Neonatal Screening for Congenital Hypothyroidism in The Netherlands: Cognitive and Motor Outcome at 10 Years of Age


Context: Patients with thyroidal congenital hypothyroidism (CH-T) born in The Netherlands in 1981–1982 showed persistent intellectual and motor deficits during childhood and adulthood, despite initiation of T4 supplementation at a median age of 28 d after birth.

Objective: The present study examined whether advancement of treatment initiation to 20 d had resulted in improved cognitive and motor outcome.

Design/Setting/Patients: In 82 Dutch CH-T patients, born in 1992 and treated at a median age of 20 d (mean, 22 d; range, 2–73 d), cognitive and motor outcome was assessed (mean age, 10.5 yr; range, 9.6–11.4 yr). Severity of CH-T was classified according to pretreatment free T4 concentration.

Main Outcome Measure: Cognitive and motor outcome of the 1992–1993 cohort in comparison to the 1981 to 1982 cohort was the main outcome measure.

Results: Patients with severe CH-T had lower full-scale (93.7), verbal (94.9), and performance (93.9) IQ scores than the normative population (P < 0.05), whereas IQ scores of patients with moderate and mild CH-T were comparable to those of the normative population. In all three severity subgroups, significant motor problems were observed, most pronounced in the severe CH-T group. No correlations were found between starting day of treatment and IQ or motor outcome.

Conclusions: Essentially, findings from the 1992–1993 cohort were similar to those of the 1981–1982 cohort. Apparently, advancing initiation of T4 supplementation from 28 to 20 d after birth did not result in improved cognitive or motor outcome in CH-T patients. (J Clin Endocrinol Metab 92: 919–924, 2007)
tained from patients born and screened in 1981–1982, examined at the age of 9.9 yr of age, in whom T₄ supplementation was initiated significantly later (1).

Subjects and Methods
Screening method and treatment strategy
The Dutch neonatal CH screening method is primarily based on the measurement of T₄ in filter paper blood spots. In 1992–1993, sampling was performed between 6 and 8 d after birth. T₄ expressed as sp score, is compared with the day mean. If T₄ was 0.8 sp or less, TSH was additionally measured. When T₄ was 3.0 or less or TSH was 50 µU/ml or more, children were referred immediately. Children with a dubious result [3.0 ≤ T₄ ≤ 2.1 sp, or 28 < TSH < 50 µU/ml (in 1992) or 20 < TSH < 50 (in 1993)] underwent a second heel puncture and were referred if the result was again dubious or abnormal. The etiological classification of CH was based on thyroid function determinants and thyroid imaging.

In 1992–1993, Dutch pediatricians were advised to start with 6–8 µg T₄/kgd. In accordance with international guidelines, T₄ dose adjustments were based on thyroid function determinants, obtained at regular outpatient follow-up visits.

Patients of the 1992–1993 cohort
The institutional review board of the Emma Children’s Hospital Academic Medical Center (AMC) and the privacy committee of the CH Screening Board approved the study protocol. The Netherlands Organization of Applied Scientific Research (TNO) documents the screening results and diagnostic findings of all children screened for CH in The Netherlands.

For the majority of children referred because of an abnormal CH screening result, blood and/or urine samples are sent to the AMC; for each patient, a record is made. Combination of the records (TNO and AMC) revealed that the complete cohort of CH patients born in The Netherlands in 1992–1993 consisted of 141 patients (Table 1). Of them, three had died, four had moved abroad, and four had transient CH. The parents of the remaining 130 patients were approached by their pediatricians, whose responses led to the exclusion of patients with a known or suspected syndrome (n = 12), exceptionally late start of treatment (n = 3), initiation of treatment > 300 d after birth), (treatment for) brain tumor (n = 1), blindness (n = 1), encephalopathy after hypoxia (n = 2), or hypoglycemia (n = 1); and patients of whom the mother was treated with T₄ during pregnancy (n = 2) (Table 1, “not suitable”). The parents of 18 patients refused participation (Table 1, “not willing”).

