Guideline Adherence and Registry Recruitment of Congenital Primary Hypothyroidism: Data From the German Registry for Congenital Hypothyroidism (HypoDok)

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Research

Keywords: standardized documentation, quality assurance, longitudinal comparison, multicentre database
Abstract

Background: Neonatal screening for congenital primary hypothyroidism (CH) is mandatory in Germany but medical care thereafter remains inconsistent. Therefore, the multicentre database HypoDok was analysed to evaluate the implementation of evidence-based guidelines in the care of children with CH and to assess the number of patients in this registry of the German society of paediatric endocrinology and diabetology (DGKED).

Methods: HypoDok includes the prospective documentation of 1,630 patients with CH from 50 centres in Germany and Austria. Inclusion criteria were (i) date of birth between 10/2001 and 05/2020 and (ii) increased TSH at screening and/or confirmation. Parameters regarding diagnosis, therapy and follow-up were extracted. The number of registered patients was compared to the number in the report of the German Society for Neonatal Screening (DGNS). The cohort was divided into 2 groups, before (A) and after (B) guideline publication in 02/2011, to assess guideline’s influence on medical care.

Results: 659 patients (62% female) were eligible and analysed as group A (n=327) and group B (n=332) representing 17.5% and 6.7% of CH patients identified in the German and Austrian neonatal screening program during the respective time period. Treatment start and thyroxin doses were similar in both groups and consistent with recommendations. Regular follow-ups were documented in both groups including five appointments in the first and three in the second year of life. Ultrasound of the thyroid gland was performed in 92.6% (A) and 92.1% (B) of the patients. In the first three years of life, 46.4% (A) and 40.0% (B) of the patients underwent audiometry, EQ/IQ testing was performed in 49.3% (A) and 24.8% (B) (p<0.01), respectively.

Summary: While documentation of care for patients with CH by paediatric endocrinologists seems to be established, only a minority of all affected patients is included in HypoDok. Thus, the care and outcome of the majority of patients with CH remains uncertain. Therefore, comprehensive documentation as an important instrument of quality assurance and evidence-based medicine should be legally enforced and officially funded in order to record, comprehend and optimize care and outcome in patients with rare diseases such as CH, irrespective of treatment provider.

Introduction

Congenital primary hypothyroidism (CH) is the most common endocrine disease with a prevalence of 1:2,000-3,000 in Europe and thereby classified as a rare disease. 160 to 280 patients with CH are detected in the neonatal screening in Germany per year [1].

After introduction of the neonatal screening in Germany and Austria in the 1970s, the symptoms of CH such as growth retardation and delay of psychomotor development can be prevented by an early treatment start with levothyroxine (L-T₄) [2, 3].
Guidelines were introduced to harmonise treatment strategies and allow evidence-based patient care [4]. Dissemination and compulsory implementation of medical guidelines in clinical care remain limited [5]. Adherence to clinical guidelines varies considerably. Reinforcement and education are essential to enhance overall adherence [6].

The German guideline for CH was published in 02/2011 in accordance with international recommendations and is currently under revision [7, 8]. The core statements reflecting evidence level S2k (consensus-based guideline), which were evaluated with the HypoDok registry, are highlighted in Table 1. The Austrian Working Group for Paediatric Endocrinology and Diabetology (APEDÖ) revised its recommendations based on the German guideline in 2017 [9].

Registries are built to improve patient care and to install instruments of quality control in treating rare endocrine diseases [10]. They also collect data for epidemiological and clinical research activities. The German society of paediatric endocrinology and diabetology (DGKED) launched the registry HypoDok as an initiative for quality improvement [11, 12]. The aim of this study was to compare the documented care for patients with CH to the evidence-based guideline recommendations in order to explore guideline adherence and to assess overall acceptance of HypoDok as a tool for quality management.

Patients/methods

Based on the anonymised multicentre data collected from the registry a descriptive evaluation was carried out as an observational study. The data were collected prospectively using the software HypoDok, which was developed at the Institute for Epidemiology and Medical Biometry at Ulm University and made available to all interested centres in Germany and Austria free of charge [12].

The registry was initiated by the German Society for Paediatric Endocrinology and Diabetology (DGKED) on 01/2000 to harmonize the quality of diagnostics and treatment of endocrine disorders across Germany and Austria. For the transfer of pseudonymised data for analysis, consent was obtained from the State Data Protection Commissioner for Saxony-Anhalt. Data collection has been approved centrally by the ethics committee of the University of Magdeburg.

