Neonatal Screening for Congenital Hypothyroidism Based on Thyroxine, Thyrotropin, and Thyroxine-Binding Globulin Measurement: Potentials and Pitfalls


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Context: The Dutch T₄-TSH-TBG-based neonatal screening program detects patients with congenital hypothyroidism (CH) of thyroidal (CH-T) as well as central (CH-C) origin. The numbers and characteristics of true-positive and false-positive referrals will differ from other, predominantly TSH-based, screening methods.

Objective: The present study describes the characteristics of the referred neonates, both CH patients and false positives, and of the reported CH patients with a false-negative screening result born in the study period.

Design, Setting, Patients, and Main Outcome Measure: For each referred child born between April 1, 2002, and May 31, 2004, screening results and first venous sample results were recorded and classified as referred neonate born between April 1, 2002, and May 31, 2004, screening results and first venous sample results were recorded and classified as transient or permanent CH-T or CH-C or as no CH.

Results: In the study period, 430,764 children were screened. Of these, 772 children with abnormal screening results, 224 (29%) had CH; another 13 CH patients did not have abnormal screening results, giving an overall CH incidence of 1:1800. Incidences of permanent CH, transient CH-T, permanent CH-C, and transient CH were 1:2200, 1:2500, 1:21,000, and 1:12,000, respectively. The most frequent explanations for the 548 false-positive referrals (71% of the referred cohort) were severe illness and TBG deficiency (occurring in 198 and 200 children, respectively).

Conclusions: The Dutch incidence figures for CH belong to the highest worldwide, suggesting that the T₄-TSH-TBG screening program is an efficient method to detect CH of variable etiology and severity. Still, a small percentage of children with CH escaped detection via this screening approach. Severe illness and TBG deficiency appear to be responsible for the majority of false-positive referrals. (J Clin Endocrinol Metab 91: 3370–3376, 2006)

Thyroid hormone is important for normal development of the central nervous system. The critical period for the central nervous system to be dependent on thyroid hormone is known to extend from fetal life until at least the first 2 yr after birth. Therefore, children with congenital hypothyroidism (CH), if left untreated, are at risk for impaired cognitive and motor development. In many countries, neonatal screening programs have been instituted aiming to prevent cerebral damage by early initiation of T₄ supplementation.

Severe countries, such as Japan, Australia, and most European countries, have a TSH-based screening program, whereas many states in North America have a T₄-based screening program with additional measurement of TSH in the samples with the lowest T₄ concentration. Both strategies are capable of detecting CH of thyroidal origin (CH-T), but will miss (the majority of) patients with CH of central origin (CH-C). Recently, the Dutch T₄-TSH-TBG screening method has proven its outstanding ability to detect patients with CH-T as well as CH-C, and the extra costs compared with other screening methods are acceptable.

In addition to the difference in the proportion of patients with CH-T and CH-C detected by a T₄-TSH-TBG screening method (true positives) compared with other methods, such an approach may also have consequences for the numbers and characteristics of patients with an abnormal screening result but without CH (false positives). In the present study, thyroid hormone determinants and clinical characteristics were analyzed for all children born in a 2-yr period with an abnormal screening result (true and false positives) and of the reported patients with CH not detected by the neonatal screening (false negatives). This design allowed us: 1) to investigate the capability of the T₄-TSH-TBG method to detect CH of various etiology and severity; and 2) to calculate the incidence of various types of CH.

