Permanent vs Transient Congenital Hypothyroidism: Assessment of Predictive Variables

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Objective: To assess clinical variables, including early thyroid scintigraphy, in predicting the outcome (permanent vs transient) in term infants with congenital hypothyroidism (CH).

Methods: In a retrospective study, 142 full-term infants with CH diagnosed between 2000 and 2012 were categorized into three groups: agenesis/ectopic thyroid and permanent CH; eutopic thyroid and permanent CH; and eutopic thyroid and transient CH. All underwent early thyroid scintigraphy and were under regular follow-up in our tertiary Pediatric Endocrine Institute.

Results: Thyroid scan showed agenesis/ectopic thyroid in 58 (41%) and eutopic thyroid in 84 (59%) infants. Imaging findings were similar in eutopic-permanent and eutopic-transient groups. At initial evaluation, TSH levels were higher in the agenesis/ectopic group than in the eutopic-permanent and eutopic-transient groups (71.5 ± 11.2 mIU/L vs 49.1 ± 27.9 mIU/L and 42.5 ± 29.1 mIU/L, respectively; $P < 0.001$). Higher L-T4 doses were required from the third month in the agenesis/ectopic than in the eutopic-permanent group ($P < 0.001$) and from the sixth month in the eutopic-permanent than in the eutopic-transient group ($P < 0.01$). Initial TSH >63.5 mU/L ($P < 0.001$) and L-T4 dose >4.6 μg/kg/d at age >6 months ($P < 0.001$) were found to be predictors for an agenesis/ectopic gland using receiver operating characteristic analysis, as was an L-T4 dose >2.2 μg/kg/d at age >6 months ($P < 0.01$) for permanent CH in patients with a eutopic gland.

Conclusions: Although early thyroid scintigraphy is reliable in predicting permanent CH when detecting agenesis or ectopic gland, it cannot differentiate between permanent and transient CH in cases with a eutopic thyroid. Confirmatory TSH at diagnosis and the L-T4 dose through treatment may better distinguish between permanent and transient CH. (***J Clin Endocrinol Metab*** **103: 4428–4436, 2018)**

Congenital hypothyroidism (CH), occurring in 1:3000 to 1:4000 newborns, is one of the most common preventable causes of mental retardation (1, 2). Newborns with CH are usually detected by routine newborn screening (NBS) programs, and treatment is promptly initiated following confirmatory measurement of serum TSH and free T4 (FT4) levels (3, 4). In most cases of CH, the underlying etiology is thyroid dysgenesis (agenesis or ectopic) or dyshormonogenesis, both requiring lifetime therapy. However, ~5% to 15% of the children diagnosed with CH will have a transient form of the disease (5, 6), which may be caused by *trans*-placental transfer of maternal thyroid-blocking antibodies, maternal and neonatal iodine deficiency or overload, or maternal antithyroid drugs (2, 7).

In 2014, the European Society for Pediatric Endocrinology consensus guidelines on screening, diagnosis,

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Abbreviations: ^{99m}Tc, technetium 99m pertechnetate; AUC, area under the curve; CH, congenital hypothyroidism; FT4, free T4; IQR, interquartile range; NBS, newborn screening; NGS, next-generation sequencing; ROC, receiver operating characteristic; TFT, thyroid function test; TT4, total T4.

and management of CH recommended imaging of the thyroid gland to determine the underlying etiology of CH (4). Radioisotope scintigraphy and ultrasonography are the most widespread and readily available imaging modalities. Yet neither is perfect, and both have clinical drawbacks (8–10). Although scintigraphy is somewhat invasive and exposes the infant to radiation, ultrasonography of the thyroid in neonates is technically challenging and operator dependent. Thyroid scintigraphy may also have diagnostic pitfalls, such as a false-negative thyroid scan due to transfer of maternal blocking antibodies to the fetus and limited ability in assessment of thyroid size and morphology. Despite its drawbacks, scintigraphy has come to be considered an important part of the initial evaluation of CH in the attempt to distinguish between permanent and transient CH and is generally performed prior to or within 7 days after treatment initiation (4). It should, however, be emphasized that imaging of the thyroid gland does not influence the decision to start thyroid hormone replacement or to determine the L-T4 dose and therefore should not postpone the initiation of treatment (4).

In accordance with the consensus guidelines, the routine practice at our tertiary pediatric care center has been that infants with confirmed biochemical CH undergo thyroid scintigraphy before initiation of L-T4 therapy. The primary objective of this retrospective study was to assess the utility of thyroid imaging at presentation of CH to distinguish between permanent and transient hypothyroidism. The secondary objective was to determine whether initial thyroid function tests (TFTs) and levothyroxine requirements could have an impact on management decisions and surveillance during infancy.