Fifty participating centres in Germany (48) and Austria (2) recorded data of a total of 1,630 patients (as of 05/2020) with CH in the HypoDok. Inclusion criteria were (i) date of birth between 10/2001 and 05/2020 and (ii) elevated screening TSH and/or elevated serum TSH at confirmation (> 10 mU/l) (Fig.1). An elevated screening TSH was defined in the database when the option "Screening TSH normal: no" was ticked or when values > 15 mU/l were entered. To gain comparable populations for data analysis nine years after the introduction of the guideline (2011), the period prior to the introduction of the guideline was equally selected as nine years. As a result, a total of 659 HypoDok patients fulfilled the inclusion criteria.

The primary target parameters were defined based on the statements of the German AWMF guideline [13]: age at start of therapy [days of life]; serum TSH [mU/l]; serum T4 [µg/dl]; serum fT4 [ng/l]; recommended
L-T₄ dose [µg/day]; duration until TSH normalization (< 10 µU/ml) after start of therapy [days]; IQ/development test result normal [yes/no]; presentation in 1/2/4 weeks after start of therapy [yes/no]; audiometry [yes/no]; thyroid ultrasound [yes/no]; thyroid scintigraphy [yes/no]; TPO-AK/TRAK determined [yes/no]. Here, a normal IQ test was defined by the previous assessment of the treatment facility: IQ/development test result normal: yes.

The target parameters were evaluated separately in a descriptive approach for the two groups using SAS Version 9.4. The results are presented as median and interquartile range (IQR; continuous variables) or as percent (binary and categorical variables). The differences between the two groups are calculated for the continuous parameters using the Wilcoxon rank sum test and for the percentages using the Chi-square test. The p-values were adjusted for multiple testing using the Holm method. A two-sided p-value of less than 0.05 was defined to be significant.

For most of the target parameters not all patients had data available, so that the number of evaluated patient data is shown separately.

To assess the coverage of the registry, the number of patients recorded in HypoDok and included in this study was compared with the number of new diagnoses of congenital hypothyroidism detected in the German/Austrian newborn screening per year. Data of the German neonatal screening report for the years 2004-2017 were available, data from Austria for the years 2014-2018.

Results

Demographic characteristics of all 659 patients (group A: n=327 patients; B: n=332 patients) are listed in Table 2. Of these patients, 2.2 % (7 in total) in group A and 6 % (20 in total) in group B were Austrian. 63.6% and 60.5% of the patients in groups A and B were female.

A comparison of patients in the registry with those from the German neonatal screening registry shows that HypoDok documents an average of 17.5 % of the patients registered by the German neonatal screening with confirmed diagnosis: before the introduction of the guideline 19.1 % of the patients, after the introduction of the guideline 15.8 % of the patients. Austrian data were only available after the introduction of the guideline, here the documentation rate in the HypoDok database was 6.7 % compared with the Austrian neonatal screening registry.

Core statements of the guideline regarding diagnostics (Table 3a)

The complete evaluation of core statements of the guideline with regard to diagnostics is listed in Table 3a. The confirmation of the diagnosis CH by determination of fT₄ and/or TT₄ was documented in 34.9% (n=327) of the patients in group A and in 24.4% (n=332) of the patients in group B (p=0.02). Audiometry was performed in 24.4 % of patients in group A (n=172) in the time period 14 days before/after the start of therapy with L-T₄ in group B in 11.8 % (n=229) within this time interval (p=0.01).
Core statements of the guideline regarding treatment (Table 3b)

With no significant differences between the groups initially, therapy was carried out according to the guidelines as shown in Table 3b.

Core statements of the guideline regarding treatment monitoring (Table 3c)

Table 3c shows the evaluation of the guideline's core statements regarding treatment monitoring. A significant difference was found with regard to the control of psychomotor development over the course of treatment; 49.3% of patients (group A, n=302) and 24.8% of patients (group B, n=327) (p<0.001) were tested.

Discussion

Our multicentre study compared CH patient care documented in HypoDok with evidence-based recommendations. The majority of the surrogate parameters which assessed the adherence to the core statements were comparable in both groups, irrespective of guideline publication. However, few significant differences between the two cohorts before and after guideline introduction were apparent. This continuously high level of care can be partly explained by the fact that the data of the registry is derived from paediatric endocrinologists, who were directly or indirectly involved in its development as being members of the guideline developing professional society.

The recommendations regarding diagnostics (structural quality) as well as therapy control (process quality) were implemented, but not fully documented.

