Predictors of Transient Congenital Primary Hypothyroidism: Data from the German Registry for Congenital Hypothyroidism (AQUAPE "HypoDok")

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Research Article

Keywords: congenital primary hypothyroidism, prediction, transient congenital primary hypothyroidism, permanent congenital primary hypothyroidism

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Abstract

Neonatal screening for congenital primary hypothyroidism (CH) may not distinguish between transient
(TCH) and permanent dysfunction (PCH), causing potential overtreatment and concerns in affected families. To specify the indication for interruption of therapy we analysed the German registry "HypoDok" for infants with CH, which oversees 1,625 patients from 49 participating centres in Germany and Austria from 1997 until today. 357 Patients with a thyroid gland in loco typico were identified and retrospectively grouped according to cessation (TCH n=24) or continuation (PCH n=333) of L-Thyroxine (L-T\textsubscript{4}) treatment at 2 years of age. The receiver operating characteristic (ROC) analysis was performed to identify cut-offs predicting TCH by screening TSH concentrations and L-T\textsubscript{4} dosages. Gestational ages, birth weights and prevalence of associated malformations were comparable in both groups.

The cut-off screening TSH concentration was 73 mU/L. The cut-off daily L-T\textsubscript{4} dosage at 1 year was 3.1 µg/kg (90% sensitivity, 63% specificity; 36 µg/d) and at 2 years of age 2.95 µg/kg (91% sensitivity, 59% specificity; 40 µg/d). At 2 years of age, specificity (71%) increased when these both parameters were considered together.

**Conclusion:** The decision to continue or cease L-T\textsubscript{4} treatment at 2 years of age in CH patients diagnosed in neonatal screening may be based on their screening TSH concentrations and individual L-T\textsubscript{4} dosages at 1 and 2 years of age. Thus, TCH and PCH may be distinguished; overtreatment avoided, and affected families reassured.

**Keywords**
congenital primary hypothyroidism, prediction, transient congenital primary hypothyroidism, permanent congenital primary hypothyroidism

**Declarations**

**Funding**
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**Conflicts of interest/Competing interests**
The authors have no conflicts of interest relevant to this article to disclose.

**Ethics approval**
The AQUAPE Hypodok initiative was approved by a central ethics committee at the University of Magdeburg, and each centre complied with local data management guidelines. The local caregivers obtained parental written consent. All data was collected during routine care.

**Consent to participate**
Written consent has been obtained from the parents/caregiver of each patient after full explanation of the purpose and nature of all procedures used.

Consent for publication
Not applicable.

Availability of data and material
All data relevant to this study are included in the manuscript.

Code availability
SAS 9.4 (SAS Inc., Cary, NC, USA) and PROC LOGISTIC.

Author’s contribution
Nicola Matejek and Markus Bettendorf contributed to the study concept and design, the analysis and interpretation of data and the preparation of the manuscript. Sascha R. Tittel and Reinhard W. Holl contributed to the study concept and design, the analysis and interpretation of data, and to the revision of the manuscript. They administered and managed the registry HypoDok. Joachim Wölfle, Tilman Rohrer and Karl-Otfried Schwab contributed to the analysis and interpretation of data and to the revision of the manuscript. Holger Haberland, Eva-Maria Busemann and Norbert Jorch contributed to revision of the manuscript. All authors participated in acquisition of data and approved the final version of the manuscript.
Abstract

Neonatal screening for congenital primary hypothyroidism (CH) may not distinguish between transient (TCH) and permanent (PCH) dysfunction causing potential overtreatment and concerns in affected families. To specify the indication for interruption of therapy we analysed the German registry "HypoDok" for infants with CH, which oversees 1,625 patients from 49 participating centres in Germany and Austria from 1997 until today. 357 Patients with a thyroid gland in loco typico were identified and retrospectively grouped according to cessation (TCH n=24) or continuation (PCH n=333) of L-Thyroxine (L-T₄) treatment at 2 years of age. The receiver operating characteristic (ROC) analysis was performed to identify cut-offs for screening TSH concentrations and L-T₄ dosages. Gestational ages, birth weights and prevalence of associated malformations were comparable in both groups. The cut-off screening TSH concentration was 73 mU/L. The daily cut-off L-T₄ dosage after 1 year was 3.1 µg/kg (90% sensitivity, 63% specificity; median 36 µg/d) and after 2 years 2.95 µg/kg (91% sensitivity, 59% specificity; 40 µg/d). At 2 years of age, specificity (71%) increased when these both parameters were considered together.