Patients and Methods

Patients

A survey from our registry of all cases of CH diagnosed and followed in the Institution for Pediatric Endocrinology at Schneider Children's Medical Center of Israel between the years 2000 and 2012 yielded 252 patients. Review of the medical files identified 142 patients who fulfilled the following inclusion criteria: full-term infants referred to our clinic due to abnormal NBS results or infants aged <2 months in whom CH was clinically suspected due to lethargy, feeding problems, constipation, or umbilical hernia despite normal NBS; confirmation of CH diagnosis by TFTs performed at our endocrine laboratory; available thyroid scan results from diagnosis; thyroid replacement therapy since infancy; and regular follow-up at our clinic with TFTs for at least 3 years. Excluded from the study were 110 patients: preterm infants (<37 weeks of gestation, n = 62); patients with genetic syndromes or chromosomal abnormalities (n = 12); patients with central hypothyroidism (n = 8); patients with chronic disease and patients treated with drugs known to affect thyroid function (n = 6); and patients with insufficient data and/or loss to follow-up (n = 22). The study was approved by the ethics committee of our institution, which waived the need to obtain informed consent.

During the study period, the routine NBS procedure in Israel included testing for CH by measuring total T4 (TT4) in heel puncture blood samples collected between days 2 to 3 of life. When the TT4 level was in the lowest 10th percentile, TSH was measured. Both TT4 and TSH were assayed in a single national laboratory using RIA until 2006 and immunoassay thereafter. Patients suspicious for CH (TSH >20 mIU/L) were recalled for confirmatory tests as were newborns clinically suspicious for CH despite a normal NBS. Confirmatory testing of FT4 and TSH was performed in our endocrine laboratory.

Treatment with L-T4 (10 to 15 μg/kg/d) was administered immediately after receipt of confirmatory abnormal serum test results. Scintigraphy was performed prior to or within the first few days of initiation of L-T4.

The first follow-up visit took place 1 to 2 weeks after initiation of L-T4 treatment, with intense follow-up over the first year of life (every 2 weeks until TSH levels were completely normalized and every 1 to 3 months thereafter). Between the ages of 1 and 2 to 2.5 years, surveillance consisted of clinic visits (anthropometric assessment, clinical and laboratory evaluations, and L-T4 dose adjustment) every 2 to 4 months.

Reevaluation of thyroid function to distinguish between permanent and transient CH was performed around the age of 2.5 to 3 years in the following cases: patients in whom initial evaluation revealed a normally located gland, with or without goiter and children who had required no increase in L-T4 dose since infancy. Initial reevaluation consisted of thyroid imaging by ultrasound. When a eutopic, normally sized gland was found, the L-T4 dose was gradually reduced until complete withdrawal, providing the TFT remained within the normal range. CH was considered transient when TFT remained normal during 12 to 18 months after L-T4 was discontinued and permanent when an increase in TSH concentration >10 mIU/L was observed during this period. In patients found to have permanent CH on reevaluation, L-T4 treatment was reinstituted.

Methods

Records were reviewed for demographic data: course of pregnancy (uncomplicated or complicated due to multiple gestation, preexisting high blood pressure requiring medication, or preeclampsia); perinatal history (uncomplicated or complicated by feeding difficulties, failure to gain weight, neonatal hypoglycemia, tachypnea/apnea or sepsis workup); relevant family history, including maternal hypothyroidism or treatment with L-T4 during pregnancy; follow-up parameters at diagnosis and at 1, 3, 6, 9, 12, and 24 months of age, including anthropometric measurements (length and weight) and signs and symptoms of hypothyroidism; prescribed L-T4 dosage calculated as dose per kilograms per day; TFT results obtained at the same time points as well as at 30 and 36 months; and imaging results [radioisotope technetium 99m pertechnetate (^{99m}Tc) scan at diagnosis and thyroid ultrasound on reevaluation].

Imaging

Scintigraphy was carried out with 30 MBq of ^{99m}Tc using the Infinia Hawkeye 4 SPECT/CT (GE Healthcare, Madison, WI). Radioisotope uptake was classified as no uptake, uptake in an

ectopic area, or uptake in the usual anatomic location classified as normal, decreased, or increased (indicating dyshormonogenesis).

According to imaging interpretation and follow-up outcome, the patients were categorized into three groups: agenesis/ectopic thyroid and permanent CH, eutopic thyroid and permanent CH, and eutopic thyroid and transient CH.

Sonography for reevaluation, when indicated, was performed by a pediatric radiologist specialized in neck ultrasound using the high-resolution (0.7 to 1.0 mm), high-frequency (10 to 15 MHz) linear array transducer [GE Voluson Expert (GE Healthcare), Philips IU22, or the Philips HDL 5500 US machine (Philips ATL, Bothell, WA)]. Ultrasound images were evaluated for anatomic location and thyroid volume.

