RESEARCH PAPER

Prediction of Transient or Permanent Congenital Hypothyroidism from Initial Thyroid Stimulating Hormone Levels

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Objective: To identify factors that discriminate between transient and permanent congenital hypothyroidism. **Methods**: Retrospective evaluation of 58 children with congenital hypothyroidism and eutopic thyroid gland. Gender, gestational age, birth weight, TSH and serum thyroxine levels at diagnosis and L-thyroxine dose at 12 and 24 months of age were analyzed. **Results**: Median (IQR) initial TSH levels were 73.3 (276.5) µIU/mL in permanent hypothyroidism and 24.24 (52.7) µU/mL in transient hypothyroidism (*P* =0.0132). The optimum cut-off value of initial TSH to predict transient hypothyroidism was 90 µIU/mL. Mean (SD) L-thyroxine doses at 24 months of age were 2.64 (0.98) µg/kg/day in permanent hypothyroidism and 1.91 (0.65) µg/kg/day in transient hypothyroidism. Requirement of L-thyroxine dose at 24 months of ≤0.94 µg/kg/day had the highest sensitivity (100%) to predict transient hypothyroidism. **Conclusions**: L-thyroxine doses at 24 months can predict transient hypothyroidism in patients with eutopic thyroid gland earlier than at 36 months.

Keywords: *Cretinism, Transient hypothyroidism, Thyroid hormones, Thyroxine.*

Congenital hypothyroidism (CH) is classified into transient CH (TH) and permanent CH (PH). TH is a temporary deficiency of thyroid hormone that recovers in the first few years of life. PH is a persistent deficiency of thyroid hormone requiring lifelong replacement therapy [1]. Current Italian recommendations [2] and European guidelines [3] suggest re-evaluation at 3 years of age for distinguishing PH from TH.

Several studies have tried to distinguish between TH and PH in order to determine when re-evaluation can be performed; however, definitive criteria have not yet been suggested [4-6]. We investigated the differences between TH and PH in patients with an eutopic thyroid gland to identify factors that could early discriminate these two conditions.

METHODS

We retrospectively analyzed medical records of 168 (56 boys) children (period 2000-2013) with a positive screening for CH (dried blood spot at 48-72 hours of life), confirmed by a venous blood sample (TSH >10 µIU/mL, normal/low free thyroxine (fT4) value) within the first month of life. L-thyroxine treatment was started at a dose of 10-15 µg/kg/day and was administrated until three years of age [2]. All the patients were followed-up according to a protocol which provides adjustments of L-T4 doses based on TSH serum values (reference value: 0.5-2.5 µIU/mL) [2]. Serum TSH, fT4, fT3, thyroglobulin levels were measured by chemiluminescent microparticle immunoassay. Thyroid ultrasonography was performed to confirm thyroid gland location and size. The normal antero-posterior diameter of thyroid gland at baseline and at three years is 5-9 mm and 7-12 mm, respectively [5]. Scintigraphy was performed in patients with non-eutopic thyroid gland on ultrasonography. We did not consider children with thyroid dysgenesis and patients who started therapy after 30 days of life showing hyperthyrotropinemia (TSH values 5-10 µIU/mL) because the treatment of this condition is still debatable [2]. In the final analysis, only patients who had minimum three years follow-up were included.

All the patients were re-evaluated at the age of 3 years. After L-thyroxine withdrawal, serum TSH, fT4, fT3 levels were determined at one month and subsequently every three months during the first year of follow-up and every six months during the second year. If the results were within normal range, they were diagnosed as TH and no further follow-up was recommended in the absence of signs or symptoms of hypothyroidism [2]. On the basis of definitive TSH values after therapy withdrawal, children were divided into two groups: TH group, including those with persistent normal TSH and fT4 levels; PH group,

including those with persistent elevated TSH levels (>10 µIU/mL). In both groups we compared sex, gestational age, birth weight, TSH and fT4 at diagnosis and L-T4 dose per kilogram body weight calculated at 12months of age (12 m dose) and at 24months of age (24m dose). The study was conducted in accordance with the ethical standards of the Helsinki Medical Declaration and its later amendments.