Patients and Methods

Screening method (Fig. 1)

The Dutch neonatal CH screening method is primarily based on T₄ measurement in filter paper blood spots. Sampling is performed between 4 and 7 d after birth. The concentration of T₄ expressed as sp
score, is compared with the day mean. If $T_4$ is $-0.8$ s.d. or less, TSH concentration (expressed in microunits per milliliter) is additionally measured. A $T_4$/TBG ratio is calculated as follows: $(T_4 \times 5.1) \times \frac{1}{[TBG]} \times 1000$. If $T_4$ is $-3.0$ or less or TSH is $50$ U/ml or more, children are immediately referred to a pediatrician. In case of a dubious result ($-3.0 < T_4 < -0.8$ s.d. in combination with a $T_4$/TBG ratio $\leq 8.5$ and/or $20 < TSH < 50$ U/ml), a second heel puncture is performed and TSH, T4, and TBG are repeated. Children are referred to a pediatrician after a second heel puncture if the result is dubious again or abnormal (4). For children born with a gestational age (GA) of 36.0 wk or less in combination with a birth weight (BW) of 2500 g or less, the referral criterion is based on TSH; if TSH is at least 20 U/ml, the child is referred, if TSH is at least 20 U/ml but less than 50 U/ml, the result is considered dubious and a second heel puncture is performed, after which the child is referred if the result is dubious again or abnormal (4).

In the following text, abnormal screening result refers to one heel puncture sampling with an abnormal screening result or two with a dubious result.

Patients

The study was coordinated and executed by the department of pediatric endocrinology of the Emma Children’s Hospital Academic Medical Center (AMC) in collaboration with the Dutch Health Administrations (DHA) and the Netherlands Organization of Applied Scientific Research (TNO). The study protocol was approved by the Institutional Review Board (which judges medical ethical aspects of research proposals) of the AMC and the Privacy Committee of the Dutch CH Screening Board (which judges logistic, scientific, and ethical aspects of research proposals concerning neonatal screening). The studied patients, living all over the country, were not actually referred to the Emma Children’s Hospital AMC; only their medical data were recorded.

When a child is born in The Netherlands, parents get a heel puncture package with written information upon registering the birth of their child. When the health worker visits the parents’ home, the heel puncture is performed only after parents give their implicit consent.

The regional CH screening laboratory notifies the DHA on abnormal and dubious CH screening results. Whenever referral to a pediatrician is indicated, the DHA immediately contacts the general practitioner. For those children born from April 1, 2002, until May 31, 2004 (referred to as the study period), with an indication for referral, the DHA has sent faxes with data containing heel puncture results, GA, BW, and the name of the general practitioner to the AMC. This enabled the researchers of the AMC to contact the pediatrician and ask for the laboratory and clinical data of the referred child.

TNO documents the screening results and diagnostic findings of Dutch children with abnormal screening results and data of CH patients missed by neonatal screening, when reported by pediatricians. All local hospitals can determine free T4 (FT4) and TSH, but for less common thyroid function tests (such as TBG, thyroglobulin, or $T_4$), material has to be sent to a few specialized laboratories (e.g., the AMC). Tests for urinary iodine and low-molecular-weight iodinated material are exclusively performed in the AMC. The AMC keeps records of patients whose blood or urine samples were sent to confirm or specify the diagnosis of CH or whose pediatrician consulted the Department of Pediatric Endocrinology for advice. Usually this concerns referred patients with abnormal CH screening results, but occasionally the records belong to CH patients with normal screening results (false negatives). To get the most complete cohort of CH patients born in the study period, datasets of TNO and AMC were combined.