Laboratory assessments

Serum TSH levels (normal range 0.64 to 6.3 mIU/L) and FT4 levels (normal range 10.3 to 20 pmol/L) were assayed in our endocrine laboratory using a chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA) and an immunoassay apparatus (ADVIA Centaur; Bayer Healthcare LLC, Tarrytown, NY), respectively.

Statistical analysis

Continuous normally distributed data are expressed as mean (± SD), nonnormally distributed continuous data are expressed as median [interquartile range (IQR) and range], and categorical data are expressed as number and percentage. The two-tailed Pearson χ^2 test and Fisher exact test were used to compare categorical variables. The independent-samples *t* test was used to compare continuous normally distributed variables between two categories or one-way ANOVA and *post hoc* analysis using the Tukey test among three categories. Mixed models with repeated-measures analyses were performed to compare longitudinal changes in TSH levels, FT4 levels, and L-T4 doses in and among the various groups (Figs. 2–4). The model was specified with a between-group factor (agenesis/ectopic thyroid, eutopic thyroid-permanent, and eutopic thyroid-transient), a within-group factor of time (baseline, 1, 3, 6, 9, 12, and 24 months), and the group × time interaction. Data are expressed as estimated marginal means and SEM. One-way ANOVA or independent-samples *t* tests were used to compare between diagnosis groups at each time point. Bonferroni correction was implemented and set on $P < 0.007$ (0.05 per seven time points). Four multivariate backward logistic regression models were designed to identify clinical and biochemical variables (the dependent variables) that might distinguish between the anatomic variants of the thyroid gland (agenesis/ectopic or eutopic) in patients with CH (models 1 and 2) or to predict the long-term outcome of CH, whether permanent or transient (models 3 and 4). Each model compared two of the three groups (agenesis/ectopic, eutopic-permanent, or eutopic-transient) at diagnosis or throughout follow-up. The following variables were entered to the first step of each of the models: model 1 and model 3: sex, pregnancy course (number of fetuses, uncomplicated/high-risk, and maternal hypothyroidism), perinatal period (birth weight and normal or complicated course), chronological age at diagnosis, and initial TFTs (TSH and FT4 at diagnosis); model 2 and model 4: the daily L-T4 dose per kilogram weight (mean daily dose at prespecified time points, at diagnosis, and at 1, 3, 6, 9, 12, and 24 months of age) throughout the 2 years of follow-up. The aim of models 2 and 4 was to identify the first L-T4 dose that can distinguish between agenesis/ectopic or eutopic thyroid (model 2) and permanent or transient CH (model 4). The dose over time was entered into the model as follows: the first analysis included the earliest dose, the second analysis, the two earliest doses, and so on, until the first dose was significant in the model; α rate was adjusted to control for multiple testing in these models: $\alpha = 0.05$/number of tests performed. (*P* values and 95% CIs were calculated for the analyses.) The efficiency of each of the parameters detected to serve as a biomarker was determined by using the receiver operating characteristic (ROC) analysis with 95% CI. For perspective, area under the curve (AUC) values from 0.5 to 0.7 for a diagnostic/prognostic test represent low accuracy, values from 0.7 to 0.9 are useful for some purposes, and values >0.9 represent high accuracy (11). The optimal cutoffs of each parameter were calculated using the Youden index (12). In accordance with the guidelines for Transparent Reporting of a Multivariate Prediction Model for Individual Prognosis or Diagnosis (13), we conducted validation analyses by resampling for all four predictive models. All analyses were performed using SPSS statistical software (release 20; SPSS Inc., Chicago, IL). A *P* value of ≤0.05 was considered significant.

Results

The study cohort

In this cohort of 142 sporadic nonfamilial cases, 58 (41%) had thyroid dysgenesis [22 (15.5%) ectopic thyroid gland and 36 (25.5%) athyreosis], and 84 (59%) patients had a eutopic gland [30 (21.1%) with an intact gland with increased uptake (dyshormonogenesis) and 54 (37.9%) with an intact gland with normal or decreased uptake]. Of the 142 patients, 125 (88%) were diagnosed with permanent CH. Of these, 58 had agenesis/ectopic gland, and 67 had a eutopic gland. Seventeen of the 142 (12%) were determined to have transient CH, based on normal TFTs following discontinuation of L-T4 at a median age of 2.8 years (IQR 0.6); all had a eutopic gland. Among the patients with eutopic gland, the distribution of intact glands with normal or increased uptake was similar in the permanent and transient CH groups ($P = 0.55$).