Comparison between groups was performed using the Fisher test for categorical variables (sex, gestational age, birth weight) and Wilcoxon test and Student t-test for continuous data (TSH and fT4 at diagnosis, 12m dose and 24m dose). A receiver operating characteristic (ROC) curve was designed to estimate the optimum cut-off value in dosage per kilogram for indicating TH. Sensitivity and specificity for the optimum value in the estimation of TH were calculated. The optimum cut-off value was defined as the highest Youden index. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS (version 18.0) and MedCalc (version 17.6).

RESULTS

Out of 168 children 90 infants with thyroid dysgenesis and 20 patients who started therapy after 30 days of life (TSH 5-10 µU/mL) were excluded. Finally, 58 patients (21 boys) with mean duration of follow-up 8.5 years were included.

At re-evaluation, 65.5% of patients showed PH. A history of prematurity was present in three cases (two PH and one TH) and birth weight <2500 g in five (two PH and three TH, *P*=0.32). Median (IQR) of initial TSH levels were 73.3 (276.5) µIU/mL in PH and 24.2 (52.4) µIU/mL in TH (*P*=0.013). Mean (SD) of baseline serum fT4 levels (*n*=56) were 1.18 (1.57) ng/dL in PH *vs* 1.10 (0.68) ng/dL in TH group, *P*= 0.84. Mean (SD) 12m dose was 3.05 (1.38) µg/kg/day in PH *vs* 2.46 (0.74) µg/kg/day in TH, *P*=0.08. Mean (SD) 24m dose was significantly higher in PH group than in TH group (2.64 (0.98) µg/kg/day *vs* 1.91 (0.65) µg/kg/day, *P*=0.005, respectively.

The area under the curve (AUC) of initial TSH for the prediction of TH was 0.7 (95% CI 0.57-0.81; *P*=0.004) and the optimum cut-off value for initial TSH was 90 µIU/mL (sensitivity 47.37% specificity 85%). The AUC of 24m dose for the prediction of TH was 0.72 (95% CI 0.59-0.83, *P*<0.001) and the optimum cut-off value was 2.47 µg/kg/day (sensitivity 55.2%, specificity 85%). 24m dose of 0.94 µg/kg/day had the highest sensitivity (100%) and dose of 3.2 µg/kg/day had the highest specificity (100%).

DISCUSSION

The present study highlights the role of baseline TSH levels and 24-month dose of L-thyroxine which were significantly higher in PH than in TH. In this study the prevalence of TH was 34.5%, in line with other studies [7]. Therefore, more than one-third of our patients did not require medications after treatment withdrawal during the period considered highlighting the role of early re-evaluation. Although several authors suggest various discriminating factors between PH and TH, markers that would allow early detection of TH are still not validated [8-12].

Our study has some limitations such as a retrospective design, a relatively small group of patients and the lack of complete data regarding maternal TRB-Ab, drug intake, and use of iodine during delivery.

In our study, serum TSH levels at diagnosis was significantly higher in PH than in TH group, as also reported by Kang, *et al*. [7]. Few authors have not reported any significant difference in TSH values postulated to variability in timing of blood sample [5,9]. In our study the 12-month dose was not significantly different between TH and PH as also showed by Zdraveska, *et al*. [14]. However, a 24-month dose <2.47 µg/kg/day was evocative of TH in the present study. Messina, *et al*. [9] in a comparable analysis, found a L-thyroxine dose <1.45 µg/kg/day and a L-thyroxine dose >4.27 µg/kg/day at 24 months as highly predictive of TH and PH, respectively. Prematurity is often reported to be associated with TH [13]. The results in present study were not significant in predicting evolution of CH, as earlier reported by Cho, *et al*. [4].

We are conscious that these results will not modify current standard of practice but we believe that our data supported by other studies may allow for earlier discrimination among TH and PH. In conclusion, the results of this study show that TSH levels at diagnosis and 24-month dose could be used to distinguish between TH and PH. Particularly, our results suggest that a 24-month dose >3.2 µg/kg/day is predictive of PH while children requiring a 24-month dose <0.94 µg/kg/day have a high probability to have TH.

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WHAT THIS STUDY ADDS?

- TSH levels at diagnosis and L-thyroxine dose per kilogram body weight calculated at 24 months of age could be used to distinguish between permanent and transient hypothyroidism in children with eutopic thyroid gland.

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