Intellectual and Motor Development of Young Adults with Congenital Hypothyroidism Diagnosed by Neonatal Screening

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The objective of this study was to examine cognitive and motor functioning in adult patients with congenital hypothyroidism, diagnosed by neonatal screening, and are scarce. Hence, it is still unclear whether the frequently reported cognitive and motor deficits observed during childhood persist in adulthood.

Objective: The objective of this study was to examine cognitive and motor functioning in young adults with congenital hypothyroidism, born in the first 2yr after the introduction of the Dutch neonatal screening program.

Design/Setting/Patients: Seventy patients were tested (mean age, 21.5yr); 49 of them were previously tested at 9.5yr. The median age at the start of treatment was 28d (range, 4–293d). Congenital hypothyroidism was classified as severe, moderate, or mild, according to pretreatment T4 concentrations.

Main Outcome Measurement: The main outcome measurement was the influence of the severity of congenital hypothyroidism and age at which T4 supplementation was started on cognitive and motor outcome.

Results: Patients, particularly those with severe congenital hypothyroidism, had significantly higher (i.e. worse) motor scores (total score, 7.8; ball skills, 2.0; balance, 4.1) compared with controls (total score, 3.2; ball skills, 0.7; balance, 1.1), and lower full-scale (95.8), verbal (96.4), and performance (95.6) intelligence quotient (IQ) scores than the normal population. No significant change in IQ from childhood to adulthood was found, and for the majority of patients, motor score classification remained the same. The severity of congenital hypothyroidism, but not the starting day of treatment, was correlated with IQ and motor scores.

Conclusions: It is concluded that the severity of congenital hypothyroidism, but not the timing of treatment initiation, is an important factor determining long-term cognitive and motor outcome. Clearly, detrimental effects on developmental outcome in patients with congenital hypothyroidism persist over time.

HYROID HORMONE PLAYS an essential role in brain development during pre- and postnatal life (1). Pre-natally, the thyroid hormone state is dependent on maternal-fetal thyroid hormone transfer and fetal thyroid hormone production starting from the second trimester onward. Congenital hypothyroidism (CH), which implies a total or partial inability to produce thyroid hormone, is notorious because the serious impairments, there is ample evidence that CH in the fetal phase on brain function in later life is largely unknown. Although it is clear that shortening the postnatal phase of hypothyroidism is highly effective in eradicating serious impairments, there is ample evidence that CH patients diagnosed by neonatal screening are still vulnerable to persistent cognitive and motor sequela (4). The magnitude of the deficits is shown to be dependent on the severity of CH, the timing of T4 treatment initiation, and the adequacy of treatment (5–9). In an earlier study, we showed that Dutch patients with CH born in 1981 and 1982 and tested at 7.5 and 9.5yr of age had motor problems and borderline intelligence scores, especially those with severe neonatal hypothyroidism (5).

Almost all outcome studies in CH only report data until late childhood. Consequently, it is not clear whether the cognitive and motor problems seen during childhood persist into adulthood. To date, only one study has reported the long-term outcome in (young) adult patients with CH (10).

The present study followed an approach in which long-term cognitive and motor outcome was assessed in young adult patients with early-treated CH born in 1981 and 1982. Outcome was analyzed in relation to the severity of CH as well as treatment variables. Furthermore, outcome obtained at an adult age was related to childhood results from the same individuals (5).

Patients and Methods

Screening method and treatment strategy

The Dutch neonatal CH screening method is primarily based on the measurement of T4 T4 expressed as an sd score, is compared with the
day's mean. In the early 1980s, sampling was performed between 7 and 14 days after birth. If T4 was <0.8 sp or less, TSH was additionally measured. If T4 was <3.0 sp or less or TSH was 50 μU/ml or more, children were referred immediately to a pediatrician for diagnostic evaluation. Children with a borderline result (<3.0 < T4-2.1 sp, or 25 < TSH <50 μU/ml) underwent a second heel puncture and were referred if the result was again borderline or abnormal. The diagnosis of CH and its etiological classification were based upon initial presentation, thyroid function determinants, and thyroid imaging.

