parameter that can help to differentiate the transient and permanent CH at the beginning or during follow-up.

Material and Methods
Data of the patients who were being followed with the diagnosis of CH between January 2010 and January 2019 in Pediatric Endocrinology Outpatient Clinic of Health Sciences University, Diyarbakir Gazi Yasargil Training and Research Hospital were examined retrospectively. The patients who have been diagnosed in another centre and were on L-Thyroxine
replacement but with lacking data about their initial L-Thyroxine doses and pretreatment TFTs, those who lost their regular follow-up, and those not yet reached 3 years of age were excluded from the study. The gender, age of diagnosis (in days), parental consanguinity, family history of thyroid disorders and complaints of presentation were recorded. The latest TSH, FT4, FT3, height SDS and weight SDS, as well as L-Thyroxine doses of the patients at the time of the diagnosis, at the 6th month of the treatment, at the end of the treatment and during follow-up were noted. Results of thyroid imaging, including ultrasonography (USG) and 99mTc scintigraphy, were recorded. Patients whose thyroid gland was in normal size and localization on thyroid USG and/or thyroid scintigraphy were defined as eutopic CH. Thyroid dysgenesis was described in case of having hypoplasia, ectopia, hemi-agenesis or complete agenesis of the thyroid gland (Dysgenetic CH). A trial of L-Thyroxine cessation at once was applied to all patients who had an eutopic thyroid gland, reached an age of 3 years and no longer required dose adjustment due to elevated TSH under L-Thyroxine therapy. TSH and FT4 were measured 4 weeks following cessation of L-Thyroxine treatment. Cases who thyroid function tests were normal 4 weeks after cessation of the L-Thyroxine treatment and remain stable over 6 months was considered as transient eutopic CH. The cases who required L-Thyroxine therapy (elevated TSH >10 µU/mL) were defined as permanent eutopic CH (8)(Figure 1).

TSH and FT4 levels were analyzed on the Abbott Architect i8000 device using the Electrochemiluminescence Immunoassay “ECLIA” method. Normal range was considered to be 0.35-4.94 µU/mL for TSH level and 0.70-1.48 ng/dL for FT4 level.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for Social Science) for Windows version 16 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD), or median (interquartile range), whereas categorical variables were presented as count and percentage (%). For evaluation of normality distribution of the data, Shapiro Wilk tests were used. For comparison of normally distributed data Student t-test was applied, whereas for comparison of non-normally distributed data Mann Whitney U test and Kruskal Wallis test were applied. A receiver operating characteristics (ROC) curve analysis was performed for determination of the best cut-off value for L-Thyroxine dose at the 6th month of the treatment between permanent and transient CH. A p value < 0.05 was considered as statistically significant.

Results

In total, 284 patients diagnosed with CH within the first 6 months of life. Fifty-eight patients were excluded from the study, as they lost their follow-up visits (Figure 1). Remaining 226 patients (123 female) recruited. The mean age of diagnosis was 41.18±39 days. At admission, the mean TSH level was 81.79±35 mIU/mL and the mean FT4 level was 0.55±0.33 ng/dL. Starting L thyroxine dose was 7.04±2.64 µg/kg/day (Table 1). Etiological evaluation of cases revealed that 186 out of 226 (82.3%) cases were diagnosed with eutopic CH, whereas 40 (17.7%) were diagnosed with thyroid dysgenesis. Of the patients with eutopic CH; 132 (71%) had permanent and 54 (29%) had transient CH(Figure 1).

While the FT4 levels measured at the time of the diagnosis were not significantly different (p: 0.44), TSH levels were significantly higher in cases with thyroid dysgenesis (p: 0.023). Initial and 6th-month L-thyroxine doses of cases with dysgenetic CH were significantly higher compared to eutopic CH patients (p: 0.001).

