Psychological consequences of congenital hypothyroidism: Cognitive, motor and psychosocial functioning
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Evaluation of cognitive and motor development in toddlers with congenital hypothyroidism diagnosed by neonatal screening

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- Vu university, Amsterdam, Department of Developmental Psychology,4 The Netherlands

Abstract

Objective: The Dutch neonatal congenital hypothyroidism (CH) screening procedure and treatment modality has been adapted several times since its national institution in 1981. The present study examined whether advancement of treatment modality has resulted in improved cognitive and motor outcomes.

Methods: In 95 toddlers with thyroidal CH (CH-T), born in 2002 through 2004 and treated at a median age of 9 days, cognitive and motor outcomes were assessed with the Bayley Scales of Infant Development-II-NL (BSID-II-NL) at 1 and 2 years of age. This outcome was also analyzed in relation to treatment variables.

Results: The mean mental developmental index (MDI) scores of the severe (initial free thyroxine [FT4] ≤ 0.4 ng/dL (≤ 5 pmol/L), moderate (0.4<initial FT4 ≤ 0.8 ng/dL (5.0<initial FT4 ≤ 10.0 pmol/L) and mild (initial FT4>0.8 ng/dL(>10.0 pmol/L) CH-T groups at 1 year and the moderate and mild CH-T groups at 2 years were similar to the population mean. The mean MDI scores of the total CH-T group and severe CH-T group at 2 years were significantly lower than the population mean (p< 0.0001). In all 3 severity subgroups significant lower psychomotor developmental index (PDI) scores (p<0.0001) were observed. No correlations were found between starting day of treatment and developmental outcome. Initial FT4 concentration and initial T4 dose were weak predictors for developmental outcome.

Conclusion: Essentially, comparable with our earlier findings, children with CH, especially those with severe CH are still at risk for motor and cognitive problems, which are probably due to the consequence of the prenatal hypothyroid state or the thyroid hormone deficiency in early life.

Key words: cognitive development, motor development, congenital hypothyroidism, neonatal screening and toddlers.
Evaluation of cognitive and motor development in toddlers with congenital hypothyroidism diagnosed by neonatal screening

**Introduction**

In children with congenital hypothyroidism (CH), thyroid hormone deficiency is present from the prenatal period onward until adequate thyroxine (T4) supplementation is provided after birth. Because thyroid hormone is essential for brain development, these children are at risk for brain damage and subsequent cognitive and motor deficits. 1-3 The early postnatal start of T4 supplementation, enabled by neonatal screening programs, aims to minimize this brain damage. Several studies on the effect of these screening programs showed that early T4 supplementation resulted in intelligence quotients within the normal range. However, subtle cognitive and motor deficits like attention and balance problems remain present in the majority of patients.4-9

To optimize the effect of early treatment on cognitive and motor outcome in CH patients, timing and treatment modality have been adapted several times over the years. For example, treatment modality gradually changed from a relatively low initial T4 dose in the early years of neonatal screening, to higher initial T4 dose in recent years.10,11 Despite the progress made in terms of standardization of screening procedures and improvements in time and in dose at starting treatment,10,12,13 controversy still exists worldwide as to the effect of these procedural changes on development. 4,10,11,14-21 Some researchers claim that early treatment with high T4 dose leads to normal brain development;14,22 others state that timing does not affect cognitive and motor development positively.4,16,19,23 Therefore, the optimal treatment modality for children with CH is still in debate worldwide.

