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

Nicola Matejek (nicola.matejek@med.uni-heidelberg.de)
Division of Paediatric Endocrinology and Diabetes, University Children's Hospital Heidelberg
https://orcid.org/0000-0003-3833-4658

Sascha R. Tittel
Central institute for Biomedical Rechnology, Institute for Epidemiology and Medical Biometry University of Ulm

Holger Haberland
Sana Hospital Lichtenberg: Sana Klinikum Lichtenberg, Berlin

Tilman Rohrer
Department of paediatrics, University hospital Homburg-Saar

Eva-Maria Busemann
Catholic Children's Hospital Wilhelmsstift, Hamburg

Norbert Jorch
Protestant Hospital Bethel: Evangelisches Klinikum Bethel gGmbH, Bielefeld

Karl-Otfried Schwab
Division of Paediatric Endocrinology and Diabetes, University Hospital Freiburg

Joachim Wölfle
Department of Paediatrics, University Hospital Erlangen

Reinhard W. Holl
Central Institute for Biomedical Technology, Institute for Epidemiology and Medical Biometry University of Ulm

Markus Bettendorf
Division of Paediatric Endocrinology and diabetes, University Children's Hospital Heidelberg

---

Research Article

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

Posted Date: February 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-219858/v1

Version of Record: A version of this preprint was published at European Journal of Pediatrics on March 25th, 2021. See the published version at https://doi.org/10.1007/s00431-021-04031-0.

Title Page

Nicola Matejek[1], Sascha R. Tittel[2], Holger Haberland[3], Tilman Rohrer[4], Eva-Maria Busemann[5], Norbert Jorch[6], Karl-Otfried Schwab[7], Joachim Wölfle[8], Reinhard W. Holl[2], Markus Bettendorf[1]

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

[1]Division of Paediatric Endocrinology and Diabetes, University Children´s Hospital Heidelberg, Germany, nicola.matejek@med.uni-heidelberg.de; markus.bettendorf@med.uni-heidelberg.de;
[2]Central Institute for Biomedical Technology, Institute for Epidemiology and Medical Biometry, University of Ulm, Germany, sascha.tittel@uni-ulm.de; reinhard.holl@uni-ulm.de;
[3]Social-Paediatric Centre, Sana-Hospital Lichtenberg, Berlin, Germany, holger.haberland@sana-kl.de;
[4]Department of Paediatrics, University Hospital Homburg-Saar, Germany, tilman.rohrer@uks.eu;
[5]Catholic Children's Hospital Wilhelmstift, Hamburg, Germany, e.busemann@kindermvz.de;
[6]Department of Paediatrics, Evangelical Hospital Bethel, Bielefeld, norbert.Jorch@evkb.de;
[7]Division of Paediatric Endocrinology and Diabetes, University Hospital Freiburg, Germany, karl.otfried.schwab@uniklinik-freiburg.de;
[8]Department of Paediatrics, University Hospital Erlangen, Germany, Joachim.Woelfle@uk-erlangen.de;

[#]Corresponding author:
Nicola Matejek, M.D.
Division of Paediatric Endocrinology and Diabetes
Department of Paediatrics, University Hospital Heidelberg
Im Neuenheimer Feld 430
D-69120 Heidelberg, Germany
Nicola.matejek@med.uni-heidelberg.de
ORCID: 0000-0003-3833-4658

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_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_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_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_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_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

Not applicable/no specific funding available.

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 availabitlity

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-T_4) treatment at 2 years of age. The receiver operating characteristic (ROC) analysis was performed to identify cut-offs for screening TSH concentrations and L-T_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 daily cut-off L-T_4 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-T_4 treatment at 2 years of age in CH patients diagnosed via neonatal screening may be based on their screening TSH concentrations and individual L-T_4 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