To ascertain that the participating patients were euthyroid (i.e. TSH 0.4–4.0 µU/ml) at the time of testing, the most recent measurement of thyroid function before the psychological tests was evaluated and, if necessary, T₄ dose was adjusted. This resulted in dose adjustments for 20 patients. Because of misunderstandings, the recommended dose adjustments were not made in time in three patients who were excluded from the analysis (Table 1, “not suitable”).

Of the 87 participating patients (62% of the original cohort), 82 had CH-T, and five had central CH (CH-C). The test results of patients with CH-C are presented separately, because of difference in etiology and treatment; all of them received besides T₄ supplementation, cortisol, and GH. Patients with CH-T were classified to subgroups based on their pretreatment free T₄ (FT₄) concentration: severe CH, initial FT₄ ≤ 0.3 ng/dl (<4 pmol/liter); moderate CH, 0.3 < initial FT₄ ≤ 0.6 ng/dl (4.0 < initial FT₄ ≤ 8.0 pmol/liter); or mild CH, initial FT₄ > 0.6 ng/dl (>8.0 pmol/liter). FT₄ reference range for children aged 2–6 wk was 0.9–2.2 ng/dl (12–28 pmol/liter) (8).

Assessments
Cognitive and motor assessments were performed in the AMC (except for seven patients who were tested in their local hospitals) by the same psychologist, who was blinded for the patient’s medical details. Patients were tested at a mean age of 10.5 yr (range, 9.6–11.4 yr).

Cognitive assessments
Intelligence was assessed with the Dutch version of the Wechsler Intelligence Scale for Children, third edition (WISC-III) (9), except for the first 10 patients who were tested with the WISC-R (10) because the WISC-III was not yet available. With the subjects’ performance on 10 subtests, three IQ scores were derived: full-scale IQ (FSIQ); verbal IQ (VIQ); and performance IQ (PIQ). In the normative population, each IQ score has a mean of 100 (sn 15). The scores of the WISC-R were recalculated into WISC-III scores in accordance with the guidelines provided in the WISC-III manual (9, 11).

Motor assessments
Motor skills were assessed with the Movement Assessment Battery for Children (MABC) (12, 13), designed for identification of impairments of motor function in children aged 4–12 yr. The test results are expressed in terms of a total motor impairment score (range, 0 to 40; mean, 5.0 in the normative population; in the text referred to as total MABC score), a manual dexterity score (0–15), a ball skills score (0–10), and a balance score (0–15); higher scores indicate more motor problems. In the normative population, 85% have no motor problems (total MABC score ≤ 9.5), 10% have borderline motor problems (9.5 < total MABC score ≤ 13.5), and 5% have definite motor problems (total MABC score > 13.5).

Patients of the 1981–1982 cohort
Data of 58 patients with CH-T born in 1981–1982 (43% of a total cohort of 136 CH patients) who were studied at a mean age of 9.9 yr (range, 9.0–10.9 yr) (1) were available for retrospective analysis. IQ was measured with the WISC-R (10). Motor skills were tested with the Test of

### TABLE 1. Etiology of CH in the 1992–1993 cohort

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Total group</th>
<th>Participants</th>
<th>Not willing</th>
<th>Nonparticipants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid agenesis</td>
<td>24</td>
<td>17</td>
<td>1</td>
<td>6 (moved abroad, 1; syndrome, 1; syndrome suspected, 2; T₄ dose not adequate, 2)</td>
</tr>
<tr>
<td>Thyroid dysgenesis</td>
<td>51</td>
<td>48</td>
<td>1</td>
<td>2 (T₄ dose not adequate, 1; euthyroid without T₄ supplementation, 1)</td>
</tr>
<tr>
<td>Thyroid dyshormonogenesis</td>
<td>24</td>
<td>17</td>
<td>4</td>
<td>2 (syndrome, 1; mother treated with T₄ during pregnancy, 2)</td>
</tr>
<tr>
<td>CH-T not otherwise specified</td>
<td>26</td>
<td>15</td>
<td>11</td>
<td>15 (moved abroad, 3; patient died, 3; euthyroid without T₄ supplementation, 3; syndrome, 5; tumor, 1)</td>
</tr>
<tr>
<td>CH-C</td>
<td>16</td>
<td>5</td>
<td>11</td>
<td>10 (blindness, 1; encephalopathy, 3; syndrome suspected, 3; late initiation of treatment, 3)</td>
</tr>
</tbody>
</table>