In The Netherlands, our nationwide study analyzed the effect of the changes in timing and treatment modality over the years by including 3 different cohorts of patients. Phase I of this study investigated cognitive and motor outcome of CH patients born in 1981 through 1982 at 20 years of age 20 and phase II investigated patients born in 1992-93 at 10 years of age.4 Patients with CH, tested at 20 and 10 years had significantly lower full-scale intelligence quotient (IQ) scores than the norm population and worse motor scores compared with controls. Both intellectual and motor outcomes were most severely affected in patients with severe CH. We concluded that severity of CH was an important factor determining long-term cognitive and motor outcomes. Surprisingly, we did not find evidence for influence of timing of early treatment on intellectual and motor functioning. However, median age at start of treatment was 28 days and 20 days after birth in the phase I 20 and phase II 4 cohorts respectively. So, it could not be ruled out whether earlier start of treatment would have had a beneficial effect. Therefore we investigated CH patients who were treated at a median age of 9 days after birth (Phase III). Furthermore, we were able to gather more information about treatment in phase III than in the phase I and phase II cohorts, like initial T4-dose and adequacy of treatment because the study started immediately after birth.
Cognitive and motor development was investigated at 1 and 2 years of age in the present study and compared with normative data. Changes over time were analyzed and outcome was investigated in relation to treatment variables (starting day of T4 supplementation, initial T4 dose and treatment adequacy) and severity of CH based on the pretreatment FT4 concentration: severe CH: initial FT4 ≤ 0.4 ng/dL (≤ 5 pmol/L); moderate CH, 0.4 < initial FT4 ≤ 0.8 ng/dL (5.0 < initial FT4 ≤ 10.0 pmol/L); or mild CH: initial FT4 > 0.8 ng/dL (>10.0 pmol/L).

**Methods**

**Screening method**

The Dutch neonatal CH screening method is primarily based on the measurement of T4 in filter paper blood spots. Sampling is performed between 4 and 7 days after birth. The midwife pays a home visit and performs the heel puncture (also for those children born in the hospital, heel puncture is performed between day 4 and day 7). The T4 concentration is compared to the day mean and expressed as standard deviation (SD) score. If T4 is ≤ -0.8 SD, thyrotropin (TSH) concentration (in mIU/l) is additionally measured. If T4 is ≤ -1.6 SD, thyroxine-binding globulin (TBG) concentration (in nanomoles/liter (nmol/l)) is also measured. A T4/TBG ratio is measured as follows: 

\[ \frac{[T4 + 5.1] 	imes [TBG]^{-1}}{1000} \]

The referral criteria were as follows: if T4 was ≤ -3.0 SD or TSH was ≥ 50 mIU/L, children were immediately referred to a pediatrician by the Dutch Health Administrations (DHA). In children with a dubious result (-3.0 < T4 ≤ -0.8 SD in combination with a T4/TBG ratio ≤ 8.5 and/or 20 ≤ TSH < 50 mIU/l), a second heel puncture was performed. Children were referred after a second heel puncture if the result was dubious again or abnormal. The diagnosis of CH and its etiological classification was based upon initial presentation, thyroid function determinants and a full set of thyroid imaging.

**Patient recruitment**

The study was coordinated and executed by the department of pediatric endocrinology of the Emma Children’s Hospital AMC (AMC) in collaboration with the Dutch Health Administrations (DHA). The study protocol was approved by the institutional review board of the AMC and the CH screening board.

Of those children born in the Netherlands between April 1, 2002 and May 31, 2004 and with an indication for referral from the DHA, the AMC received, in addition to the normal procedure, faxes with data containing heel puncture results, gestational age, birth weight and the name of the family doctor of the child. After an abnormal screening result, the child is usually seen the same day, or at the latest the following day by a pediatrician.

This enabled the researchers of the AMC to immediately contact the pediatrician to
whom the child was to be referred. The pediatrician was invited to participate in the study. Subsequently, the pediatrician was provided with information by letter or fax. This included detailed written information for the parents, and their invitation to participate in the study.

In some children, the diagnosis of CH was established incidentally by the AMC, for example, when their urine or blood was sent for diagnostic work-up. Parents of these patients were also invited for the study. They received written study information via their pediatricians.

Patients
The complete cohort of patients with permanent CH born in The Netherlands between April 2002 and May 2004 consisted of 199 patients (Table 1). Patients were classified as CH-T (CH of thyroidal origin), CH of central origin (CH-C) or CH not yet specified. CH-T was further classified as CH-T due to thyroid dysgenesis, CH-T with normal located thyroid gland, CH-T not yet specified, and CH-T_{21} (i.e. CH-T characteristic for patients with trisomy 21). In this study, only children with CH-T were included. To ascertain that the participating patients were euthyroid (i.e. TSH 0.4-4.0 mIU/L) at the time of testing, the most recent measurement of thyroid function prior to the psychomotor tests was evaluated and if necessary T4 dose was adjusted.