Clinical findings at diagnosis, TFTs, and L-T4 requirements during follow-up

Clinical and biochemical characteristics at diagnosis

The percentage of females was significantly higher in patients with CH with agenesis/ectopic thyroid than in those with a eutopic thyroid (74% vs 49%; $P = 0.015$) (Table 1). In patients with eutopic thyroid, whether permanent or transient CH, the percentage of females was similar (53.7% and 41.2%, respectively). Pregnancy course (uncomplicated vs complicated) and outcome (singleton vs multiple pregnancy); positive history of maternal hypothyroidism; average birth weight; the percentage of newborns born small, appropriate, or large for gestational age; weight at diagnosis; and perinatal

Table 1. Clinical Characteristics of the Study Cohort

	Permanent CH		Transient CH	
	Agenesis/Ectopic (n = 58)	Eutopic (n = 67)	Eutopic (n = 17)	*P*
Sex				
Male, n (%)	15 (25.8)	31 (46.3)	10 (58.8)	0.015
At diagnosis				
Age, days, median (IQR)	10 (7–19)	13 (9–17)	10 (7–19)	0.730
Weight, kg, mean ± SD	3.48 ± 0.62	3.25 ± 0.63	3.24 ± 0.48	0.926
Pregnancy, n (%)				
Singleton	54 (93.1)	64 (95.5)	15 (88.2)	0.193
Twin/triplets	4 (6.9)	3 (4.5)	2 (11.8)	
Uncomplicated	54 (93.1)	55 (82.1)	14 (82.4)	0.170
High-risk pregnancy	4 (6.9)	12 (17.9)	3 (17.6)	
Maternal hypothyroidism	4 (6.9)	13 (19.4)	3 (17.6)	0.869
Birth parameters				
Weight, kg, mean ± SD	3.3 ± 0.5	3.0 ± 0.6	2.9 ± 0.6	0.100
AGA, n (%)	54 (93.1)	62 (92.5)	16 (94.1)	
SGA, n (%)	1 (1.7)	2 (3.0)	1 (5.9)	0.796
LGA, n (%)	3 (5.2)	3 (4.5)	0 (0.0)	
Perinatal history				
Normal, n (%)	52 (89.7)	53 (79.1)	13 (76.5)	0.358
Complicated, n (%)	6 (10.3)	14 (20.9)	4 (23.5)	

The *P* value represents comparison between groups using χ^2 test for categorical variables and Mann-Whitney *U* test for numerical variables with skewed distribution.

Abbreviations: AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

history (normal vs complicated) were all similar in patients with agenesis/ectopic thyroid or eutopic thyroid, with either permanent or transient CH.

Chronological age at diagnosis was similar in the entire cohort. Subtle signs and symptoms of CH were noticed in 13 patients, with no noticeable difference between those with agenesis/ectopic thyroid or eutopic gland and the subsequent diagnosis of either permanent or transient CH (data not shown). Mean weight at diagnosis was similar in the three groups. Initial TFT results showed a significant difference between patients with agenesis/ectopic thyroid gland and those with eutopic gland with either permanent or transient CH (Fig. 1): mean TSH levels were significantly higher (71.5 ± 11.2 mIU/L vs 49.1 ± 27.9 mIU/L vs 42.5 ± 29.1 mIU/L, respectively; $P < 0.001$), whereas mean FT4 levels were significantly lower (6.8 ± 4.9 pmol/L vs 11.4 ± 6.4 pmol/L vs 12.5 ± 5.1 pmol/L, respectively; $P < 0.001$). Initial L-T4 dose was 12.6 ± 3.7 μg/kg/d, with no significant difference among the groups. Within 4 weeks of L-T4 therapy initiation, 99 out of 142 (69.7%) patients with CH had a normal TSH, and 138 out of 142 (97.2%)