Three groups are presented: the total group, the group of participating patients (with either CH-T or CH-C), and the group of nonparticipants, either because patients were considered not suitable (with the reason specified in parentheses) or because parents were not willing. The number of patients in each etiological classification subgroup is given for each group.
Motor Impairment (TOMI) (14). The TOMI later evolved into the MABC, and both contain comparable items. The total motor impairment score (referred to in the text as total TOMI score) ranges from 0 to 20; higher scores indicate more motor problems. In the normative population, 85% have no motor problems (total TOMI score < 4), 10% have borderline motor problems (4 ≤ total TOMI score < 6), and 5% have definite motor problems (total TOMI score ≥ 6).

**Statistical analysis**

Comparisons of IQ and motor scores were made between the following subgroups: severe vs. moderate vs. mild CH-T and early-treated vs. late-treated patients with severe, moderate, or mild CH-T (i.e. before or after the mean starting day of treatment). FSIQ scores and the percentage of patients with motor problems of the 1992–1993 and 1981–1982 cohorts were compared.

One-sample t tests were used to determine whether the IQ scores in the total CH-T group and the severity subgroups differed from the norm of 100. Binomial tests were conducted to test whether the percentage of CH-T patients in the severity subgroups that had a motor score more than 9.5 differed from the percentage in the normative population.

ANOVA was used for group comparisons on continuous variables; post hoc group comparisons were performed with Bonferroni post hoc analysis. χ² tests were used for categorical variables. For variables in which the distributions of scores differed significantly from the normal distribution, nonparametric tests such as the Mann-Whitney U tests were used. Linear regression models were fitted for IQ and motor scores with severity (initial T₄ concentration) and starting day of treatment as independent variables. In addition, bivariate correlation analyses between severity of CH-T, starting day of treatment, or initial T₄ dose, and IQ or motor scores were performed and between FSIQ and total MABC score. It was not necessary to correct for parental educational level, a potential confounder, because this appeared to be distributed equally over the subgroups: parental educational level by severity (χ² = 1.260; P = 0.868) and parental educational level by early or late treatment (χ² = 2.435; P = 0.096).

**Results**

**Patients with CH-T**

Characteristics of the participants are given in Table 2. Of the 82 patients with CH-T (53 girls, 65%), 50% had severe CH-T, of whom the majority had thyroid agenesis (39%) or dysgenesis (39%), and 50% had moderate or mild CH-T, of whom the majority had thyroid dysgenesis (78%). In patients with severe and moderate CH-T, the mean age at initiation of T₄ supplementation was younger than in patients with mild CH-T. The median age at initiation of T₄ supplementation for the total CH-T group was 20 d (mean, 22 d).

**Intellectual and motor outcome**

Mean FSIQ, VIQ, and PIQ scores of the total CH-T group were not significantly different from the population means (Table 3). The mean total MABC score was subnormal for the total CH-T group and significantly different from the mean of the normative population (P < 0.001; Table 4).

Mean FSIQ, VIQ, and PIQ scores in the severe CH-T group differed significantly from the population means (P = 0.004, P = 0.039, P = 0.003, respectively; Table 3), whereas in the moderate and mild CH-T group mean IQ scores were not significantly different from the population means. In the severe CH-T group, FSIQ and PIQ scores were significantly lower than in the mild CH-T group (P = 0.007, P = 0.005, respectively; Table 3).