Table 1. Etiology of Congenital Hypothyroidism in the 2002-2004 cohort

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Non-Participants</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Gender*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>34.6 (53)</td>
<td>44.8 (26)</td>
<td>28.4 (27)</td>
</tr>
<tr>
<td>female</td>
<td>65.4 (100)</td>
<td>55.2 (32)</td>
<td>71.6 (68)</td>
</tr>
<tr>
<td>Diagnosis **</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH-T due to thyroid dysgenesis</td>
<td>51.6 (79)</td>
<td>32.8 (19)</td>
<td>63.2 (60)</td>
</tr>
<tr>
<td>CH-T with normal located thyroid gland</td>
<td>24.8 (38)</td>
<td>22.4 (13)</td>
<td>26.3 (25)</td>
</tr>
<tr>
<td>CH-T not yet specified</td>
<td>23.5 (36)</td>
<td>44.8 (26)</td>
<td>10.5 (10)</td>
</tr>
<tr>
<td>Total eligible</td>
<td>100 (153)</td>
<td>100 (58)</td>
<td>100 (95)</td>
</tr>
<tr>
<td>Excluded diagnosis</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>CH-T_{21}</td>
<td>15</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>CH-C</td>
<td>21</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>CH not yet specified</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Total Cohort</td>
<td>199</td>
<td>104</td>
<td>95</td>
</tr>
</tbody>
</table>

* p<0.05; χ^2(1)=4.45: participants differed from non-participants with regard to gender.
** p<0.001; χ^2(2)=40.5: participants differed from non-participants with regard to diagnosis.
CH, congenital hypothyroidism;
CH-C, congénital hypothyroidism of central origin; CH-T, CH of thyroidal origin.
In the present study, parents of 16 children did not give their informed consent. In addition, 76 patients were considered 'not suitable' for the following reasons: CH-C (n=21), CH not yet specified (n=10), CH-T₂ (n=15), Johansson-Blizzard syndrome (n=1), Turner syndrome (n=1), Beckwith-Wiedeman syndrome (n=1), an undefined syndrome (n=4, delayed initiation of treatment (>2 months after birth; n=2)), a severe cardiac defect necessitating long-term hospitalization (n=1), parents who had severe difficulties with the Dutch language (n=6), prematurity (either born <32 weeks GA or birth weight <1.5 kg; n=4); 1 patient had died; 1 patient had moved abroad and 7 patients were not treated adequately. The remaining participants patients with CH-T (n=107), without a remarkable medical history besides their CH, were then classified to subgroups based on the pre-treatment FT₄ concentration: 'severe CH': initial FT₄ ≤ 0.4 ng/dL (≤ 5 pmol/L); 'moderate CH': 0.4 < initial FT₄ ≤ 0.8 ng/dL (5.0 < initial FT₄ ≤ 10.0 pmol/L); 'mild CH', initial FT₄ > 0.8 ng/dL (>10.0 pmol/L); 'reference range FT₄', 10 to 23 pmol/L (0.78-1.79 ng/dL).

**Treatment strategy**

During the study period, Dutch pediatricians were advised on treatment modalities and to start with T₄ supplementation in a dose of approximately ± 10 µg/kg per day in all children, whereas in those children with an initial FT₄ concentration <8 pmol/L, it was advised to give a single additional dose of 10 µg/kg about 12 hours after the first dose. Some pediatricians followed the guideline introduced in 1997 (i.e. to start with 50 µg as an initial dose, followed by 10 µg/kg per day for the following days). Dose of T₄ was subsequently adjusted according to further thyroid function determinants, which were measured during regular controls at the outpatient clinic, according to international guidelines. In general, children are initially seen twice a week, for 2 to 3 weeks. From then on, the period in between controls is gradually extended to once a month in the first year. In the second year children are seen once every 2 to 4 months.