The low percentage of patients with documented TT4/fT4 serum concentration at initial diagnosis is one example of suggested documentation gaps, as low TT4/fT4 levels are precondition for diagnosis confirmation. This may arise due to a structural fault of the database, that the date of diagnosis can be entered without underlying TT4/fT4 levels.

Another example is the low number of documented hearing tests at the start of treatment, although newborn hearing screening has been a standard service of public health insurance since 01/2009 in Germany and has been regularly reimbursed since 10/2010 [14]. This problem of incomplete documentation in the HypoDok, especially at the beginning of treatment, is well known and has already been described by Ellerbroek et al. [11]. The reason for this may be that many patients were only referred to paediatric endocrinologists over the course of the first months, as the guideline only recommends referral within 3 months. Subsequent documentation seems incomplete.

Furthermore, improvement of psychomotor development assessment documentation is required, especially in group B (24.8%; group A 49.3%). It can be assumed that these assessments were only carried out during the course of therapy if there was a clear clinical indication for developmental retardation. Experienced examiners seem to preselect patients who need a formal assessment, which is however in contrast to current guideline recommendations. The rate of IQ/EQ testing may be
underestimated in group B, as some patients are still very young and therefore not all data have been collected so far. Further reasons why psychomotor development has not been regularly checked may be additionally a lack of compliance in the patient family. This may be due to fear of receiving an unfavourable result, a lack of understanding of the importance of the test and the time required for the extensive testing procedure [11]. Here, the implementation of shorter screening tests could increase patient compliance.

In general, a very variable level of adherence to existing guidelines has already been observed by the treating physicians for a wide range of paediatric diseases. Guideline adherence regarding the use of antibiotics in infectious disease is a highly investigated subject [15-17]. The studies showed no change of management in urinary tract infections after introduction of the guideline, whereas the use of antibiotics in CAP was evidence-based. Overall, it could be shown that disregarding evidence-based recommendations carries risks.

Vezzani et al. examined guideline adherence in adult patients with primary hypothyroidism [18]. Here, a satisfactory adherence to the European recommendations was found, with the exception of the L-T4 starting dose.

The time period, in which guidelines are strictly adhered to has been analysed by Ament et al. The authors could show that already one year after the publication of guidelines the degree of their implementation is starting to decrease [19]. Since the importance of guidelines can also be demonstrated by a systematic review [20], existing considerations for improving the implementation of guidelines should also be considered for CH. The successful integration of guideline recommendations can lead to a high, uniform standard of care, save financial resources and improve patient outcome [21]. The aim to improve guideline implementation should also include the elevation of patient compliance. Provision of practice aids like checklists or reminders on the side of clinicians and implementation of diaries on the side of patients may improve the problem next to a clear documentation of patient history by healthcare providers [22].

Matlock et al. followed this two-sided approach and presented methods to equally promote guideline adherence by improvement of patient care through the responsible physicians and also in a CH patient-based manner: [23]: these included, e.g., compiling and continuation of patient records in a database, and education programs of treating physicians and patient families on guideline recommendations. Furthermore, patient registries should also be strengthened as a suitable instrument for quality assurance [24].

The HypoDok registry documents a satisfactory adherence to the core statements of the guideline regarding treatment. Thus, the basic preconditions for achieving the best possible patient outcome with adequate therapy were given in both cohorts [25-27]. The adherence concerning diagnostics and treatment monitoring by professionals however can be improved in both groups. Alternatively, guideline recommendations on IQ/EQ-testing in routine care might require re-evaluation.
Overall, the results cannot easily be transferred to the overall quality of care of patients with CH in Germany and Austria, as only 17.5% of expected patients with CH in Germany and even 6.7% in Austria are currently documented in *HypoDok* at the time interval analysed here. This low reporting frequency is due to the fact that the database is known and used among experts (paediatric endocrinologists), but not widely used by paediatricians in private practice. This could indicate that a significant number of patients with CH are not seen by paediatric endocrinologists. The use of the *HypoDok* registry should be seen as an opportunity to document and ensure the quality of care for patients with CH and to adapt it to current clinical standards. This way, the treating physician can also compare and adapt patient care with the existing data on the basis of regular database reports. Compiling of genetic sequencing data combined with clinical information and phenotypic data including blood tests could further help to subtype patients suffering from CH into clinically relevant subgroups. Overall, management of patients in databases has not only been identified by the professional society as one of the appropriate instruments for quality assurance. Administrative bodies such as the European Commission or the US-American National Institute of Health also started programs for rare diseases. One example is the European initiative of European Reference Networks (ERN) for different specialities like Endo-ERN for rare endocrine conditions in order to share knowledge to assure and maintain high level of patient care across Europe. As part of this initiative, patient cohort documentation in databases in the care of rare diseases such as CH is important to ensure structural quality. In case of CH in Germany and Austria, the centre-specific obligation for documentation will have to be strengthened, for example by means of financial incentives. The authors acknowledge that the current setup of the registry (local documentation with periodic extraction of pseudonymized data) may not be optimal for paediatricians taking care of very few patients with CH. Long-lasting adherence to guidelines and respective documentation remains difficult, since in principle, it is easier to motivate participating professionals and patients over a limited period of time [28].