The mean total MABC scores in the severe, moderate, and mild CH-T subgroups were significantly different from the mean of the normative population (P < 0.001, P = 0.003, P = 0.001, respectively; Table 4). Patients with severe CH-T had significantly worse scores on total MABC and manual dexterity than patients with moderate CH-T (P = 0.023, P = 0.004, respectively; Table 4). The percentages of patients in the severe, moderate, and mild CH-T subgroups, with a subnormal total MABC score (70, 37, and 59%, respectively) were significantly higher than in the normative population (P < 0.001, P = 0.016, P < 0.001, respectively). The difference between severe and moderate CH-T in percentages of patients with a subnormal total MABC score was significant (P = 0.023).

In the severe CH-T group, IQ and motor scores did not differ in patients treated less than 19 d after birth vs. patients treated 19 d or more after birth. IQ and motor scores were not different in the moderate and mild CH-T group when treatment was initiated before or after 19 and 31 d, respectively.

In a multiple regression analysis with severity of CH-T (expressed as the initial plasma FT4 concentration) and starting day of treatment as independent variables, only the severity of CH-T appeared to be a significant predictor of FSIQ (Table 5).

In a bivariate correlation analysis, the initial FT₄ concentration appeared to be associated with FSIQ (r = 0.298; P = 0.015), PIQ (r = 0.314; P = 0.010), and manual dexterity (r =

**TABLE 2. Characteristics of the participants**

<table>
<thead>
<tr>
<th>Initial TSH (U/ml) (range)</th>
<th>Initial FT4 (ng/dl) (range)</th>
<th>Total defectsa</th>
<th>Agenesis</th>
<th>Dyshormonogenesis</th>
<th>Partial defectsb</th>
<th>Dysgenisis</th>
<th>Dyshormonogenesis</th>
<th>Age at start of T₄ supplementation (d) (range)</th>
<th>Initial T₄ dose (µg/kg/d) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>693 (254–1500)</td>
<td>0.1 (0.0–0.3)</td>
<td>16</td>
<td>1</td>
<td>7</td>
<td>16</td>
<td>10</td>
<td>2</td>
<td>19 (10–43)</td>
<td>7.0 (3.2–12.9)</td>
</tr>
<tr>
<td>493 (163–760)</td>
<td>0.4 (0.3–0.6)</td>
<td>15</td>
<td>1</td>
<td>7</td>
<td>15</td>
<td></td>
<td></td>
<td>19 (9–41)</td>
<td>6.6 (4.0–10.3)</td>
</tr>
<tr>
<td>120 (28–502)</td>
<td>1.0 (0.7–1.6)</td>
<td>7</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31 (2–73)</td>
<td>5.0 (2.8–9.0)</td>
</tr>
<tr>
<td>4 (2–5)</td>
<td>0.6 (0.4–0.7)</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34 (14–58)</td>
<td>8.1 (4.2–11.1)</td>
</tr>
</tbody>
</table>

Initial plasma FT₄ and TSH concentrations, the age at start of treatment, and the initial T₄ dose are expressed as mean (range).

a Reference range for FT₄ in children aged 2 to 6 wk, 0.9–2.2 ng/dl, 12–28 pmol/liter (8).

b Reference range for TSH in children aged 2 to 6 wk, 1.7–9.1 µU/ml (8).

c Only for patients with CH-T.
Differences were not significant.  

The 1981–1982 cohort (impairment score was higher in the 1992–1993 cohort than in the percentage of patients with a subnormal total motor score between the two cohorts. In patients with mild CH-T, for severe, moderate, and mild CH-T, respectively). FSIQ for severe CH-T group, starting day of treatment or initial T4 dose did not correlate with IQ or motor scores. 

FSIQ and total MABC score were not significantly correlated (r = −0.247; P = 0.047). No correlation was found between starting day and IQ or motor scores; nor was there a correlation between initial T4 dose and IQ or motor scores. Also within the severe CH-T group, starting day of treatment or initial T4 dose did not correlate with IQ or motor scores.