**Treatment adequacy**

All FT₄ and TSH concentrations during the first 2 years of treatment were evaluated. From these data, we analyzed the day at which FT₄ was >12 pmol/L for the first time, and the day TSH was <10 mU/L for the first time. Furthermore, we calculated the number of times in the first and second year that (1) FT₄ was <12 pmol/L, regardless of TSH, (2) FT₄ was <18 pmol/L in combination with TSH >4.0 mU/L, (3) FT₄ was >23 pmol/L in combination with TSH <0.4 mU/L, and (4) FT₄ was >29 pmol/L in combination with TSH <0.4 mU/L. The percentage was calculated by dividing this number with the total number of venipunctures during the first or second year of life. If the percentage in the first or second year of life was ≥20, treatment was scored as (possibly) inadequate; being ‘undertreated’, ‘possibly undertreated’, ‘possibly overtreated’ or ‘overtreated’, for the first, second, third, and fourth combination, respectively.
Instruments
All development assessments were carried out in the AMC except for 10 patients who were tested in their local hospitals. The same psychologist (L.S.V.) who was blinded for the patients’ medical details, conducted all the assessments.

The Bayley Scales of Infant Development version II (BSID-II-NL) 25 was used to assess cognitive and motor development at the age of 1 and 2 years. The developmental skills that are assessed with the BSID-II include the use of active and passive language, imitation, memory, eye-hand coordination, and fine and gross motor skills. The mental developmental index (MDI) and the psychomotor developmental index (PDI) were scored based on the number of items successfully completed. Scores were converted into age-normalized values, as derived from Dutch norms. In the norm population, both MDI and PDI have a mean of 100 and a standard deviation of 15. Most patients were tested at the age of 13 and 25 months, so that 4 scores (MDI, PDI at 13 and 25 months) could be used as outcome measure in the present study.

Statistical analysis
Data were analysed using SPSS version 15.0 (SPSS Inc., Chicago, IL). Chi-square-tests were conducted to test differences between participants and non-participants, regarding gender and diagnosis.

One-sample t tests were performed to test whether the MDI and PDI scores in the different severity CH subgroups differed from the normative value of 100. Paired sample t-tests were used to test the differences over time; MDI and PDI scores at the age of 13 months were compared with those at the age of 25 months.

Analysis of variance (ANOVA) was used to test the differences between the 3 severity groups (severe, moderate and mild) on PDI and MDI mean scores. To adjust for multiple testing, Bonferroni analyses were used. Linear regression analyses were performed to investigate the impact of the following clinical determinants: severity (initial FT4 concentration), starting day of treatment, and initial T4 dose on MDI and PDI at the age of 1 and 2 years. It was not necessary to correct for parental educational level (a potential confounder) because parental educational level appeared to be distributed equally over the subgroups.

The difference in MDI and PDI at the age of 2 years between the adequately and (dubiously) inadequately treated groups was calculated using Mann- Whitney U tests.

Results
Patient characteristics
Of the 107 included toddlers with thyroidal congenital hypothyroidism (CH-T), 19 were considered ‘not suitable’ because intercurrent illness at the time of psychological assessments
(n=1), less than 3 of the 4 BSID-II-NL scores were available (n=11). The remaining 95 were considered the participants at the age of 1 and 2 years.

Participants were classified as CH-T due to thyroid dysgenesis (63.2%), CH-T with normal located thyroid gland (26.3%), or CH-T not yet specified (10.5%), which was different from the distribution of diagnosis in non-participants (see table 1). Other baseline characteristics of the participating CH-T patients are given in Table 2. Of the 95 patients (68 females, 72%), 28 patients (30%) had severe CH-T. Moderate and mild CH-T were seen in 24 (25%) and 43 (45%) patients respectively.

The mean age at start of thyroxine (T4)-supplementation was 10.6 days (median, 9 days; range, 2-32 days). Children with severe and moderate CH-T started significantly earlier with T4 than children with mild CH-T (p=0.0001 and p=0.016 respectively). The mean initial T4 dose was 11.4µg/kg per day (range 5.4-20.1 µg/kg per day).