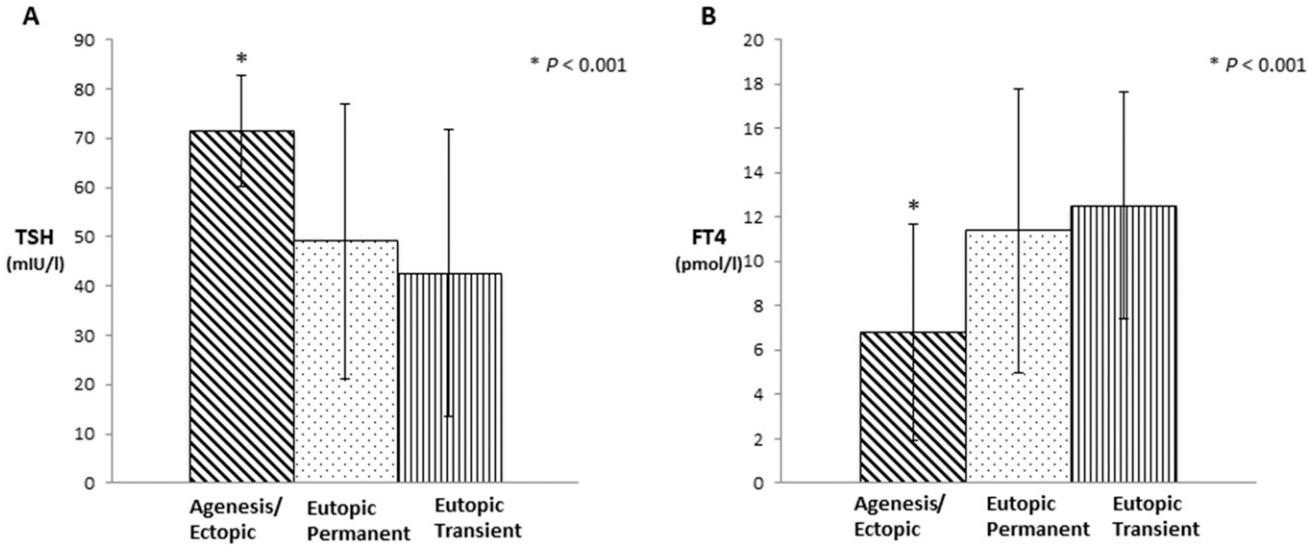

Figure 1. TFT results at diagnosis of CH in full-term newborns: comparison between infants with agenesis/ectopic thyroid gland vs eutopic gland and permanent CH vs eutopic gland and transient CH. (A) TSH. (B) FT4.

patients with CH had a normal FT4. One to two months after initiation of L-T4, TSH and FT4 levels were within the normal range in the entire cohort (Fig. 2).

Longitudinal follow up of L-T4 doses revealed a progressive decrease of daily requirements in the entire cohort. From the sixth month of treatment, the daily L-T4 requirements were significantly lower in patients with CH with eutopic glands than in those with agenesis/ectopic glands [mean (SEM): 4.1 (0.3) μg/kg/d vs 5.1 (0.3) μg/kg/d; $P < 0.001$]. The differences between the two groups became more pronounced by the end of the second year of therapy [mean (SEM): 3 (0.3) μg/kg/d vs 4.5 (0.3) μg/kg/d; $P < 0.0001$]. The interaction between group and time was found to be nonsignificant (indicating a similar pattern of change over time in both groups) (Fig. 3). In patients with eutopic glands, the daily doses of L-T4 were significantly lower in those with transient CH than in those with permanent CH. These differences were apparent at 6 and 12 months of therapy [mean (SEM): 2.7 (0.7) μg/kg/d vs 4.1 (0.3) μg/kg/d, $P = 0.004$; and 2.1 (0.8) vs 3.4 (0.3), $P = 0.003$] and became less pronounced by the end of the second year of therapy [mean (SEM): 1.9 (0.8) μg/kg/d vs 3 (0.3) μg/kg/d; $P = 0.027$]. The interaction between group and time was found to be significant ($P = 0.02$) (Fig. 4).

Models predicting the underlying diagnosis of CH and the overall outcome

Agenesis/ectopic thyroid vs eutopic-permanent thyroid

Model 1: at diagnosis. TSH level at diagnosis was the only parameter that could distinguish between agenesis/