Mean FSIQ and the percentage of patients with motor impairment score was higher in the 1992–1993 cohort (P < 0.001). This was also true for patients with moderate CH-T (P = 0.087). The initial T4 dose of patients in the severity subgroups was not significantly different between the 1981–1982 and the 1992–1993 cohort (P = 0.086, P = 0.938, P = 0.248 for severe, moderate, and mild CH-T, respectively). FSIQ scores of the severity subgroups were not significantly different between the two cohorts. In patients with mild CH-T, the percentage of patients with a subnormal total motor impairment score was higher in the 1992–1993 cohort than in the 1981–1982 cohort (P = 0.013); for severe and moderate CH-T, differences were not significant.

Patients with CH-C

The five patients with CH-C (four boys) had a mean initial T4 concentration between that of patients with moderate and mild CH-T (Table 2); none of the CH-C patients had a mean initial T4 concentration less than 0.3 ng/dl (<4 pmol/liter). T4 supplementation was initiated at a mean age of 34 d after birth. Patients with CH-C had a mean FSIQ of 99.0 (range, 92.5–105.5); mean VIQ was 96.6 and mean PIQ was 102.2. The mean manual dexterity score was 8.4, ball skills 1.2, and balance 4.9. The mean total MABC score (14.5) was substantially higher than the mean of the normative population (5.0), four of the five patients had a subnormal score (i.e. >9.5).

Discussion

The present study analyzed cognitive and motor outcome in a Dutch cohort of 10-yr-old children with early treated CH. IQ scores for the total CH-T group, in whom treatment was initiated at a median age of 20 d, were not significantly different from the normative population. Within the subgroup of severe CH-T patients, however, cognitive outcome was less favorable. With regard to motor skills, the total CH-T group had substantial motor problems, which were slightly more pronounced in severe CH-T patients. Severity of CH-T correlated significantly with FSIQ, PIQ, and manual dexterity score. No correlation, however, was found between the starting day of treatment (median, 20 d; range, 2–73 d) or initial T4 dose (range, 2.8–12.9 μg/kg/d) and IQ or motor scores.

The current findings are in line with our recent observations of persistent cognitive and motor deficits in adult Dutch CH-T patients, born in 1981–1982, in whom treatment was initiated at a median age of 28 d (range, 4–293 d). Also in the 1981–1982 cohort, severity of CH-T was an important predictor of long-term outcome, but not timing of treatment initiation (2). Over the course of the first decade after introduction of the nationwide CH screening, treatment initiation for CH patients was substantially advanced; patients with severe CH-T born in 1981–1982 were treated from a mean age of 29 d (median, 29 d), whereas those born in 1992–1993 were treated from a mean age of 19 d (median, 17 d). Apparently, this advancement did not result in an improvement in intellectual development. It is conceivable that also in the 1992–1993 cohort the time frame for a preventive effect of early treatment initiation had elapsed, as was previously supposed for the 1981–1982 cohort (2). Alternatively, (irreversible) brain damage in severe CH might have accrued in the

### Table 3. IQ scores of the CH-T group

<table>
<thead>
<tr>
<th></th>
<th>FSIQ</th>
<th>P (t)</th>
<th>Verbal IQ</th>
<th>P (t)</th>
<th>Performance IQ</th>
<th>P (t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe CH-T (n = 41)</td>
<td>93.7 (89.5–97.9)</td>
<td>0.004 (−3.0)</td>
<td>94.9 (90.1–99.7)</td>
<td>0.039 (−2.1)</td>
<td>93.9 (90.0–97.8)</td>
<td>0.003 (−3.1)</td>
</tr>
<tr>
<td>Moderate CH-T (n = 19)</td>
<td>96.2 (88.9–103.5)</td>
<td>0.290 (−1.1)</td>
<td>95.4 (87.9–102.9)</td>
<td>0.210 (−1.3)</td>
<td>98.0 (91.1–104.9)</td>
<td>0.550 (−0.6)</td>
</tr>
<tr>
<td>Mild CH-T (n = 22)</td>
<td>105.0 (99.5–110.4)</td>
<td>0.073 (1.9)</td>
<td>103.6 (98.2–109.1)</td>
<td>0.182 (1.4)</td>
<td>105.3 (99.3–111.3)</td>
<td>0.082 (1.8)</td>
</tr>
<tr>
<td>Total (n = 82)</td>
<td>97.3 (94.2–100.4)</td>
<td>0.088 (−1.7)</td>
<td>97.4 (94.1–100.6)</td>
<td>0.113 (−1.6)</td>
<td>97.9 (94.8–100.9)</td>
<td>0.172 (−1.4)</td>
</tr>
</tbody>
</table>