Table 2. Characteristics of the subgroups of participating CH-T patients with different severity of CH

<table>
<thead>
<tr>
<th></th>
<th>Severe CH-T</th>
<th>Moderate CH-T</th>
<th>Mild CH-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (male:female)</td>
<td>28 (5:23)</td>
<td>24 (6:18)</td>
<td>43 (16:27)</td>
</tr>
<tr>
<td>Mean initial FT4 in ng/dl (range) [in pmol/l (range)]</td>
<td>0.2 (0.1-0.4)</td>
<td>0.6 (0.4-0.8)</td>
<td>1.1 (0.8-1.6)</td>
</tr>
<tr>
<td>Mean initial TSH in mIU/l (range)</td>
<td>378 (75-970)</td>
<td>337 (41-639)</td>
<td>85 (11-340)</td>
</tr>
<tr>
<td>CH-T thyroid dysgenesis</td>
<td>25</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>CH-T with normally located thyroid</td>
<td>3</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>CH-T not specified</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Mean age at start of T4 suppl. in days (range)</td>
<td>8.5 (6-14)</td>
<td>9.5 (2-32)</td>
<td>12.7 (6-31)</td>
</tr>
<tr>
<td>Mean initial T4 dose in µg/kg per day (range)</td>
<td>12.3 (9.0-20.1)</td>
<td>11.8 (8.3-19.9)</td>
<td>10.3 (5.4-14.3)</td>
</tr>
</tbody>
</table>

CH-T, thyroidal hypothyroidism ; FT4: free thyroxine; TSH: thyrotropin.

Developmental outcome in relation to severity

The mental developmental index (MDI) and the psychomotor developmental index (PDI) scores of the CH patients tested at 1 year (13 months) and 2 years (25 months) are shown in Table 3. The mean MDI scores of the total, severe, moderate and mild CH-T group at 1 year were similar to the population mean (total: t = 1.034 p = 0.304; severe: t = 0.630, p = 0.6; moderate: t = 1.341, p = 0.193; mild: t = 0.933, p = 0.356). The mean PDI scores of the total, severe, moderate and mild CH-T group were significantly lower than the population mean at 1
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year (Total: $t = -7.083$, $p < 0.0001$; severe: $t = -4.842$, $p < 0.0001$; moderate: $t = -2.464$, $p = 0.022$; mild: $t = -4.847$, $p < 0.0001$). The mean MDI score of the total CH-T group and severe CH-T group at 2 years were significantly lower than the population mean (total: $t = -2.842$, $p = 0.006$; severe: $t = -5.417$, $p < 0.0001$), whereas the mean MDI scores of the moderate and mild CH-T group were similar to the population mean (moderate: $t = -0.935$, $p = 0.360$; mild: $t = 0.058$, $p = 0.954$). At 2 years, the mean PDI scores of the total, severe, moderate and mild CH-T group were significant lower than of the population mean (total: $t = -7.747$, $p < 0.0001$; severe: $t = -6.479$, $p < 0.0001$; moderate: $t = -3.262$, $p = 0.004$; mild: $t = -4.100$, $p < 0.0001$).

Mean MDI scores did differ significantly ($p < 0.001$) at 2 years between the CH-T severity subgroups ($F(2.94) = 8.161$, whereas PDI scores did not. At 2 years, the MDI scores of the severe CH-T group were significantly lower than those of the mild and moderate CH-T groups ($p < 0.001$; $p < 0.05$, respectively; Table3).

Table 3. Mental developmental index (MDI) and Psychomotor developmental index (PDI) scores in the subgroups of participating CH-T patients