When cases of transient and permanent CH were compared, no difference was determined in any parameter except for the L-thyroxine dose at the 6th month and discontinuation of the treatment (Table 2). Of the permanent cases; 54 (58%) had eutopic CH and 40 (42%) had dysgenetic CH. The ratio of consanguinity in permanent cases was similar in both groups (55.5%). L-thyroxine dose at the 6th month was higher in cases with permanent CH (2.92±1.2 mcg/kg) then the dose of cases with transient CH (2.13±0.88 mcg/kg) (p < 0.001) (Table 2). Doses at 6th month were higher in dysgenetic cases compared to the eutopic cases (3.26±1.1 mcg/kg; 2.60±1.18 mcg/kg, respectively) (p: 0.001).

In the ROC analysis, regardless of the aetiology, the optimum cut-off value for L-thyroxine dose at the 6th month for transient vs. permanent CH was 2 mcg/kg/day (AUC: 0.713; sensitivity 77%; specificity 55%; p<0.001). The optimum cut-off value for L-thyroxine dose at the 6th month for transient permanent vs. eutopic transient CH was also 2 mcg/kg/day (AUC: 0.677; sensitivity 72%; specificity 54%; p<0.001). The positive predictive value of the treatment dose of 2 µg / kg/day at 6 months in patients with eutopic CH was 59.2% (Figure 2).

Discussion

In the present study evaluating 226 patients with CH, a high rate of transient cases was observed. The sixth-month L-Thyroxine doses were lower in transient cases and suggested to be a marker for differentiating permanent and transient CH. Although a nation-wide neonatal screening program is available in our country, the age of presentation for our cases (44.18±39 days) was a bit late than expected. This inconvenience was attributed to the fact that the majority of patients were from rural areas and probably have some difficulties in accessing their results of screening as well as in admission to our tertiary pediatric endocrine centre. While in some studies, a female predominance has been reported, some others, showed a male predominance (8,9,10,11,12,13,14). In the present study, there was a slight female predominance.

Regarding the aetiology of CH, 186 out of 226 cases (82.4%) had eutropic thyroid gland. Of which 132 (71%) cases had permanent CH. Patients with eutopic thyroid gland account for (54%) of cases with permanent CH (Figure 1). When considering the aetiology of permanent CH, in previous studies, thyroid dysgenesis was reported to cause 75-85 % of permanent CH cases which was followed by eutopic (dyshormonogenesis) cases (5,13). However, a considerable shift has been observed in the incidence rate as well as the ratio of transient and permanent cases with a change in the cut-off values which had been used for neonatal screening programs (5, 8, 15). In our series increase in the number of cases with transient hypothyroidism can be attributed to moderate iodine deficiency, while the high rate of permanent cases attributed to the high rate of consanguinity (55%) which may associate with increased risk of dyshormonogenesis (5, 16, 17, 18).

Prompt and correct diagnosis and differential diagnosis of cases admitted from neonatal screening program are critically important for avoiding missing cases as well as introducing the most appropriate treatment. Indeed, unnecessary and overtreatment may associate with an economic burden and poor neurodevelopmental outcome (3,19). Nevertheless, the presenting hormonal features are usually overlapping and do not allow to make a differential diagnosis of transient and permanent CH. In similar, transient CH accounts for 55% of our cases and cases with transient and permanent CH had not a
statistically significant different TSH and FT4 levels (Table 2). There was also no difference between permanent and transient CH in cases with a eutopic thyroid gland. However, when dysgenetic and eutopic CH were compared, dysgenetic cases had higher mean TSH and lower mean FT4 levels (Table 2). Although this data may help to estimate dysgenetic cases, this is not a reliable method as these values may overlap frequently. There are also studies reporting that TSH level at admission is higher in patients with permanent congenital hypothyroidism compared to transient congenital hypothyroidism (20).