IQ scores, expressed as mean (confidence interval), are presented for the total CH-T group and the three severity subgroups. P values (with t value in parentheses) refer to the comparison with the normative population.

* P < 0.01 compared to the population mean.

** P < 0.05 compared to the population mean.

*** P < 0.01 compared to mild CH-T.

### Table 4. Motor scores of the CH-T group

<table>
<thead>
<tr>
<th></th>
<th>Total MABC score</th>
<th>Manual dexterity</th>
<th>Ball skills</th>
<th>Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe CH-T (n = 41)</td>
<td>14.37 (11.8–16.8)</td>
<td>8.2 (7.0–9.5)</td>
<td>2.4 (1.5–3.3)</td>
<td>4.1 (3.2–5.0)</td>
</tr>
<tr>
<td>Moderate CH-T (n = 19)</td>
<td>9.7 (6.8–12.5)</td>
<td>5.1 (3.5–6.6)</td>
<td>1.6 (0.6–2.6)</td>
<td>3.0 (1.9–4.1)</td>
</tr>
<tr>
<td>Mild CH-T (n = 22)</td>
<td>11.6 (8.7–14.6)</td>
<td>6.0 (4.1–7.8)</td>
<td>1.6 (0.7–2.6)</td>
<td>4.0 (2.7–5.4)</td>
</tr>
<tr>
<td>Total (n = 82)</td>
<td>12.4 (10.8–14.0)</td>
<td>6.8 (6.0–7.7)</td>
<td>2.0 (1.4–2.6)</td>
<td>3.8 (3.2–4.5)</td>
</tr>
</tbody>
</table>

Motor scores, expressed as mean (confidence interval), are presented for the total CH-T group and the three severity subgroups.

* P < 0.01 compared to the normative population.

** P < 0.01 compared to moderate CH-T.

*** P < 0.05 compared to moderate CH-T.
fill the gap in fetal T4 production. Maternal T4, transferred via the placenta, is not sufficient to
in mind that CH is already expressed in fetal life and that
nitive and motor deficits in the offspring (15). One has to keep
hypothyroidism during pregnancy is known to result in cog-
investigate outcome of patients with severe CH as a subgroup.
However, a series of follow-up studies on the cohorts who
were originally screened showed that children still had persis-
table. However, a series of follow-up studies on the cohorts who
in a small increase of 3.6 IQ points (5). No distinction was made
according to severity of CH because of small group size.
To what extent the initial T4 dose is a key factor in preserving
optimal brain development in CH patients is unclear (18); even
recent reports about this issue gave contradictory results. Selva
et al. (6), considering a mean initial T4 dose of 10.9 μg/kg/d as
relatively low, found that patients with CH, receiving this dose
at a mean postnatal age of 10.9 d, had lower FSIQ scores than
controls (89.7 vs. 100.2). However, Bongers-Schokking and de
Muinck Keizer-Schrama (5), considering a similar dose of 10.6
μg/kg/d, as relatively high, found that patients with CH, rece-
ving this dose at a mean postnatal age of 10.8 d, scored equal
to controls (104.6 vs. 105.0 Rakit IQ score). Any effect of both
initial and long-term T4 supplementation on cerebral develop-