Conclusion: The decision to continue or cease L-T₄ treatment at 2 years of age in CH patients diagnosed via neonatal screening may be based on their screening TSH concentrations and individual L-T₄ dosages at 1 and 2 years of age. Thus, TCH and PCH may be distinguished; overtreatment avoided, and affected families reassured.

Author's summary

What is Known:

- The course of congenital primary hypothyroidism may be transient, causing potential overtreatment.
- The dose of L-Thyroxine at 1 or 2 years of age may predict a transient course of primary congenital hypothyroidism.

What is New:

- TSH screening concentration and L-Thyroxine dosages at 1 and 2 years of age represent reliable predictors for transient congenital primary hypothyroidism with higher sensitivity and specificity when considered together in order to select eligible patients who qualify for treatment withdrawal.
List of Abbreviations:

ATD: anti thyroid drugs
BMI: body mass index
CH: congenital primary hypothyroidism
DGKED: German society of paediatric endocrinology and diabetology
fT₄: free serum thyroxine
HypoDok: Specialized prospective documentation software for CH
L-T₄: L-Thyroxine
PCH: permanent congenital primary hypothyroidism
ROC: receiver operating characteristic
SDS: standard deviation score
TCH: transient congenital primary hypothyroidism
TSH: Thyreotropin stimulating hormone
Introduction

Congenital primary hypothyroidism (CH) is suspected in neonatal screening when capillary TSH concentrations are elevated (>15 mU/L in Germany). Diagnosis is confirmed by measuring venous TSH and \( fT_4 \) concentrations before the start of treatment (1). Not all infants with confirmed CH necessarily receive lifelong \( L-T_4 \) treatment. Transient congenital hypothyroidism (TCH) occurs in up to 35% of children with CH (2). Lowering the threshold screening TSH concentrations for diagnosing CH may suggest an increased prevalence, overtreatment and impaired outcome in children that only have transient or mild hypothyroidism (3). Gene mutations of \( DUOX2 \) and \( TSH-R \) have been described in cases with mild transient hypothyroidism (4,5,6,7). National and international guidelines recommend confirming CH after the second birthday in case an unequivocal diagnosis has not been established during the neonatal period. \( L-T_4 \) treatment is then paused for 4 to 6 weeks in order to assess endogenous thyroid function. Earlier withdrawal is discussed when transient elevations of neonatal TSH concentrations are likely and there is impending overtreatment (7,8,9,10). Paediatric endocrinologists tend to conduct therapy in the first 2 years of life in order to avoid defects in the myelinisation of the central nervous system and to assure normal neurodevelopmental outcomes. A reevaluation of thyroid function is indicated if the thyroid gland is developed normally and elevated TSH serum levels are not observed or there has been no need to adjust the dosage of \( L-T_4 \) during the course of treatment. However, standard recommendations for interruption of treatment are lacking (11).

We analysed data from the German registry of CH in order to determine whether screening and serum TSH concentrations and \( L-T_4 \) dosages at 1 and 2 years of age are sufficient parameters to anticipate a transient nature of thyroid dysfunction warranting its re-evaluation.
Methods: “HypoDok” is a prospective documentation software for CH supported by the German Society of Paediatric Endocrinology and Diabetes (DGKED), with contributions from 49 participating centres in Germany and Austria currently including 1,625 patients. The inclusion criteria were the availability of screening TSH concentrations (mU/L), a thyroid gland in loco typico, visualised by ultrasound, and the L-T₄ dosages (µg/kg/day, µg/day) at diagnosis and at 1 and/or 2 years of age, respectively. The end of L-T₄ treatment was documented by checking a corresponding box on the date of withdrawal. The following items were extracted from the registry: L-T₄ dosages at 6 months of age, weeks of gestation, birth weight (g), Apgar-Score, serum TSH (mU/L) and fT₄ (ng/dl) concentrations at confirmation, as well as relevant maternal and patient’s history (selection options: yes/no): gender male, maternal hypothyroidism, maternal treatment with L-T₄ during pregnancy, hyperthyroidism, antithyroid drugs (ATD) during pregnancy, iodine medication in pregnancy and delivery, diagnosis of Trisomy 21, dopamine-treatment of the neonate. Additional diagnoses or malformations captured as free text documentation were also considered in the analyses. The height (cm) and body mass index (kg/m²) expressed as standard deviation scores (SDS) (12) at the age of 2 years, the L-T₄ withdrawal period of 4 to 6 weeks and the results of psychomotor testing at the age of 2 years were extracted. L-T₄ dosage changes were collected from each visit. The screening TSH concentrations were measured in dry-blood spots by the regional neonatal-screening laboratories in mU/L. The serum TSH (mU/L) and fT₄ (ng/dl) concentrations were measured in the laboratory of the respective centre for paediatric endocrinology. 357 patients treated in 37 German centres were eligible and were grouped according to continuation of L-T₄ beyond the 2nd year of life (PCH) or cessation (TCH) of L-T₄ treatment within the first two years of life.