fT_4: free serum thyroxine

HypoDok: Specialized prospective documentation software for CH

L-T_4: 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-T_4 dosages (µg/kg/day, µg/day) at diagnosis and at 1 and/or 2 years of age, respectively. The end of L-T_4 treatment was documented by checking a corresponding box on the date of withdrawal. The following items were extracted from the registry: L-T_4 dosages at 6 months of age, weeks of gestation, birth weight (g), Apgar-Score, serum TSH (mU/L) and fT_4 (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-T_4 during pregnancy, hyperthyroidism, anti-thyroid 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/m^2) expressed as standard deviation scores (SDS) (12) at the age of 2 years, the L-T_4 withdrawal period of 4 to 6 weeks and the results of psychomotor testing at the age of 2 years were extracted. L-T_4 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-T_4 beyond the 2^{nd} year of life (PCH) or cessation (TCH) of L-T_4 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-T_4 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-T_4 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-T_4 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-T_4 treatment for 4 to 6 weeks (n=111, 33%) and had to continue the treatment thereafter and/or required L-T_4 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 fT_4 concentrations were similar at confirmation of the diagnosis (table 2). L-T_4 dosages at start of therapy in PCH and in TCH were comparable (p=1.0). L-T_4 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-T_4 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-T_4 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-T_4 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-T_4 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-T_4 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-T_4 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-T_4 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-T_4 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-T_4 dosage is identical, as well the dosage for the highest specificity. Similar to the overall group we suggest a TCH predicting L-T_4 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-T_4 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-T_4 dosage was required in almost all of PCH patients (table 1B) while L-T_4 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-T_4 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-T_4 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-T_4 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-T_4 treatment in infancy in order to re-evaluate endogenous thyroid function may be made.

When calculating the exact L-T_4 dosage per kg body weight, the available galenic preparations and their strengths should be considered, the smallest incremental change in L-T_4 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-T_4 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-T_4 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.

References:

1. Krude H (2010): Diagnose, Therapie und Verlaufskontrolle der Primären, angeborenen Hypothyreose. https://www.awmf.org/leitlinien/detail/ll/027-017.html
2. Messina MF, Aversa T, Salzano G, Zirilli G, Sferlazzas C, De Luca F, Lombardo F (2015): Early discrimination between transient and permanent congenital hypothyroidism in children with eutopic gland. Horm Res Paediatr 84: 159-164
3. Lain S, Trumpff C, Grosse SD, Olivieri A, van Vliet G: Are lower TSH cutoffs in neonatal screening for congenital hypothyroidism warranted? Eur J Endocrinol. (2017) Nov; 177(5):D1-D12
4. De Deken X (2019): DUOX defects and their roles in congenital hypothyroidism. Methods Mol Biol 1982: 667-693
5. Fu C (2015): Mutation screening of DUOX2 in Chinese patients with congenital hypothyroidism. J Endocrinol Invest 38(11): 1219-24
6. Peters C, Nicholas A, Schoenmakers E, Lyons G, Langham S, Serra EG, Sebire NJ, Muzza M, Fugazzola L, Schoenmakers N (2019): DUOX2/DUOXA2 mutation frequently cause congenital hypothyroidism that evades detection on newborn screening in the united kingdom. Thyroid 29 (6): 790-97
7. Rabbiosi S, Vigone MC, Cortinovis F, Zamproni I, Fugazzaloa L, Persani L, Corbetta C, Chiumello G, Weber G (2013): Congenital Hypothyroidism with eutopic thyroid gland: Analysis of clinical and biochemical features at diagnosis and after re-evaluation. J Clin Endocrinol Metab 98 (4): 1395-1402
8. Scavone M, Carboni E, Stefanelli E, Romano G, Vero A, Giancotti L, Miniero R, Talarico V (2018): Prediction of transient or permanent congenital hypothyroidism from initial thyroid stimulating hormone levels. Indian Pediatr 55: 1059-61
9. Kanike, N., Davis, A., Shekhatwat, PS. (2017): Transient hypothyroidism in the newborn: to treat or not to treat. Transl Pediatr 17; 6(4): 349-358
10. Asena M, Demiral M, Ünal E, Öcal M, Demirbilek, H, Özbek MN (2020): Validity of 6th month L-Thyroxine Dose for Differentiation of Transient-Permanent Congenital Hypothyroidsm. J Clin Res Pediatr Endocrinol 12(3): 275-280