Evaluation of L-thyroxine doses in dysgenetic-eutopic, total transient-permanent and eutopic transient-permanent CH, revealed a significant difference in doses they received at the age of 6 months (Table 2). ROC analysis revealed an optimal cut-off value of 2 µgr/kg/day for L-thyroxine dose at the sixth month, for differentiation of cases with eutopic transient and eutopic permanent CH, with a sensitivity of 72% and a specificity of 54% (Figure 2). Similarly, Oran et al. have reported a cut-off value for 6th-month L-thyroxin dose as 2.2 µgr/kg in retrospective analysis of 142 cases (21). However, in the study of Saba et al. (22) the cut-off value for treatment doses at the sixth month of 49 transient and 43 permanent CH patients with a eutopic thyroid gland was reported as 3.2 µgr/kg/day, with a sensitivity of 71% and a specificity of 79%. The mean time of discontinuation of treatment of transient cases was 1.5 years of age. The treatment dose at the sixth month was higher than the required cut-off value we reported for our eutopic transient and permanent CH patients. For our cases, mean FT4 at the sixth month was 1.28 ± 0.51 and the mean time of discontinuation of treatment in eutopic transient cases was 26 months. The discrepancy between the cut-off values in our and Saba’s study could be attributed to higher L-thyroxine doses they have used in their patients.

In a multi-centre retrospective study evaluating L-thyroxine doses of cases with CH for 12 years, L-thyroxine doses received per kg of body weight was shown gradually decreased every year starting from the sixth month of the age (21). By the 12th year, while eutopic CH cases were receiving a mean dose of 1.72 µgr/kg/day, patients with eutopic and agenesis required a dose of 2.1 and 2.2 µgr/kg/day, respectively, with no statistically significant difference (21). L-thyroxine dose at the sixth month was lower in cases with eutopic CH compared to the other two groups. In the study by Unuvar et al. in which they compared cases with permanent CH and hyperthyrotropinemia, they did not observe any difference between the groups other than the required L-thyroxine dose at the 1st year (10). In a study of 204 case series from a neighbouring country, Iran, they reported a statistically significant difference only in total L-thyroxine doses they received between transient and permanent CH (9).

Messina et al. have reported that L-thyroxine doses at 1st, 2nd and 3rd years were predictive in early differentiation of transient and permanent CH (23). They reported that predictive cut-off values for transient eutopic CH were 1.7 µgr/kg/day, 1.45 µgr/kg/day and 0.98 µgr/kg/day, respectively with a sensitivity of 100%. However, they have not evaluated the dose at the 6th month, either.

In conclusion, setting a lower TSH level as cut-off in neonatal screening program have an increasing trend. This had resulted in diagnosing much more transient CH thereby need for making a decision to stop the therapy earlier. L-thyroxine doses required at the 6th month could be a good marker for predicting transient-permanent eutopic CH patients. As the delay in discontinuation of treatment and overtreatment can associate with worse neurological outcome, increased anxiety for both families and physicians, as well as for insurance systems, our results would contribute deciding earlier discontinuation of the therapy. Studies including larger series of cases with transient and permanent CH and evaluating L-thyroxine doses required at the 6th month in combination with other characteristics for determination of markers that help to differentiate transient and permanent eutopic CH are warranted.

"Acknowledgment: we thank to professor Feyza Darendeliler for her advice to design this study"

References


Figure 1: A flow-diagram of all patients with congenital hypothyroidism
Figure 2: The ROC analysis for L-thyroxine dose at the 6th month for eutopic transient vs. permanent CH
Table 1: Patient’s clinical and laboratory findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis age (day)</td>
<td>44.18±39 (4-180)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>123 (54.2%)/103 (45.8%)</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>126 (55.5%)</td>
</tr>
<tr>
<td>Birth weight (gr)</td>
<td>3113.39±554.87 (1470-4500)</td>
</tr>
<tr>
<td>First TSH (µIU/mL)</td>
<td>81.79±65.61 (10.20-315.30)</td>
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<tr>
<td>FT4 (ng/dl)</td>
<td>0.55±0.33 (0.01-1.75)</td>
</tr>
<tr>
<td>FT3 (ng/dl)</td>
<td>3.08±1.54 (0.03-6.49)</td>
</tr>
<tr>
<td>L-Thyroxin dose at diagnosis (µgr/kg)</td>
<td>7.04±2.64 (0.9-10.0)</td>
</tr>
<tr>
<td>6th month TSH (µIU/mL)</td>
<td>2.46±3.6 (0.01-23.9)</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td>1.28±0.51 (0.5-4.19)</td>
</tr>
<tr>
<td>L-Thyroxin dose at 6th month (µgr/kg)</td>
<td>2.71±1.19 (0.01-8.30)</td>
</tr>
<tr>
<td>L-Thyroxin cessation age (month)</td>
<td>27.04±14.42 (3-93)</td>
</tr>
<tr>
<td>Permanent CH/Transient CH</td>
<td>171 (75.3%)/54 (24.2%)</td>
</tr>
</tbody>
</table>