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MDI 1 year</th>
<th>n</th>
<th>MDI 2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe CH-T</td>
<td>28</td>
<td>98.8 (93.9-103.6)</td>
<td>26</td>
<td>88.0 **** (83.3-92.6)</td>
</tr>
<tr>
<td>Moderate CH-T</td>
<td>24</td>
<td>103.7 (98.0-109.3)</td>
<td>24</td>
<td>97.9 * (93.3-102.5)</td>
</tr>
<tr>
<td>Mild CH-T</td>
<td>43</td>
<td>101.7 (98.1-105.3)</td>
<td>42</td>
<td>100.1 (96.4-104.3)</td>
</tr>
<tr>
<td>Total CH-T</td>
<td>95</td>
<td>101.3 (98.8-103.8)</td>
<td>92</td>
<td>96.1 * * (93.4-98.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PDI 1 year</th>
<th>n</th>
<th>PDI 2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe CH-T</td>
<td>27</td>
<td>85.6 *** (79.5-91.7)</td>
<td>26</td>
<td>83.8 *** (78.7-99.0)</td>
</tr>
<tr>
<td>Moderate CH-T</td>
<td>24</td>
<td>91.7 * (84.7-98.7)</td>
<td>21</td>
<td>91.2 ** (85.6-96.8)</td>
</tr>
<tr>
<td>Mild CH-T</td>
<td>43</td>
<td>88.5 *** (83.4-93.1)</td>
<td>37</td>
<td>90.8 *** (86.3-95.4)</td>
</tr>
<tr>
<td>Total CH-T</td>
<td>94</td>
<td>88.4 *** (85.1-91.6)</td>
<td>84</td>
<td>88.9 *** (85.9-91.6)</td>
</tr>
</tbody>
</table>

MDI and PDI expressed as mean with confidence interval between parentheses

*p<0.05; **p<0.001; ***p<0.0001 difference between CH-T patients and normative population (based on one sample t-tests).

*p<0.0005 significant change over time; difference between CH-T patients at 1 year and 2 years of age (based on paired t-test).

CH-T: Thyroidal congenital hypothyroidism.
Change over time
The results of a paired t-test showed a significant decrease over time on the MDI for the total and severe CH groups (t=3.720, df=91, p<.0005, two tailed) (Table 3). The mean difference between the MDI scores over the years was 5.17 and the 95% confidence interval for the estimated population mean difference is between 2.41 and 7.93. There was no significant difference over time on the PDI, (t = 0.816, df = 82, p<.417, two tailed). The mean difference between the PDI scores over the 2 years was -1.41 and the 95% confidence interval for the estimated population mean difference is between -4.84 and 2.03.

Developmental outcome at 1 and 2 years in relation to medical determinants
The multiple regression analyses for MDI and PDI with initial FT4 concentration, starting day of T4 supplementation and initial T4-dose, resulted in a significant model for MDI score at the age of 2 years: F (3,84) = 4.186, p=0.008 (table 4). The model explained 9.9% of the variance. Initial FT4 concentration contributed significantly to the model, whereas the other variables did not. Starting dose of T4 appeared to be a predictor of MDI at the age of 1 year and of the PDI at the age of 1 and 2 years (table 4).

Table 4. Multiple regression analysis, MDI and PDI scores

<table>
<thead>
<tr>
<th></th>
<th>MDI 1 year</th>
<th>PDI 1 year</th>
<th>MDI 2 year</th>
<th>PDI 2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial T4 concentration</td>
<td>B</td>
<td>-0.003</td>
<td>-0.0255</td>
<td>0.732</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>0.01</td>
<td>-0.084</td>
<td>0.313</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.990</td>
<td>0.470</td>
<td>0.007</td>
</tr>
<tr>
<td>Starting day of treatment</td>
<td>B</td>
<td>-0.055</td>
<td>0.122</td>
<td>-0.232</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>-0.023</td>
<td>0.038</td>
<td>-0.924</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.840</td>
<td>0.735</td>
<td>0.395</td>
</tr>
<tr>
<td>T4 Starting dose</td>
<td>B</td>
<td>-1.290</td>
<td>-1.730</td>
<td>-0.703</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>-0.296</td>
<td>-0.301</td>
<td>-0.154</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.007</td>
<td>0.007</td>
<td>0.150</td>
</tr>
<tr>
<td>R2 adjusted</td>
<td></td>
<td>0.054</td>
<td>0.053</td>
<td>0.099</td>
</tr>
<tr>
<td>Model significance</td>
<td>F(3,87)=2.710</td>
<td>F(3,86)=2.672</td>
<td>F(3,84)=4.186*</td>
<td>F(3,76)=2.394</td>
</tr>
</tbody>
</table>