11. Kemper AR, Grosse SD, Baker M, Pollock AJ, Hinton DF, Shapira S (2020): Treatment Discontinuation within 3 Years of Levothyroxine Initiation among Children diagnosed with Congenital Hypothyroidism. J Pediatr 223: 136-40
12. Kromeyer-Hauschild K, Moss A, Wabitsch M (2015). Referenzwerte für den Body-Mass-Index für Kinder, Jugendliche und Erwachsene in Deutschland. Anpassung der AGA-BMI-Referenz im Altersbereich von 15 bis 18 Jahren. Adipositas 9: 123-127
13. Ruopp MD, Perkins NJ, Whitcomb BW, Schisterman EF (2008): Youden Index and optimal cou-point estimated from observations affected by a lower limit of detection. Biom J 50(3): 419-430
14. Nennstiel U e.a. National Screening Report Germany (2017) https://www.screening-dgns.de/Pdf/Screeningreports/DGNS-Screeningreport-d_2017.pdf
15. Krude H & Blankenstein O (2011): Treating patients not numbers: the benefit and burden of lowering TSH newborn screening cut-offs. Archives of Disease in Childhood 96 121–122
16. Cho MS, Cho GS, Park SH, Jung MH, Suh BK, Koh DG (2014): Earlier re-evaluation may be possible in pediatric patients with eutopic congenital hypothyroidism requiring lower L-Thyroxine doses. Ann Pediatr Endocrinol Metabol 19: 141-45
17. West R, Hong J, Derraik JG, Webster D, Heather NL (2020): Newborn screening TSH values less than 15 mIU/L are not associated with long-term hypothyroidism or cognitive impairment. J Clin Endocrinol & Metab 105 (9): e3329-38
18. Mengreli C, Kanaka-Gantenbein C, Panagiotis G, Magiakou MA, Christakopoulou I, Giannoulia-Karantana A, Chrousos GP, Dacou-Voutetakis C (2010): Screening for congenital hypothyroidism: The significans of threshold limit in false-negative results. J Clin Endocrinol Metabol Sep;95(9):4283-90
19. Srinivasan R, Harigopal S, Turner S, Cheetham T (2012): Permanent and transient congenital hypothyroidism in preterm infants. Acta Paediatr 101:e179-82
20. Léger J, Olivieri A, Donaldson M, Torresani T, Kurde H, van Vliet G, Polak M, Butler G (2014): European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis, and Management of Congenital Hypothyroidism. J Clin Endocrinol Metab 99: 1-22

21. Congenital hypothyroidism: 2020 consensus guideline update An ENDO-EUROPEAN NETWORK (ERN) initiative endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. Thyroid. 2020 Dec 3.doi: 10.1089/thy.2020.0333. Epub anhead of print. PMID:33272083
22. Oron T, Lazar L, Shimon BY, Tenenbaum A, Yackobovitch-Gavan M, Meyerovitch J, Philip M, Lebenthal Y (2018): Permanent vs transient congenital hypothyroidism: Assessment of predictive variables. J Clin Endocrinol Metab 103(12): 4428-4436
23. Lain SJ, Bentley JP, Wale V, Roberts CL, Jack M, Wilcken B & Nassar N (2016): Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcome: a population-based record-linkage study. Lancet: Diabetes and Endocrinology 4: 756–765
24. Park IS, Yoon JS, So CH, Lee HS, Hwang JS (2017): Predictors of transient congenital hypothyroidism in children with eutopic thyroid gland. Ann Pediatr Endocrinol Metab 22(2)
25. Higuchi S, Hasegawa Y (2019): Levothyroxine dosages less than 2.4 μg/kg/day at 1 year and 1.3 μg/kg/day at 3 years of age may predict transient congenital hypothyroidism. Clin Pediatr Endocrinol 28(4): 127–133
26. Di Dalmazi G, Assunta M, Carlucci DS, Cesidio G, Napolotano G, Patrizio C, Bucci I (2020): A detailed analysis of the factors influencing neonatal TSH: Results from a 6-year congenital hypothyroidism screening program. Front Endocrinol 17 July
27. Favresse J, Burlacu MC, Maiter D, Gruson D (2018): Interferences With Thyroid Function Immunoassays: Clinical Implications and Detection Algorithm. Endocrine reviews 39(5): 830-850
28. Van der Kaay DC, Wassermann JD, Palmert MR (2016): Management of neonates born to mothers with graves´disease. Pediatrics137(4):e20151878.
29. Berger R, Rath W, Abele H, Garnier Y, Kuon RJ, Maul H (2019): Reducing the risk of preterm birth by ambulatory risk factor management. Dtsch Ärzteblatt Int. Dec 13; 160(50): 858-864
30. Bongers-Schokking JJ, Resing WCM, de Rijke YB, de Ridder MA, de Muinck Keizer-Schraman SMPF (2013): Cognitive development in congenital hypothyroidism: Is overtreatment a greater threat than undertreatment? J Clin Endocrinol. Nov; 98(11):4499-506.