Furthermore, a legal requirement to keep these patients in registries should be discussed. As the low number of documented CH patients shows, the implementation of the guidelines recommendations of the professional society can only be checked and improved by either obligation or standardized acquisition of data that facilitates documentation in order to guarantee adequate care.

The fact that legal requirements and financial support by the state are helpful in this respect is not only reflected in the reporting frequency of newborn screening, but also in other fields of paediatrics. For example, in oncology approximately 95 % of childhood cancers are documented in the German Childhood Cancer Registry by appropriate legal requirements [29].

**Conclusions**

In summary, the presented data suggest that in both groups a guideline-adherent treatment initiation is implemented. This is the prerequisite to achieve a regular physical and psychomotor development in patients with CH. However, direct documentation of IQ/EQ seems difficult in routine care. *HypoDok* can currently only monitor a small proportion of affected patients, primarily those treated by paediatric endocrinologists. In order to maintain the best possible standard of care, this rare disease should be
treated in a centre with expertise in paediatric endocrinology [13]. In order to monitor and further optimize care, complete documentation in a registry designed for this purpose such as HypoDok is mandatory. Here, support through development of law enforced requirements may increase the frequency of documentation.

**Abbreviations**

Ab= antibody

APEDÖ= Austrian Working Group for Paediatric Endocrinology and Diabetology

AWMF= Association of the Scientific Medical Societies of Germany

CH= congenital primary hypothyroidism

DGKED= German Society for Paediatric Endocrinology and Diabetology

DGNS= German Society for Neonatal Screening

ERN= European Reference Network

fT4= free thyroxine

HypoDok= German registry for congenital hypothyroidism

L-T_{4}= levothyroxine

S2k = consensus-based guideline

TRH= thyrotropin-releasing hormone

TSH= thyroid-stimulating hormone

TSHR-Ab= Thyroid stimulating hormone (TSH) receptor antibody

TT4 = total thyroxine

**Declarations**

**Ethics approval and consent to participate**

For the transfer of pseudonymised data for analysis, consent was obtained from the State Data Protection Commissioner for Saxony-Anhalt. Data collection has been approved centrally by the ethics committee of the University of Magdeburg.

**Consent for publication**
Not applicable.

**Availability of data and materials**

The datasets generated and analysed prospectively in the registry *HypoDok* are available in the *HypoDok* repository, [https://buster.zibmt.uni-ulm.de/projekte/Hypothyreose/update](https://buster.zibmt.uni-ulm.de/projekte/Hypothyreose/update).

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

None.

**Authors' contributions**

J. Thomann, M. Bettendorf: contribution to study concept and design, analysis and interpretation of data, preparation of manuscript; S. R. Tittel, R. W. Holl: contribution to study concept and design, analysis and interpretation of data, revising manuscript, administration of *HypoDok*-registry; J. Wölle: analysis and interpretation of data, revising manuscript; E. Voss, R. Oeverink, K. Mohnike, S. Fricke-Otto, K. Kapelari: revising manuscript

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We highly acknowledge the work of all clinicians who helped to set up the *HypoDok* database through their documentation.

**References**


**Tables**

**Table 1** Excerpt of statements included in the German Guideline for Primary Congenital Hypothyroidism (CH) [13]
| Statement 1 | Initial TSH determination sufficient to initiate confirmation, TRH test not required |
| Statement 2 | Confirmation of CH by low serum fT4 or TT4 concentrations |
|            | Premature infants/neonates in intensive care: fT4 and TT4 are required at same time |
| Statement 3 | Ultrasonography of thyroid gland should be performed |
|            | Only restrictive use of scintigraphy |
| Statement 4 | Hearing test: at confirmation and in the course of treatment |
| Statement 7 | Start L-T₄-Therapy as early as possible |
|            | At least before day 14 |
| Statement 8 | Initial daily dose 10 µg/kg - 15 µg/kg |
| Statement 9 | Timepoints for follow-up: |
|            | After 1, 2 and 4 weeks after start of therapy |
|            | Subsequently at 3-month intervals during the first two years of life |
| Statement 11 | Monitoring of psychomotor development: |
|              | During the first two years of therapy |
|              | Before start of school |