Statistics: Descriptive data were presented as the median and interquartile range for continuous values and percentage for binomial/categorial values. Wilcoxon’s rank sum test was used to compare continuous variables between groups, while nominal variables were analysed by chi-squared test. The results were considered significant at p<0.05. The receiver operating characteristic (ROC) analysis was performed to identify cut-offs predicting TCH by screening TSH concentrations and L-T₄ dosages (µg/kg/d and µg/d) at 6 month, 1 and 2 years of age, respectively. We used SAS 9.4 (SAS Inc., Cary, NC, USA) and PROC LOGISTIC to calculate predicted probabilities of the patients to belong either to the TCH or PCH group, as well as their sensitivity and specificity based on the respective screening TSH concentration or L-T₄ dosage. The optimal cut-off for each parameter was calculated by
maximizing Youden index (13). Using linear regression made differences of screening TSH between
patients with and without L-T₄ withdrawal period, means are presented as least square means with
95% confidence interval.

Results:
357 infants with congenital primary hypothyroidism met the inclusion criteria (figure 1). They were
grouped retrospectively as PCH (n=333) and TCH (n=24). All patients with TCH terminated therapy
after 2 years of age (24/24). 95.2% of patients with PCH temporarily paused L-T₄ treatment for 4 to 6
weeks (n=111, 33%) and had to continue the treatment thereafter and/or required L-T₄ dosage
increase during the treatment course (n=316, 95%). Screening TSH concentrations were lower in
neonates with TCH (55.8 mU/L) than in those with PCH (150.0 mU/L, p=0.06) whereas serum TSH
and fT₄ concentrations were similar at confirmation of the diagnosis (table 2). L-T₄ dosages at start of
therapy in PCH and in TCH were comparable (p=1.0). L-T₄ dosages per kilogram body weight at 6
months of age were similar, and receiver operating characteristic calculation revealed 27µg/d as
predicting cut-off for TCH (Sensitivity 77%, Specificity 54%). At 1 year of age the L-T₄ dosages were
significantly higher in PCH (4.52µg/kg/d, total dose 45 µg/d) than in TCH (2.96 µg/kg/d, p<0.01, 30
µg/d, p<0.01), and were also higher at 2 years of age in PCH (4.03 µg/kg/d, 50 µg/d) than in TCH (2.5
µg/kg/d, p<0.01, 37 µg/d, p<0.01) (table 2).
Infants with a L-T₄ withdrawal period had significant lower screening TSH: 142.6 mU/L (119.2-166) vs.
186.2 mU/L (159-213.4, p=0.02), shown by linear regression analysis.
The cut-off screening TSH concentration by ROC was 73 mU/L (figure 2A). The cut-off L-T₄ dosage at
1 year of age was 3.1 µg/kg/d (figure 2B) and 2.95 µg/kg/d after 2 years (figure 2C) (table 3A). The L-
T₄ dosage with 99% sensitivity was 2.0µg/kg/d (20µg/d) and 6.3µg/kg/d (60µg/d) with 96% specificity
at 1 year of age. At 2 years of age the L-T₄ dosage was 2.0µg/kg/d (25µg/d) and 99% sensitive for
TCH and 5.0µg/kg/d (55µg/d) was 96% specific for PCH (table 3A).
In a subgroup with screening TSH concentration below 73 mU/L (n=109) the proportion of TCH (16%)
was twice as high as in the total cohort (PCH n=94 vs. TCH n=15). The total L-T₄ dosage at the age of
1 year (27.5 µg/d, 2.9 µg/kg/d) (table 3B, figure 2D) and at the age of 2 years (38 µg/d, 2.96 µg/kg/d)
(table 3B, Figure 2E) predicted a transient CH course with a slightly lower sensitivity at 1 year and
similar sensitivity at 2 years with more specificity (71%). Predicting L-T₄ dosages with highest
sensitivity and specificity were slightly higher for TCH (2.2µg/kg/d) and for PCH (6.6µg/kg/d) at 1 year.
of age in this subgroup compared to the overall group. The L-T₄ dosage with the highest sensitivity for
TCH at 2 years of age is lower than in the entire group (1.85µg/kg/d), but the total daily L-T₄ dosage is
identical, as well the dosage for the highest specificity. Similar to the overall group we suggest a TCH
predicting L-T₄ dosage of 27.5µg/kg/d (sensitivity 62% and specificity 70%) at 6 months of age.
The demographic characteristics of patients are listed in table 1B. Maternal hypothyroidism and
treatment with L-T₄ during pregnancy were similar in both groups as well as the number of infants with
other congenital malformations (data not shown). Exposure to iodine medication during pregnancy or
delivery was comparable in both groups (data not shown). Neonates with TCH were more frequently
treated with dopamine than those with PCH (8.3% vs. 0.9%, p=0.07) and mothers of neonates with
TCH were more often treated with ATD (p=0.1). An increase of the L-T₄ dosage was required in almost
all of PCH patients (table 1B) while L-T₄ withdrawal was only carried out in one third of PCH patients.
At 2 years of age median heights and BMI of all patients with TCH and PCH were similar (p=1.0,
p=0.8) (table 1A). The results of developmental tests were documented in 141/333 PCH und in 8/24
TCH patients and revealed normal results in 89% and 100% (p=1.0) of patients, respectively.