The conviction prevailing in the prescreening era that early
treatment would prevent mental retardation has led to the
introduction of neonatal screening once the appropriate tech-
niques (Guthrie card and radioimmunoassays) became avail-
able. However, a series of follow-up studies on the cohorts who
were originally screened showed that children still had persistent
subtle deficits, despite early treatment (1,2). Several studies
have investigated the possible benefits of advancing the initi-
tion of T4 supplementation on outcome in CH patients
detected by neonatal screening. As in our study, Boileau et al. (16)
investigated the impact of changes in the screening procedure
over a 15-yr period: IQ scores of CH patients in whom T4
supplementation was initiated before 21 d after birth were sim-
ilar to controls, whereas IQ scores of patients treated after this
age were significantly lower. This study, however, did not
investigate outcome of patients with severe CH as a subgroup.
Dubuis et al. and Simoneau-Roy et al. have shown that intel-
lectual outcome in patients with severe CH, in whom treatment
was initiated at a median age of 14 d with a mean initial T4 dose
of 12.1 μg/kg/d, was normal both at 18 months (3) and 5 yr
of age (17). Their patient groups, however, were rather small
(n = 8 and 9, respectively). In a sample of Dutch CH patients born
between 1993 and 1996, Bongers-Schokking et al. (4) have
shown that in severe CH, a treatment delay of 6 d, in patients
receiving an initial T4 dose of 10.8 μg/kg/d, led to a loss of 25
points on the Mental Developmental Index of the Dutch version
of the Bayley Scales of Infant Development, when measured
between 11 and 30 months of age. Remarkably, retesting at 5.5–7
yr of age gave contrasting results: a treatment delay of 7 d resulted
in a small increase of 3.6 IQ points (5). No distinction was made
according to severity of CH because of small group size.

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### Table 5. Multiple regression analysis for IQ and motor scores

<table>
<thead>
<tr>
<th></th>
<th>FSIQ</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
<th>Total MABC</th>
<th>Manual dexterity</th>
<th>Ball skills</th>
<th>Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial plasma FT4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentration B</td>
<td>0.816</td>
<td>0.760</td>
<td>0.753</td>
<td>−0.202</td>
<td>−0.121</td>
<td>−0.082</td>
<td>−0.023</td>
</tr>
<tr>
<td>β</td>
<td>0.296</td>
<td>0.277</td>
<td>0.262</td>
<td>−0.142</td>
<td>−0.156</td>
<td>−0.156</td>
<td>−0.039</td>
</tr>
<tr>
<td>P</td>
<td>0.034</td>
<td>0.051</td>
<td>0.057</td>
<td>0.324</td>
<td>0.276</td>
<td>0.268</td>
<td>0.786</td>
</tr>
<tr>
<td>Starting day of T4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>supplementation B</td>
<td>0.005</td>
<td>−0.110</td>
<td>0.124</td>
<td>−0.062</td>
<td>−0.018</td>
<td>−0.017</td>
<td>−0.036</td>
</tr>
<tr>
<td>β</td>
<td>0.005</td>
<td>−0.101</td>
<td>0.110</td>
<td>−0.110</td>
<td>−0.060</td>
<td>−0.084</td>
<td>−0.156</td>
</tr>
<tr>
<td>P</td>
<td>0.973</td>
<td>0.470</td>
<td>0.420</td>
<td>0.443</td>
<td>0.674</td>
<td>0.549</td>
<td>0.276</td>
</tr>
<tr>
<td>R² adjusted</td>
<td>0.060</td>
<td>0.030</td>
<td>0.080</td>
<td>0.015</td>
<td>0.006</td>
<td>0.014</td>
<td>0.000</td>
</tr>
<tr>
<td>Model significance</td>
<td>F(2,63) = 3.077, F(2,63) = 2.014, F(2,63) = 3.817, F(2,60) = 1.471, F(2,62) = 1.179, F(2,63) = 1.457, F(2,62) = 1.008, P = 0.053</td>
<td>P = 0.142</td>
<td>P = 0.027</td>
<td>P = 0.238</td>
<td>P = 0.314</td>
<td>P = 0.241</td>
<td>P = 0.371</td>
</tr>
</tbody>
</table>

Results of multiple regression analysis are given with initial plasma FT4 concentration and starting day of T4 supplementation as independent variables and IQ scores and motor scores as dependent variables.