**Table 2** Demographic characteristics of CH patients, compared before and after guideline appearance (groups A and B)
<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
<td>40 (38;41) (n=314)</td>
<td>40 (38;41) (n=327)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Birth weight [g]</strong></td>
<td>3,370 (2,951;3,690) (n=320)</td>
<td>3,395 (2,970;3,730) (n=330)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Birth length [cm]</strong></td>
<td>51 (49;53) (n=259)</td>
<td>51 (49;53) (n=324)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>10 min-APGAR-Score</strong></td>
<td>10 (8;10) (n=322)</td>
<td>10 (8;10) (n=319)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Parental target height (Tanner) [cm]</strong></td>
<td>172.5 (168.5; 176.5) (n=271)</td>
<td>172.3 (168;176) (n=274)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Female [%]</strong></td>
<td>63.6 (n=327)</td>
<td>60.6 (n=332)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Premature babies (&lt;37 weeks) [%]</strong></td>
<td>8.6 (n=314)</td>
<td>10.4 (n=327)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Thyroid disorder of the mother [%]</strong></td>
<td>17.2* (n=303)</td>
<td>27.0* (n=307)</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>anti-thyroid drug intake during pregnancy [%]</strong></td>
<td>2.0 (n=98)</td>
<td>4.0 (n=75)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Results are given as median (Q1;Q3) or in %. Q1= first quartile, Q3= third quartile, Statistics: Wilcoxon Rank Sum Test/Chi-Square Test, *p<0.05

Table 3 Description and comparison of both groups according to the guideline recommendations: a) Diagnostic, b) Treatment, c) Treatment monitoring
<table>
<thead>
<tr>
<th></th>
<th>Group A „before guideline“</th>
<th>Group B „after guideline“</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a) Diagnostics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT4 and/or fT4 determined at diagnosis [%]†</td>
<td>34.9* (n=327)</td>
<td>24.4* (n=332)</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum TSH determined at diagnosis [%]†</td>
<td>36.1* (n=327)</td>
<td>23.2* (n=332)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ultrasonography performed [%]</td>
<td>92.6 (n=323)</td>
<td>92.1 (n=328)</td>
<td>0.86</td>
</tr>
<tr>
<td>Scintigraphy performed [%]</td>
<td>5.0 (n=318)</td>
<td>1.6 (n=309)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hearing test 14 days around start of treatment [%]</td>
<td>24.4* (n=172)</td>
<td>11.8* (n=229)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>b) Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at start of treatment [d]</td>
<td>6 (5;9) (n=316)</td>
<td>6 (5;8) (n=318)</td>
<td>0.55</td>
</tr>
<tr>
<td>Dose of L-T4 at start [µg/d]</td>
<td>50 (50;50) (n=122)</td>
<td>50 (50;50) (n=131)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>c) Treatment monitoring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow ups during first year of life (n)</td>
<td>5 (3;7) (n=293)</td>
<td>5 (3;7) (n=320)</td>
<td>0.58</td>
</tr>
<tr>
<td>Follow ups during second year of life (n)</td>
<td>3 (2;4) (n=255)</td>
<td>3 (2;4) (n=259)</td>
<td>0.33</td>
</tr>
<tr>
<td>Follow up 1 week after start of treatment [%]</td>
<td>24.2 (n=327)</td>
<td>32.5 (n=332)</td>
<td>0.17</td>
</tr>
<tr>
<td>Follow up 2 weeks after start of treatment [%]</td>
<td>31.2 (n=327)</td>
<td>38.0 (n=332)</td>
<td>0.41</td>
</tr>
<tr>
<td>Follow up 3-4 weeks after start of treatment [%]</td>
<td>34.0 (n=327)</td>
<td>41.9 (n=332)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
Results are given as median (Q1;Q3) or in %. Q1= first quartile, Q3= third quartile, statistics: Wilcoxon Rank Sum Test/Chi-Square Test, *p<0.01, †= even though “serum TSH determined at diagnosis” is part of the inclusion criteria for CH, the percentage of documented measurements is low as “abnormal screening TSH” is sufficient for patient’s inclusion in HypoDok. A documentation gap is to be assumed, since confirmatory testing is essential for diagnosis.

Figures

Figure 1

HypoDok eligible patients according to inclusion criteria (abnormal screening TSH/venous TSH > 10 mU/L)