Classification based on screening results and diagnostic work-up

For all subjects born during the study period, CH screening results, first venous plasma FT4 and TSH (and optionally TBG), GA, BW, and any remarkable clinical characteristics (e.g., family history and maternal thyroid function) were recorded. Based on the provided information, diagnosis was classified as no CH, transient CH, or permanent CH. The category of no CH was subdivided according to the alleged reason of the abnormal screening result: severe illness, TBG deficiency (total when $TBG < 300$ nmol/liter; partial when $TBG < 300$ nmol/liter), errors in the screening procedure, exchange blood transfusion, delayed blood sampling, pre-/dysmaturity, and no obvious explanation. The diagnosis of transient CH was further classified into transient CH-T or transient CH-C. When known, the cause of transient CH was documented. The diagnosis of permanent CH was further classified into CH-T, CH-T21 (i.e., CH-T related to trisomy 21) (8), CH-C, or CH not yet specified.
Reference ranges for children born at term at the age of 2–6 wk for $T_4$, $FT_4$, TSH, and TBG are 6.5–16.3 μg/dl (84–210 nmol/liter), 0.9–2.2 ng/dl (12–28 pmol/liter), 1.7–9.1 μU/ml, and 1.0–4.5 mg/dl (160–750 nmol/liter), respectively (9). For 2-wk-old preterm children, the reference ranges of $T_4$, $FT_4$, and TSH (mean ± sd) of Williams et al. (10) were adopted: for GA 23–27 wk, $T_4$ is 1.4 ± 0.5 ng/dl (18.6 pmol/liter), and TSH is 3.9 ± 2.7 mU/liter; for GA 28–30 wk, $T_4$ is 6.6 ± 2.3 μg/dl (85 nmol/liter), $FT_4$ is 1.6 ± 0.4 ng/dl (21.2 pmol/liter), and TSH is 4.9 ± 1.2 mU/liter; and for GA 31–34 wk, $T_4$ is 9.1 ± 3.6 μg/dl (117 nmol/liter), $FT_4$ is 2.0 ± 0.4 ng/dl (25.2 pmol/liter), and TSH is 3.8 ± 9.3 mU/liter.

### Results

Between April 1, 2002, and May 31, 2004, 432,082 children were born in The Netherlands of whom 430,764 (99.7%) participated in the neonatal screening program. In total, 772 children (one for every 558 screened children) with an abnormal CH screening result were referred, 534 after one heel puncture, 238 after the second one. In 190 patients (25%), permanent CH and in 34 (4%) transient CH was diagnosed (Table 1). Of those children referred because of $T_4$ of 3.0 sd or less (n = 474), 72 (15%) had permanent CH, 12 (3%) had transient CH, and 390 (82%) had no CH (Table 1). All 112 children (one for every 558 screened children) with an abnormal result, was performed despite a normal first result; in two, both with $T_4$ of 3.0 sd or less and a delay of more than 2 wk in heel puncture sampling (n = 2500 g) in combination with normal GA (>36.0 wk) with:

### TABLE 1. Classification of CH according to the (first) heel puncture $T_4$

<table>
<thead>
<tr>
<th>Heel puncture measurements</th>
<th>TSH (μU/ml)</th>
<th>Interpretation</th>
<th>No CH</th>
<th>Transient CH</th>
<th>Permanent CH</th>
<th>No. of referrals</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_4 ≤ -3.0$</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>$TSH ≤ 50$</td>
<td>0</td>
<td></td>
<td>2</td>
<td>2</td>
<td>53</td>
<td>11</td>
</tr>
<tr>
<td>$20 ≤ TSH &lt; 50$</td>
<td>1</td>
<td></td>
<td>7</td>
<td>3</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>$TSH &lt; 20$</td>
<td>389</td>
<td></td>
<td>5</td>
<td>16</td>
<td>410</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>390</td>
<td></td>
<td>12</td>
<td>72</td>
<td>474</td>
<td></td>
</tr>
<tr>
<td>$-3.0 &lt; T_4 ≤ -0.8$</td>
<td></td>
<td></td>
<td>0</td>
<td>2</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>$TSH ≥ 50$</td>
<td>0</td>
<td></td>
<td>2</td>
<td>2</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>$20 ≤ TSH &lt; 50$</td>
<td>158</td>
<td></td>
<td>8</td>
<td>18</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>$TSH &lt; 20^a$</td>
<td></td>
<td></td>
<td>158</td>
<td>22</td>
<td>118</td>
<td>298</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>158</td>
<td></td>
<td>22</td>
<td>118</td>
<td>298</td>
<td></td>
</tr>
<tr>
<td><strong>Total (of 430,764 screened neonates)</strong></td>
<td><strong>548</strong></td>
<td></td>
<td>34</td>
<td>190</td>
<td>772</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>71</td>
<td></td>
<td>4</td>
<td>25</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ In combination with a $T_4$/TBG ratio of ≤8.5 (see also Fig. 1).