Discussion:
In this study we assessed screening serum TSH concentrations and dosages of L-T₄ at 6 months, 1
and 2 years of age in infants with CH and a eutopic thyroid gland registered in "HypoDok" in order to
predict transient or permanent hypothyroidism. At the incidence of 160 to 280 patients with CH,
detected in the neonatal screening in Germany per year (14) due to the percentage of 18% are
registered in "HypoDok". In Germany it is not mandatory to register patients for treatment.
Detection of milder forms of CH has refocused attention on the initial intent of neonatal screening,
namely prevention of mental retardation. Lowering the threshold of TSH concentrations in the neonatal
screening prompted an increase of positive CH results (15) and more cases with mild hypothyroidism
and transient courses were detected (15,16). The decrease of the TSH threshold in all likelihood
increased the laboratory and economic burden of neonatal screening programs as well as the concern
of affected families, but it is not clear whether these patients actually benefit from early detection and
treatment (17,18,19). A lower TSH threshold in the neonate screening in other countries outside of
Germany (>15mU/l) could explain the higher percentage of TCH in other studies (19,20).
Retrospective studies showed that neonates with a mildly elevated screening TSH (<15 and <20mU/L)
are at risk for permanent hypothyroidism (3,9,19). As up to 35% of patients may be affected by TCH,
defining these criteria seems worthwhile. Our analyses revealed a rate of 7% for TCH, which is lower than reported in previous studies (2,8,9,16). In order not to treat infants with TCH unnecessarily for too long, a safe approach for infants with TCH should be defined in guidelines (1,20,21). Current Guidelines recommend re-evaluation of the thyroid axis after 2 years of age and after completion of CNS myelination (1,20) but concise evaluation criteria for this are lacking so far (22,23). The current recommendations of the 2020 consensus congenital hypothyroidism guideline update may raise the prevalence of TCH, as treatment of hyperthyreotropinemia is recommended from the second week of life (21). The differentiation of isolated hyperthyreotropinemia and hypothyroidism in neonates proves challenging (23).