<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>FSIQ score</th>
<th>Percentage of patients with motor problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.5</td>
<td>93.7 (89.5–97.9)</td>
<td>94.3 (87.9–100.8)</td>
</tr>
<tr>
<td>9.9</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Initial T4 dose (μg/kg/d)</td>
<td>7.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Moderate CH-T (n = 19a and 17b)</td>
<td>96.2 (88.9–103.5)</td>
<td>98.9 (91.6–106.3)</td>
</tr>
<tr>
<td>Age at start of T4 supplementation (d)</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>Initial T4 dose (μg/kg/d)</td>
<td>6.6</td>
<td>7.4</td>
</tr>
<tr>
<td>Mild CH-T (n = 22c and 14d)</td>
<td>105.0 (99.5–110.4)</td>
<td>98.7 (89.2–108.2)</td>
</tr>
<tr>
<td>Age at start of T4 supplementation (d)</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>Initial T4 dose (μg/kg/d)</td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Total group</td>
<td>97.3 (94.2–100.4)</td>
<td>96.8 (92.7–100.9)</td>
</tr>
</tbody>
</table>

FSIQ, expressed as mean (confidence interval), and percentages of patients with a subnormal MABC (i.e. >9.5, 15% in the normative population) or TOMI (i.e. >4, 15% in the normative population) score are presented, as well as the number of patients, the mean age at start of T4 supplementation, and the mean initial T4 dose for each severity subgroup and the total group.

a Number of patients for each severity subgroup in the 1992–1993 cohort.
b Number of patients for each severity subgroup in the 1981–1982 cohort.
ment is ultimately mediated by the intracellular thyroid hormone receptor occupation, established via the plasma FT4 concentration. Consequently, establishing adequate plasma FT4 concentrations as soon as possible after initiation of T4 supplementation and the maintenance of adequate FT4 concentrations thereafter are considered important factors determining outcome of CH patients. However, in a previous study we could not demonstrate a solid correlation between the height of the initial T4 dose and the time needed to reach a plasma FT4 concentration within the reference range (19). This probably explains why we could not find a correlation between the height of the initial T4 dose and outcome.

A limitation of the current study is that motor performance in both CH cohorts had to be assessed with slightly different test methods, as they evolved over time. The MABC, used in the 1992–1993 cohort, contains test items comparable to the TOMI, used in the 1981–1982 cohort, but is considered more sensitive because items are scored on a six-point instead of a three-point scale and because a larger reference group is used (12, 14). Therefore, although it may seem that motor outcome in the 1992–1993 cohort is worse in comparison to the 1981–1982 cohort, this effect may be the consequence of the higher sensitivity of the MABC.

An advantage of the current study is that the design provided the opportunity to study the influence of substantially advanced treatment initiation by comparing data of two large nationwide recruited cohorts of CH patients. In fact, age at treatment initiation was the only variable that essentially distinguished the two cohorts.

Finally, this is the first report on developmental outcome of patients with central CH detected by neonatal screening. The challenge in this group is timely and adequate multiple hormonal suppletions to establish normal growth and brain development, and, especially, to prevent hypoglycemia. The percentage of CH-C patients considered not suitable to participate was relatively high, inherent to their (syndromal) condition of multiple pituitary hormone deficiencies. However, the results of the participating patients are encouraging in that timely and adequate hormonal supplementation established IQ and motor scores not different from patients with moderate CH-T.

In conclusion, this study has shown substantial cognitive and motor deficits in patients with severe CH-T, whose treatment with T4 was initiated at a mean age of 19 d after birth. Mildly and moderately affected CH-T patients had a fair prognosis for IQ, but they too experienced motor problems.

Despite a substantially advanced treatment initiation, as spinoff of a decade of experience with neonatal screening, the increment in LT4 dose in screened congenital hypothyroidism: which was the consequence of the prenatal hypothyroid state.

Acknowledgments

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