### TABLE 2. Classification of CH according to the (first) heel puncture TSH

<table>
<thead>
<tr>
<th>Heel puncture TSH (μU/ml)</th>
<th>Classification of CH</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>$TSH ≥ 50$</td>
<td>0</td>
<td>110</td>
</tr>
<tr>
<td>$20 ≤ TSH &lt; 50$</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>$TSH &lt; 20$</td>
<td>547</td>
<td>34</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>548</strong></td>
<td>190</td>
</tr>
</tbody>
</table>

TBG deficiency was diagnosed in 200 children (36% of those with no CH), of whom 77 (39%) had total TBG deficiency. Plasma $FT_4$ measured in the first venous blood sample ranged from 0.5–3.7 ng/dl (6.3–47.8 pmol/liter). Of the nine children with $FT_4$ less than 0.9 ng/dl (<12 pmol/liter), eight had total TBG deficiency at verification and one had a very low TBG (0.3 mg/dl; 58 nmol/liter) in the heel puncture (no confirmatory TBG was available). Of the 12 children with a plasma $FT_4$ more than 2.3 mg/dl (>30 pmol/liter), 11 had a total TBG deficiency (TBG < 0.3 mg/dl).

In seven children, an error was made in the screening procedure: in two, both 36.0 wk GA or less and 2500 g BW or less, their GA and BW were not reported correctly on the filter paper; in two, initial $T_4$ determination, upon which the child was referred, turned out to be normal after repeated measurement on the same heel puncture sample (executed because of the mismatch between the results of heel puncture and venous blood sampling); in one, a second heel puncture, with an abnormal result, was performed despite a normal first result; in two, both with $T_4$ of −3.0 sd or less and normal TSH, the filter paper blood spots arrived at the laboratory with a delay of more than 2 wk.

In 57 children, the abnormal screening results could be ascribed to an exchange blood transfusion (n = 2), a delay of more than 2 wk in heel puncture sampling (n = 9), low BW (≤2500 g) in combination with normal GA (>36.0 wk) with:
out severe illness (n = 16) and low GA (≤36.0 wk) in combination with normal BW (>2500 g) without severe illness (n = 30).

In the remaining 86 children, there was no obvious reason for the abnormal screening results. Their heel puncture T4 concentration ranged from 4.8–10.3 μg/dl (62–133 nmol/liter) with TSH 2–10 μU/ml and TBG 1.8–4.1 mg/dl (305–678 nmol/liter).

**Transient CH**

In 34 patients, the abnormal CH screening result led to the diagnosis of transient CH.

Twenty-four were diagnosed with transient CH-T. Their heel puncture T4 varied from 0.8–13.1 μg/dl (10–169 nmol/liter) and TSH varied from 18–67 μU/ml. Nine patients were born 36.0 wk GA or earlier, of whom six had BW of 2500 g or less. Six patients had been exposed to excessive amounts of iodine during cesarean section (n = 1), neonatal surgery (n = 4), and treatment with amiodarone because of cardiac arrhythmia (n = 1); two patients were born to a mother with autoimmune thyroid disease.

Ten were diagnosed with transient CH-C. Their heel puncture T4 varied from 2.7–9.0 μg/dl (35–120 nmol/liter), TSH 2–10 μU/ml, and TBG 1.8–4.1 mg/dl (305–678 nmol/liter).

**Permanent CH**

In 190 patients, the abnormal CH screening result led to the diagnosis of permanent CH; 16 patients were born 36.0 wk GA or earlier, of whom 11 had BW of 2500 g or less; 11 had BW of 2500 g or less and GA more than 36.0 wk.

In this group, 151 patients (79%) had CH-T, 15 patients (8%) had CH-T21, and 15 patients (8%) had CH-C. In the CH-T group, 78 (52%) had thyroid dysgenesis and 21 (14%) had thyroid dyshormonogenesis, and in 52 (34%), the diagnosis is not yet further specified (Table 4). In the CH-C group, one patient had septo-optic dysplasia and one had trisomy 13.