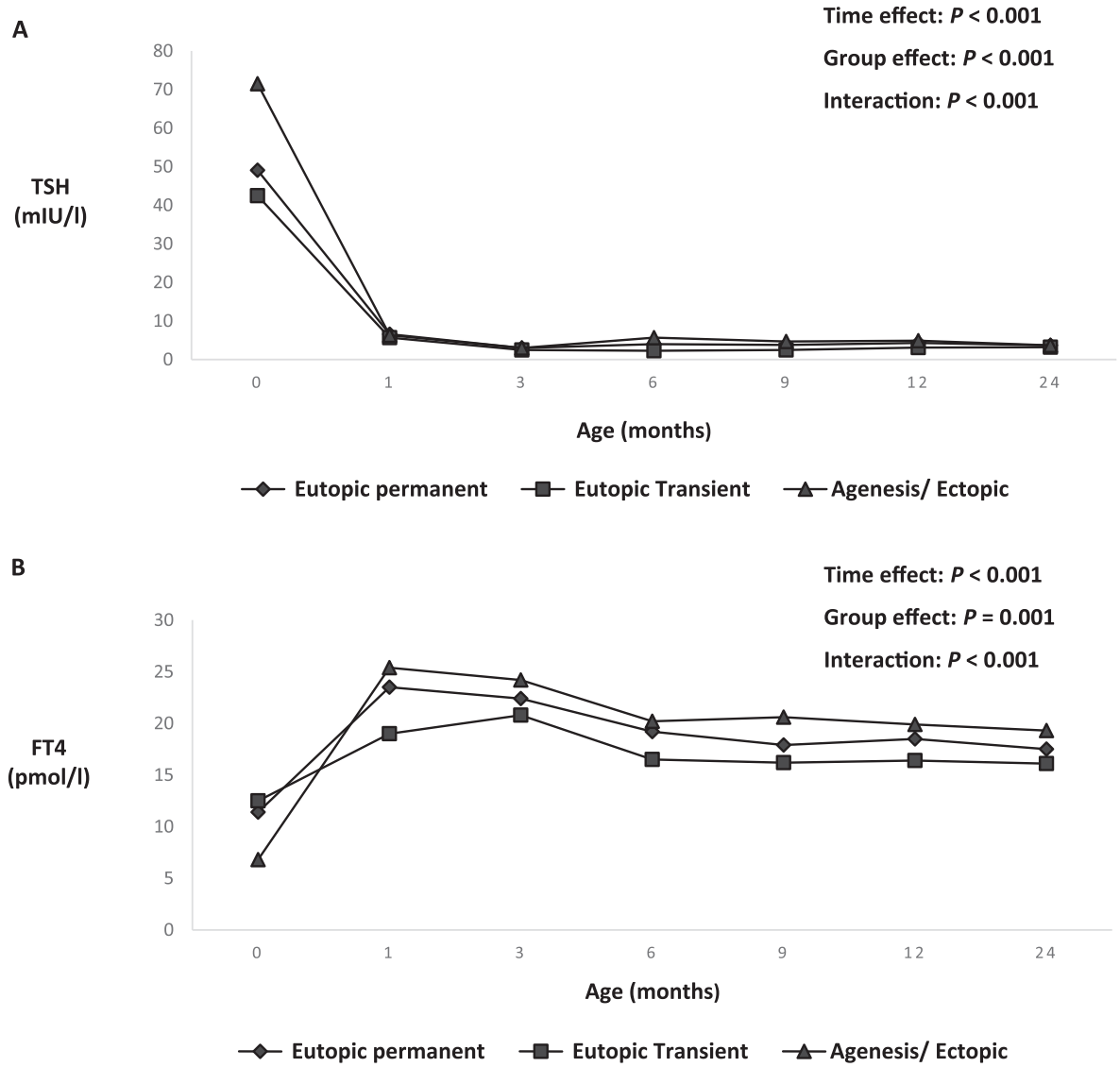

Figure 2. TFT results from birth to 2 y of age: comparison between infants with agenesis/ectopic thyroid gland vs eutopic gland and permanent CH vs eutopic gland and transient CH. A statistically significant difference between groups in TSH and FT4 was shown at diagnosis ($P < 0.001$). (A) TSH. (B) FT4.

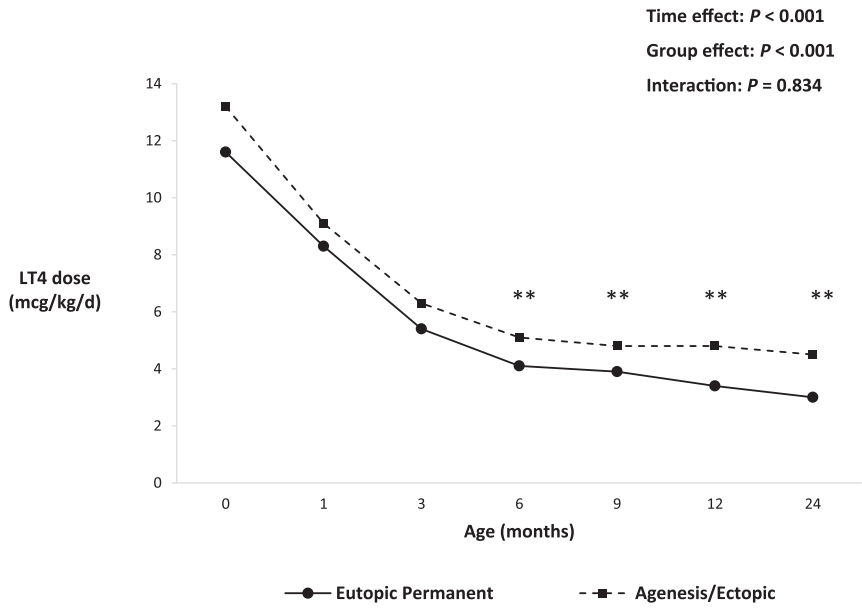

Figure 3. L-T4 treatment dose from birth to 2 y of age: comparison between infants with agenesis/ectopic thyroid gland vs eutopic gland and permanent CH. **Significant difference after Bonferroni correction for multiple comparisons ($P < 0.007$).

ectopic and eutopic thyroid glands [OR 1.053 (95% CI 1.030 to 1.080); $P < 0.001$]. The odds for agenesis/ectopic thyroid were elevated by 5.3% for an increase of 1 mIU/L in TSH. The calculated AUC for TSH at diagnosis using the ROC analysis was 0.73 (95% CI 0.62 to 0.82), with an optimal cutoff of 63.5 mIU/L ($P < 0.001$; sensitivity 0.86; specificity 0.53). No other parameters at the time of diagnosis were able to distinguish between agenesis/ectopic or eutopic thyroid.