Figures

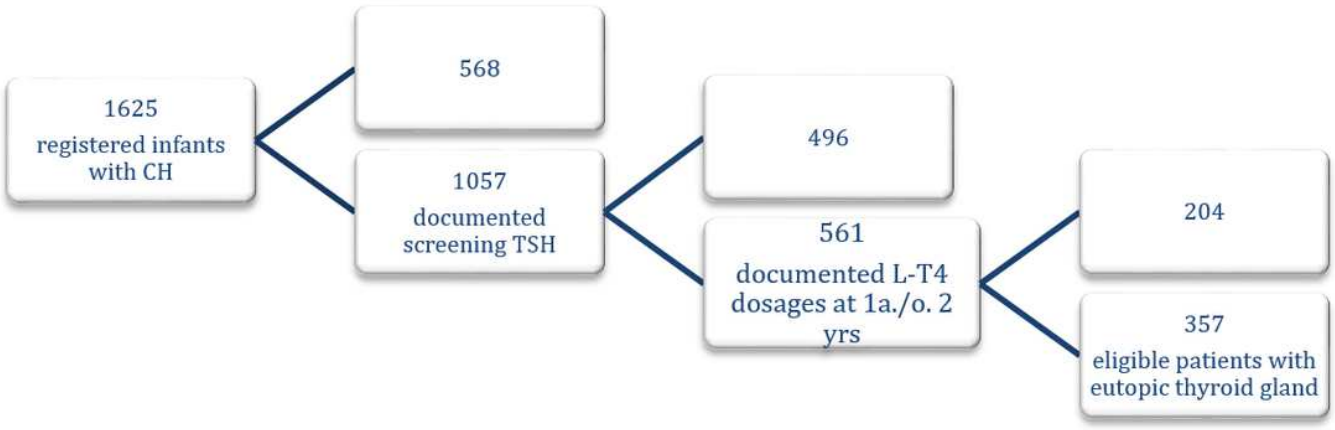

Figure 1

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

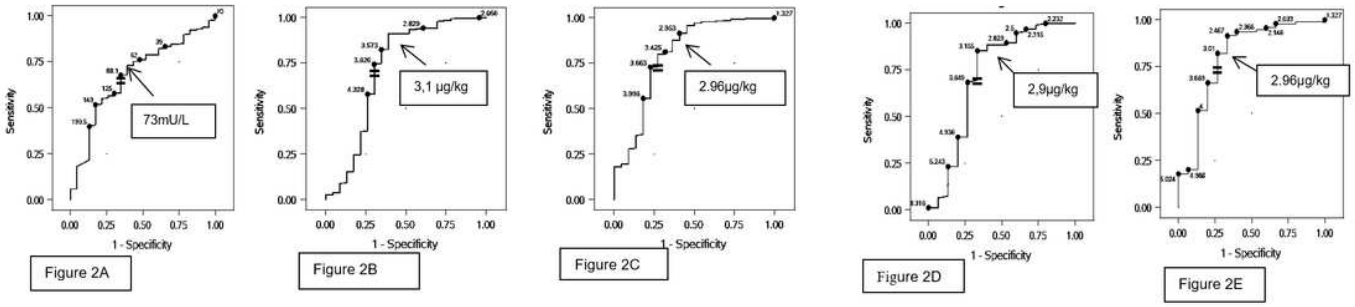

Figure 2

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.