*p<0.01. MDI, mental developmental index; PDI, psychomotor developmental index; T4: thyroxine.
Evaluation of cognitive and motor development in toddlers with congenital hypothyroidism diagnosed by neonatal screening

Treatment Adequacy
For the total group, FT4 was above 12 pmol/L for the first time at a mean duration of 2.1 days after the treatment initiation (95% confidence interval [CI], 1.6-2.7; range 0-18). In severe, moderate, and mild CH-T patients, FT4 was above 12 pmol/L for the first time at a mean duration of 4.0, 2.7, and 0.5 days after treatment initiation, respectively. In the total CH-T group, TSH was <10 mU/L for the first time at a mean duration of 18.7 days after the start of treatment (95% CI 12.9-23.4, range 2-180). In severe, moderate, and mild CH-T patients, TSH was <10 mU/L for the first time at a mean duration of 28.0, 15.7, 14.4 days after the start of treatment, respectively. Within the severe CH-T group, there was no correlation between the day at which FT4 was>12 pmol/L for the first time or TSH<10 mU/L for the first time and the MDI or PDI score at the age of 2 years.

A FT4 concentration<12 pmol/L occurred only once in 1 child in the first year, and once in 1 child in the second year. For the patients who were possibly undertreated, possibly overtreated or overtreated, MDI and PDI scores at the age of 2 years did not differ from those patients who were treated well. At the age of 2 years, MDI and PDI scores did not correlate with the percentage of venipunctures with FT4<18 and TSH>4 or FT4>23 and TSH<0.4 or with FT4>29 and TSH<0.4.

Discussion
Our study shows that toddlers with thyroidal congenital hypothyroidism (CH-T), who were screened and treated according to national recommendations and current practice, had subtle deficiencies in cognitive development at 2 years of age. This was most prominent in toddlers with severe CH-T. In addition, toddlers with CH-T had significantly lower psychomotor developmental index (PDI) scores than the population mean at 1 and 2 years of age, irrespective of severity of hypothyroidism.

The most striking result in our study was that no correlation was found between the starting day of treatment (range 2-32 days) and cognitive and motor development. The possible effects of the starting day of treatment, initial dose of thyroxine (T4) and CH-T severity on developmental outcome of patients detected by neonatal CH screening have been object of many studies. However, the results are often difficult to compare with each other because screening method, guidelines for treatment (starting day of treatment and initial T4 dose, quality of treatment), sample size, and criteria for CH-T severity differ among these studies. A striking example is that in one study, the same initial starting dose gave a favorable outcome if it was defined as high, and a suboptimal outcome when defined as a low dose. To overcome these limitations, we tested a large cohort of CH-T patients and we used the same psychological tests carried out.
by one psychologist. In addition, all patients were treated by pediatricians who followed the national guidelines for treatment, and at the time of psychological assessments, all patients had plasma TSH concentrations within the reference range. Furthermore, the cohort was carefully characterized in terms of etiology and initial disease characteristics. Since the national institution of the Dutch neonatal screening procedure, treatment initiation for CH patients has been advanced considerably. Over the years, the start of treatment has changed from a mean age of 29 days (in 1981-1982), a mean age of 19 days (1992-1993) to 10 days (born in 2002-2004). All cohorts showed subtle deficits in cognitive and motor outcomes, which indicate that timing of treatment initiation is not a predictor of long-term motor and cognitive outcomes.

 Apparently, brain development is thyroid hormone dependent not only in the neonatal period but also prior to birth. Apparently, maternal T4, transferred via the placenta, is not sufficient to prevent any brain damage. Possibly the subtle deficits found, might not solely be the result of prenatal thyroid hormone deficiency, and that, for example, inadequate treatment may play a role as well. We made our own definition because an international guideline to define “adequate treatment” is not available. Analysis showed that only a minority of patients during the first or second year of life had >20% of the vena punctures with values deviating from the norm. So, we can conclude that the majority of our patients were adequately treated during their first 2 years of life. Moreover, no differences were found in developmental outcomes between the patients with >20% of blood values deviating from the norm from those with <20% of blood values deviating from the norm.