Model 2: during follow-up. L-T4 daily dose per kilogram of weight at the sixth month (and thereafter) was able to distinguish between patients with agenesis/ectopic and eutopic glands [OR 1.756 (95% CI 1.264 to 2.441); $P = 0.001$]. The model remained significant after adjustment to control for multiple testing: $P < 0.05$ for four tests. An increase of 1 μg/kg/d of L-T4 increased the odds for agenesis/ectopic thyroid by 75.6%. The AUC for L-T4 dose at 6 months using the ROC analysis was calculated at 0.70 (95% CI 0.6 to 0.8), with an optimal cutoff of 4.6 μg/kg/d ($P < 0.001$; sensitivity 0.6; specificity 0.67). No other parameters were able to distinguish between agenesis/ectopic or eutopic thyroid.

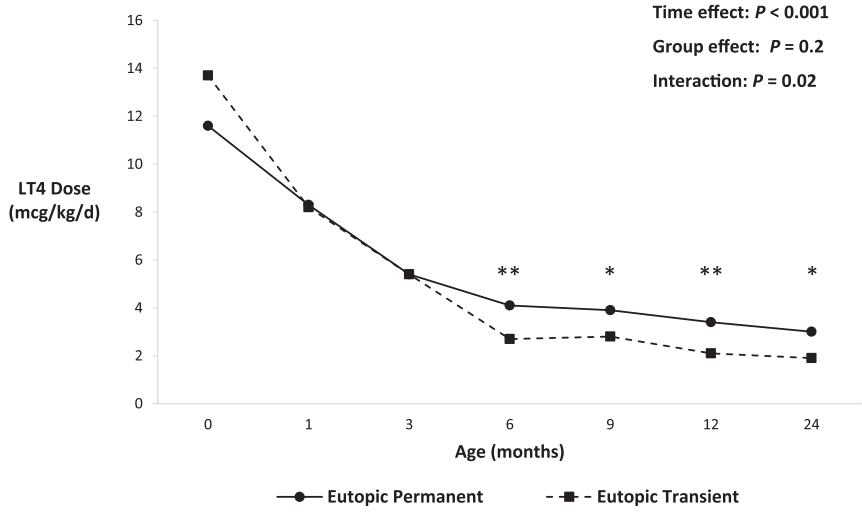

Figure 4. L-T4 treatment dose from birth to 2 y of age: comparison between infants with eutopic gland and permanent CH vs eutopic gland and transient CH. *Significant at $0.007 < P < 0.05$ (nonsignificant after Bonferroni correction); **significant difference after Bonferroni correction for multiple comparisons ($P < 0.007$).

Eutopic-permanent vs eutopic-transient thyroid

Model 3: at diagnosis. None of the parameters at the time of diagnosis were able to distinguish between the characteristics of the thyroid gland or to predict the outcome of the CH.

Model 4: during follow-up. L-T4 daily dose per kilogram of weight at the sixth month (and thereafter) enabled us to distinguish between permanent and transient CH in patients with a eutopic gland [OR 1.900 (95%CI 1.182 to 3.055); $P = 0.008$]. The model remained significant after adjustment to control for multiple testing: $P < 0.05$ for four tests. An increase of 1 μg/kg/d of L-T4 raised the odds for permanent CH by 90%. The AUC for L-T4 dose using the ROC analysis at 6 months was calculated at 0.73 (95% CI 0.57 to 0.89), with an optimal cutoff of 2.2 μg/kg/d ($P < 0.01$; sensitivity 0.9; specificity 0.57).

Validation analyses using resampling showed that each of the four models was stable and valid.

Discussion

In this study, we assessed a number of clinical variables, including early thyroid scintigraphy, in predicting the outcome (permanent vs transient) in term infants with CH. The main finding in this retrospective study was the failure of thyroid scan at presentation of CH to distinguish between permanent and transient CH in cases with a eutopic thyroid; confirmatory TSH at diagnosis and the L-T4 dose at

6 months of age were better predictors of the outcome. Interestingly, we observed a relatively high prevalence of eutopic thyroid gland among the term infants with permanent CH.

CH is a heterogeneous disorder with various underlying etiologies (2). Historically, most cases of CH were presumed to be due to thyroid dysgenesis (agenesis or an ectopic gland) (1, 2). In our cohort, only 41% of the cases were found to have thyroid dysgenesis. These findings are similar to those in recently published reports of large cohorts of patients with CH (14, 15). The higher prevalence of CH with a eutopic thyroid gland (4, 14) may stem from increased screening of patients at higher risk (those with very low birth weight or premature infants), a higher detection rate, and the introduction of progressively lower TSH cutoffs (16–18).