In nine of the 190 patients (5%), insufficient data were available to classify the origin of the CH as thyroidal or central: one patient had a congenital nephrotic syndrome (in fact a type of CH caused by the loss of thyroid hormone in the urine) and one had Xp22 deletion with partial trisomy 19p.

**CH with normal CH screening result (Table 5)**

Three patients (nos. 1 and 2 with permanent CH-T and no. 3 with transient CH-C) had already started T4 supplementation before the heel puncture was performed. Ten patients had false-negative screening results.

In one patient with permanent CH-T (no. 4), hypothyroidism was too mild for detection by screening. The coexistence of Johansson-Blizzard syndrome led to the diagnosis of CH. The other patient with permanent CH-T (no. 5) was supported by a heart-lung machine at the time of heel puncture sampling because of a congenital heart defect. Routine thyroid function determination after weaning led to the diagnosis of CH.

Of the six patients with permanent CH-C, two were diagnosed in the first year after birth because of failure to thrive (nos. 6 and 7); three, of whom two were born at 36.0 wk GA or earlier with a BW of 2500 g or less, were diagnosed with CH-C because of the coexistence of Cornelia de Lange syn-
In the other 10 patients, the CH screening result was really false negative. ID, Numbers that refer to those mentioned in the text.

In 224 (29%) of the 772 children born between April 1, 2002, and May 31, 2004, and referred because of abnormal screening results, the diagnosis CH, either permanent or transient, could be confirmed. Another 13 CH patients, born in the same period, were not detected by screening. Of them, three children started with T4 supplementation before heel puncture was performed, and 10 had false-negative screening results. Sensitivity and specificity of the Dutch screening approach were 95.8 and 99.9%, respectively.

Among the 430,764 screened children, the incidence of CH was 1:1,800, of whom 85% had permanent CH (incidence 1:1,200). The incidences of transient CH-T (1:2,200) and permanent CH-C, if an elevated TSH concentration had been used as the first clue to both the infant’s thyrotropic dysfunction and the mother’s thyroid disease. Therefore, whenever CH-C is suspected, we recommend screening the mother for thyroid disease before the diagnosis CH-C is made (with an abnormal CH screening result).

In two previous publications, it was concluded that the Dutch T4-TSH-TBG screening approach provided an excellent strategy to detect CH of variable etiology, including mild cases. The incidence of transient CH is 5- to 6-fold reduced from 1:2,200 in 1981–1982 (11) to 1:12,000 at present. This substantial reduction is probably because of the reduced perinatal use of iodine-containing disinfectants and possibly because of reduced use of iodine-containing x-ray contrast agents.

We classified children with CH-C resulting from inadequately treated maternal Graves’ disease as having transient CH-C because it has been reported that pituitary function recovers after some time (12, 13). From our present data, an incidence of 1:33,000 for transient CH-C related to maternal Graves’ disease could be calculated (n = 13), which is substantially higher than in 1981–1982, when only one of 346,335 screened children had been diagnosed with this type of CH (11). We have to be aware that even in the present cohort some cases might have escaped diagnosis. In four mother-child pairs, the abnormal neonatal screening result was the first clue to both the infant’s thyrotropic dysfunction and the mother’s thyroid disease. Therefore, whenever CH-C is suspected, we recommend screening the mother for thyroid disease in addition to screening of the child for additional pituitary hormone deficiencies (5).

In two previous publications, it was concluded that the Dutch T4-TSH-TBG screening approach provided an excellent strategy to detect CH of thyroidal as well as central origin (4, 6). In the present cohort, early detection would have failed in 47 CH patients, including 15 patients with permanent CH-C, if an elevated TSH concentration had been used.
as the only referral criterion. Especially in permanent CH-C, early detection is of vital importance because of the possible coexistence of other pituitary hormone deficiencies for which adequate and timely supplementation will reduce morbidity and prevent mortality.