A limitation of the study is that no definite conclusions can be drawn on the cognitive and motor capabilities of CH patients at older age. The BSID-II-NL is a different test than the IQ tests we used for the 10 year olds. Therefore it is advisable to retest the children at 10 years of age. Another shortcoming of the study is that a control group of age-matched norms was not available. Although including a control group could optimize comparison on motor and mental development next to the normative data, the BSID is a reliable standardized international developmental test, whereby the use of normative data is well accepted.

A surprising result in the present study was that the mean mental developmental index (MDI) score of the severe CH patients at the age of 1 year was similar to the population mean, whereas the mean MDI score of the severe patients at the age of 2 years was significantly lower than the population mean. Explanations for these findings could be that cognitive problems only become evident at older age. Another explanation could be that the psychological tests used in older children are more sensitive to detect differences or are more reliable than the instruments used in younger children. This explanation is confirmed by the study of Westra et al. They found that the Dutch normative values of the BSID are maybe not sufficiently reliable for use at the ages of 6 and 12 months. It should also be taken into account that the 2002-2004 cohort was very young at the time of this first evaluation. Testing of a young child is difficult, and the predictive value
of the test outcomes for future cognitive and motor functioning increases with age. Therefore, it is difficult to draw conclusions based on the outcome at 1 year of age. The norms are more reliable at the age of 2 years. 27

Even if we take the limitations into account, our data are convincing in that children with CH-T, even when treated within a few days after birth, still suffer from subtle cognitive and motor delays. To get more insight into the depth of these delays, it is important to study cognitive and motor functioning of CH-T patients in more detail, for example to examine additional neuropsychological domains like attention and memory and specific motor functioning. Unfortunately, with the BSID-II, 25 it was not possible to split motor function in specific motor areas. With the new version of the BSID, version III, it is possible to examine motor development more in depth. However this version was not yet available during our inclusion period. Future studies should take in consideration the use of instruments that are able to differentiate between domains of functioning. Reevaluation of these subjects at an older age when domains such as attention and memory can be more accurately assessed will be helpful.8

Our consistent findings over time warrant for sensitive monitoring of motor functioning. Pediatricians should be aware of these motor problems to make early identification and intervention possible. Tailored support with respect to movement and sports should be considered as an early intervention. In addition, we recommend referring all children with severe CH-T to a physiotherapist as part of standard health care. Furthermore, our results underscore the importance of monitoring general and language development of toddlers with a severe form of CH-T. Referral for developmental assessment and, if needed, for speech therapy are possible interventions.

Our data strongly indicate that the prenatal hypothyroid state is responsible for the postnatal outcome, and hence, it may be concluded that the current neonatal screening program on CH is optimal, as it is. Future research should focus on improvements of the prenatal thyroid hormone state.

Finally, international guidelines for optimal treatment are desirable and needed. Consensus with respect to treatment (starting day of treatment, initial T4-dose, quality of treatment) and criteria for CH-T severity are of utmost importance to provide direction for helping children with CH and personalizing their medicine. Therefore, recent literature provides recommendations regarding the treatment of children with CH. 10,11,26,28 Furthermore, promising new guidelines from the European Society for Pediatric Endocrinology (ESPE) are underway, so it is important to take these in consideration in clinical practice and future research, when published. However, pursuing research in this area seems important.

In conclusion, this study has shown subtle cognitive and motor deficits in patients with severe CH, whose treatment with T4 was initiated at a mean age of 10.6 days after birth. Mildly and moderately affected CH patients had a fair prognosis for mental developmental
index, but they do also experience motor problems. Furthermore, we conclude that although the development of children with CH is considerably improved by neonatal screening and improvement of treatment, they are still at risk for motor and cognitive delays. These delays are due to the consequence of the prenatal hypothyroid state or the thyroid hormone deficiency in early life. Most of all, our findings add to the evidence for motor and cognitive problems in relation to CH. Health care physicians should be observant of these problems and refer the patients for more detailed psychological assessment if necessary.
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