Surveillance of our patients with CH during the first years of life revealed that most had permanent hypothyroidism regardless of scintigraphy findings. These observations are in line with previous studies, suggesting that most cases of CH are permanent irrespective of the presence or absence of the thyroid gland (19, 20). Only 12% of our entire cohort, representing ~20% of the patients with eutopic gland, was found to have transient hypothyroidism. These rates are lower than previously reported. A plausible explanation could be the fact that our study included only term infants, whereas in other reports, the cohort studied also included preterm infants, in whom transient disease with a eutopic gland is more prevalent (15, 21).

The rationale for performing early imaging of the thyroid gland is to determine the underlying etiology of CH (4) and to anticipate whether it would be transient or permanent (22). Our clinical observation that a substantial number of patients with CH with a eutopic thyroid gland proved to have permanent CH raises doubts regarding this assumption. Although radioisotope scintigraphy with ^{99m}Tc, used by most centers, is the most sensitive and reliable modality in diagnosing athyreosis or ectopic thyroid tissue (23), it has several pitfalls. Absence of uptake by a eutopic gland may occur upon transfer of maternal TSH receptor-blocking antibodies to the fetus or with exposure of the newborn to exogenous iodine. Other drawbacks of this modality include the need for insertion of an IV line to the neonate and exposure to radiation of ~1 millisievert (0.1 rad), a limited ability to assess thyroid size and morphology (24), and the inconvenience of performing the thyroid scan within a few days of treatment initiation, as well as the parental stress and anxiety accompanying the procedure (9). The actual utility of early radioisotope scintigraphy is further challenged by the findings of our study, which showed that it was inconsistent in predicting the overall outcome in patients with a eutopic gland (irrespective of the radioisotope uptake level, whether increased, normal, or decreased) and did not influence decision making along the clinical course (3).

In view of these limitations of early thyroid scintigraphy, alternative tools to assess and predict the course and outcome in neonates with CH are needed. In our cohort, TSH at diagnosis and the daily L-T4 dose were able to predict the existence of a eutopic gland and assist in differentiating between permanent and transient CH. These findings are in line with those of Hanukoglu *et al.* (25) and Oren *et al.* (20) and in contrast to those of Eugster *et al.* (9), who reported two patients with transient CH whose initial TSH levels were extremely elevated. In our study, predictive factors for permanent CH were an initial TSH >63.5 mIU/L ($P < 0.001$) and daily dose of L-T4 >4.6 μg/kg from the sixth month of therapy and thereafter ($P < 0.001$). A daily L-T4 dose >2.2 μg/kg from the sixth month of therapy and thereafter ($P < 0.01$) could distinguish between permanent and transient CH in patients with a eutopic thyroid gland. Thus, our model served to add valuable information regarding the course and outcome of CH.

The major importance of this longitudinal study conducted in a single tertiary care center is that it provides data on early thyroid scan in a relatively large cohort of children with CH born at term. Although one of its limitations is its retrospective design, it must be stressed that the management and surveillance of these children were uniform. This uniform standard of care, which included further diagnostic evaluation (confirmatory TFTs and thyroid scanning) as well as comprehensive clinic visits with TFTs and consequent L-T4 adjustment, enabled us to assess the utility of thyroid imaging as a predictor of the outcome of CH in early childhood.

It must be noted that our study cohort did not undergo genetic analysis. Recently, next-generation sequencing (NGS) platforms have introduced a major change in the traditional approach to diagnosis and understanding of the molecular basis of CH, with the detection of several novel genes involved in the organogenesis of the thyroid tissue (26, 27). Furthermore, targeted NGS panels already provide an efficient tool for identifying gene mutations in the coding region of CH genes (28). Thus, in the near future, genetic testing is likely to become a powerful tool for clinicians to identify the genetic etiology of CH and its anticipated phenotype. However, with increased use of genetic testing, the spectrum of clinical expression will widen, and it is probable that there may be shortfalls between genotype and phenotype in regard to predicting permanent vs transient CH.

Conclusion

When assessing the hypothyroid infant, one does not expect a single test to provide a complete picture for diagnosis, course, and outcome. Thyroid scintigraphy at presentation of CH enables the clinician to determine permanent hypothyroidism in cases in which agenesis or ectopic gland is detected. Yet, in infants with a eutopic gland, thyroid scan plays a limited role in predicting the course and outcome of CH. Our findings suggest that TSH levels at diagnosis and the L-T4 dose through treatment may better distinguish between permanent and transient CH. Future prospective studies using more sophisticated imaging techniques and targeted NGS are warranted to identify more accurate predictive features for the course and outcome of CH.

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