*Mean±SD (minimum-maximum), **n (%)
<table>
<thead>
<tr>
<th>Time</th>
<th>CH group</th>
<th>Permanent</th>
<th>Transient</th>
<th>P</th>
<th>Dysgenetic</th>
<th>Eutopic</th>
<th>P</th>
<th>Permanent Eutopic</th>
<th>Transient Eutopic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis</td>
<td>TSH (µIU/mL)</td>
<td>82.59±34.5</td>
<td>78.99±39.1</td>
<td>0.51*</td>
<td>93.37±20.09</td>
<td>79.32±37.6</td>
<td>0.023*</td>
<td>79.1±37.1</td>
<td>79.54±39.2</td>
<td>0.93*</td>
</tr>
<tr>
<td></td>
<td>FT4 (ng/dl)</td>
<td>0.55±0.31</td>
<td>0.57±0.21</td>
<td>0.98*</td>
<td>0.51±0.4</td>
<td>0.56±0.2</td>
<td>0.44*</td>
<td>0.56±0.31</td>
<td>0.54±0.21</td>
<td>0.64*</td>
</tr>
<tr>
<td></td>
<td>L-Thyroxin dose (µg/kg/day)</td>
<td>7.12±2.52</td>
<td>6.78±2.8</td>
<td>0.4*</td>
<td>8.23±2.09</td>
<td>6.79±2.6</td>
<td>&lt;0.01*</td>
<td>6.81±2.6</td>
<td>6.72±2.83</td>
<td>0.84*</td>
</tr>
<tr>
<td>At 6th months</td>
<td>TSH (µIU/mL)</td>
<td>1.44±2.4</td>
<td>1.06±0.91</td>
<td>&lt;0.05†</td>
<td>2.68±7.22</td>
<td>1.2±1.67</td>
<td>&lt;0.05†</td>
<td>1.31±2.04</td>
<td>1.06±0.92</td>
<td>&gt;0.05†</td>
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<tr>
<td></td>
<td>FT4 (ng/dl)</td>
<td>1.1±0.8</td>
<td>1.19±0.32</td>
<td>&gt;0.05†</td>
<td>1.3±0.96</td>
<td>1.1±0.3</td>
<td>&lt;0.05†</td>
<td>1.1±0.31</td>
<td>1.19±0.33</td>
<td>&gt;0.05†</td>
</tr>
<tr>
<td></td>
<td>L-Thyroxin (µg/kg/day)</td>
<td>2.92±1.2</td>
<td>2.13±0.82</td>
<td>&lt;0.001*</td>
<td>3.26±1.1</td>
<td>2.6±1.1</td>
<td>0.001*</td>
<td>2.8±1.22</td>
<td>2.14±0.81</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>At Cessation</td>
<td>L-Thyroxin (µg/kg/day)</td>
<td>2.64±1.39</td>
<td>1.39±0.66</td>
<td>&lt;0.001*</td>
<td>3.54±1.33</td>
<td>2.09±1.22</td>
<td>&lt;0.001*</td>
<td>2.35±1.29</td>
<td>1.41±0.66</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Age(month)</td>
<td>-</td>
<td>27.04±14.4</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>26.98±14.5</td>
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**Data are presented as mean±SD, while comparison was performed using *Independent sample t-test or †Kruskal Wallis test according to the distribution of the data**