The relatively high number of referred children in whom the diagnosis of hypothyroidism could not be confirmed at the time of referral is considered a drawback of the \( T_4 \)-TSH-TBG approach. In over one third of these false-positive cases, partial or total TBG deficiency was diagnosed. We chose a cutoff of 1.8 mg/dl (300 nmol/liter) for the diagnosis of partial TBG deficiency, even though this is higher than the lower limit of the reference range as reported in the literature of 1.3 mg/dl (14) and 1.0 mg/dl (9) in children aged 2–6 wk. However, because of the high-affinity binding between \( T_4 \) and TBG, we hold the relatively low TBG responsible for the low heel puncture \( T_4 \) in these children. Determination of TSH and TBG in all children with \( T_4 \) of \(-3.0 \) sp or less before the indication for referral was made could have prevented referral of all 77 cases with total TBG deficiency. However, this would have caused immeasurable delay in referral of those children with severe CH.

In general, TBG deficiency is considered a harmless condition, not influencing thyroid function. Nevertheless, in children with total TBG deficiency, we often encountered \( T_4 \) concentrations below as well as above the reference range, dependent on the \( T_4 \) assay used. Indeed, methodological limitations might make \( T_4 \) assays unreliable in case of total absence of TBG (15, 16). Therefore, the diagnosis of TBG deficiency should be based on determination of plasma TBG rather than \( FT_4 \).

The other major subgroup of referred children in whom none of the classical types of CH could be diagnosed (about one fourth of all referrals) consisted of severely ill neonates hospitalized on an intensive care unit at the time of heel puncture sampling. Most likely, their severe illness was responsible for the decreased heel puncture \( T_4 \), whereas medication or the use of iodine might have transiently disturbed their thyroid hormone state (17, 18). The decreased heel puncture \( T_4 \) in these severely ill children somewhat resembles that of children born prematurely (19). Because early postnatal \( T_4 \) levels are strongly related to GA and BW (20, 21), Dutch children born 36.0 wk or earlier and at 2500 g or less BW are referred only if screening TSH is elevated. Using this TSH-only referral criterion also for severely sick children would have caused impermissible delay in referral of those infants with delayed TSH elevation still escape early detection (as was presumably the case in patient no. 5 in Table 5).

The present study showed that in 15 patients with trisomy 21, CH was detected by screening, i.e. about 3% of the patients with trisomy 21 born in the study period. This is quite similar to the 3.5% reported by van Trotsenburg et al. (24) in a cohort of Dutch patients with trisomy 21 born in 1996–1997. Recently, it has been shown that as a group, these patients have a persistent mild type of CH, presumably of thyroidal origin (CH-T21) and that \( T_4 \) supplementation started early subtly improves early motor development and growth (8, 25). This indicates that also in patients with mild CH not related to trisomy 21, it should be established whether \( T_4 \) supplementation is beneficial for brain development.

In summary, the \( T_4 \)-TSH-TBG screening method as used in The Netherlands has the potential to detect CH of thyroidal as well as of central origin, either permanent or transient, severe or mild. The Dutch incidence figures belong to the highest worldwide, both for CH-T and CH-C. Among the referred children in whom the diagnosis of CH could not be confirmed, TBG deficiency and severe illness could be held responsible for the great majority of low heel puncture \( T_4 \) concentrations.

An important pitfall of any screening method is the occurrence of false-negative results. For the Dutch CH screening in particular, this pitfall concerns children with very mild types of CH having \( T_4 \) concentrations within the normal range and prematurely born babies with CH-C.

Neonatal screening has proven its benefits in terms of improving development in patients with the classical types of (severe) CH. Future studies should focus on severely ill neonates and the very mild cases of CH-T and CH-C to investigate whether these patients might also benefit from (temporary) \( T_4 \) supplementation in terms of reduction of morbidity or improvement of developmental outcome.

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