Reliable predictors represent the basis for the recommendation to withdraw L-T₄ in infancy when the diagnosis of hypothyroidism remains uncertain for neonates with a normally located thyroid gland. Serum TSH concentrations at diagnosis were similar for all patients with TCH and PCH, which confirms previous analyses on discrimination between TCH and PCH in children with a eutopic gland (24,25). As neonatal screening is scheduled for a fixed period of time (1,21), age dependent variations of serum TSH concentrations are expected to have a minor effect. Serum TSH concentrations may be affected by daytime, gender (26) and specific assay modalities such as range and sensitivity (27).

Treatment of mothers with iodine, anti-thyroid drugs or dopamine medication in neonates frequently causes TCH, because these drugs suppress thyroid function in the neonate temporarily (26,27). In our study in the TCH group dopamine medication was more often used in the neonatal period as expected. The prevalence of TCH and PCH was similar in our analyses when mothers were treated with anti-thyroid drugs during pregnancy, but insufficiently treated Morbus Basedow is a rare disease during pregnancy (prevalence 1:100.000 – 1:310.000 neonates, 28). The proportion of preterm infants in our analysis is comparable to the overall premature birth rate in Germany (29). Premature neonates have a higher risk of TCH, mediated by immaturity and medications during the intensive care period (19). Thus, these cases will not to be reported to “HypoDok”, if temporary treatment is expected.

L-T₄ treatment dosages at various time points during the first three years have been reported to discriminate TCH from PCH (2,7,8,9,10,16). Based on these parameters, the decision to withdraw L-T₄ treatment in infancy in order to re-evaluate endogenous thyroid function may be made. When calculating the exact L-T₄ dosage per kg body weight, the available galenic preparations and their strengths should be considered, the smallest incremental change in L-T₄ concentration that is possible, is 5 µg/drop or 2 µg/0.1 ml liquid. Our results add to those of other groups who examined
infants with CH and a eutopic thyroid gland (2,7,8,16). Our findings suggest the predicting cut-off for TCH at 2 years of age is the L-T4 dosage of 2.0µg/kg/d and accordingly 25µg/d, whereas other study groups ranged from 0.94µg/kg/d (8) to 2.8µg/kg/d (16).

Our data show that the concentration of screening-TSH below 73mU/ml can assume TCH. The screening TSH is a useful parameter for predicting TCH: The median of the comparison groups is almost significant, the sensitivity for screening TSH ≤ 73U/ml shown by ROC is reliable and the impact of low screening TSH to decide on the withdrawal period is significant. More reliable prediction of TCH and PCH can be made by the L-T4 dosages at 1 and 2 years of age in infants with CH and a eutopic thyroid gland.

We are the first to report that a combination of both parameters increases the sensitivity and specificity of either TCH or PCH prediction.

This study has limitations due to the retrospective study design, the limited number of patients resulting from the limited overall CH patient coverage of “HypoDok” and the potential selection bias of patients included in the optional registry by the treating physicians. The optional participation in the “HypoDok” registry results in incomplete documentation and causes low numbers of eligible patients. A register-analysis is not allowed to publish cut-off values with the highest sensitivity predicting TCH and with the highest specificity predicting PCH, because the anonymity of patient data may be compromised. Therefore, we present values with reliability over 95% or median values of 100%.

However a large population could be analysed, reflecting routine CH patient care in Germany. Thus, our results can provide a basis for selection of those CH patients who qualify for treatment cessation in infancy. Overtreatment can influence the physical, neurological or behavioural development of young infants with life-long consequences and may increase uncertainties for both families and physicians (15,30). Future studies aimed to confirm these parameters as prognostic markers for TCH should be planned prospectively and the molecular analyses should be considered.
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Figures

Figure 1

Selection of eligible patients according to the inclusion criteria: Screening TSH concentrations, a eutopic thyroid gland visualised by ultrasound and the L-T4 dosages at diagnosis and at 1 and 2 years of age.

Figure 2

Receiver operating characteristic (ROC) for screening TSH concentration (A), dosages of L-T4 at the age of 1 (B) and 2 (C) years in patients with CH predicting TCH. Subgroup analyses in patients with screening TSH <73 mU/L: dosages of L-T4 at the ages of 1 (D) and 2 (E) years.