In the early 1980s the national guideline for treatment was to start with one of two schemes. In scheme 1, patients started with T3 supplementation. After 1 wk, T4 was added (4 μg/kg/d), with a gradual increase to 8–10 μg/kg/d after 2 wk. With the start of T4 supplementation the T3 dose was gradually diminished and was stopped after 3 wk. In scheme 2, patients started with T4 (6 μg/kg-d), which was increased to 8–10 μg/kg/d after 1 wk. Thereafter, T4 supplementation doses were adjusted based on thyroid hormone determinants, measured during regular out-patient visits, according to international guidelines.

**Patients at 21.5 yr of age**

The complete cohort of CH patients born in The Netherlands between 1981 and 1982 consisted of 136 patients (Table 1). Medical data for these patients were available in the Academic Medical Center because of previous studies (5, 11). From the original cohort, four patients had died, and three had moved abroad; five had severe mental retardation related to chromosomal abnormalities (n = 4) or unclassified syndrome with deafness (n = 1; Table 1, nonparticipants, not suitable). In 2001, at the start of this study, the remaining 124 patients were contacted via their physicians and asked to participate. A total of 82 patients (66%) gave their written informed consent; their initial thyroid hormone concentrations and treatment modality were recorded. Of this group, 12 patients were excluded from the study because of central CH (n = 1; all other patients had thyroidal CH), exceptionally late (i.e., >4 yr of age) start of treatment (n = 5), discontinuation of treatment at a young age (n = 4), treatment was never initiated (n = 1), or the patient was unwilling to complete the assessments (n = 1; Table 1, nonparticipants, not suitable).

The remaining 70 patients (Table 1, participants at 21.5 yr), 51% of the original cohort, were classified into subgroups according to arbitrarily chosen cut-off levels for severity of postnatal hypothyroidism: severe CH: initial T4 less than 2.3 μg/dl (<30 nmol/liter); moderate CH: 2.3 or less than initial T4 less than 4.7 μg/dl (30 ≤ initial T4 <60 nmol/liter); or mild CH: initial T4 4.7 μg/dl or more (≥60 nmol/liter). The T4 reference range in children aged 2–6 wk is 6.5–16.3 μg/dl (84–210 nmol/liter) (12). The subgroups severe CH and moderate CH were further classified according to starting day of T4 treatment: early (age, <27 d) or late (age, ≥27 d) and initial treatment protocol.

The study protocol was approved by the institutional review board of the Academic Medical Center.

**Assessments at 21.5 yr of age**

Cognitive and motor assessments were carried out in the 70 participating patients at the Academic Medical Center in Amsterdam (except for four patients who were tested in their local hospitals) by the same psychologist, who was blinded for the patients' medical details. Patients were tested at a mean age of 21.5 yr (range, 21.0–22.3 yr). To ascertain that 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 assessments was evaluated. In those patients with plasma TSH concentrations outside the reference range, the T4 dose was adjusted. This resulted in dose adjustments for 25 patients; in one patient treatment compliance was optimized.

**Cognitive assessments**

Intelligence was tested with the Dutch version of the Wechsler Adult Intelligence Scale III (13). With the subjects' performances on 11 subtests, three intelligence quotients were derived: full-scale intelligence quotient (IQ), verbal IQ, and performance IQ. In the normal population, each IQ score has a mean of 100 and an sd of 15.

**Motor assessments**

Motor skills were assessed with the movement assessment battery for children (MABC) (14, 15). The MABC is designed for identification of motor impairments in children. The manual provides normative data for children 4–12 yr of age. The test results are expressed in terms of a total motor impairment score (MABC ranging from 0–40), a manual dexterity score (range, 0–15), a ball skills score (range, 0–10), and a balance score (range, 0–15); higher scores indicate more motor problems. By convention, 85% of the normal population have no motor problems (total motor impairment score MABC, >9.5), 10% have borderline motor problems (score, 10–13), and 5% have definite motor problems (score, >13.5).

In the absence of normative data for young adults, the CH patients were compared with a group of 66 healthy controls (41 females), tested at a mean age of 21.3 yr. Controls were recruited among students, hospital employees, and hobby club members. Scores for patients and controls were interpreted using the normative data of 12-yr-old children.

**Patients and assessments at the age of 9.5 yr**

A total of 63 CH patients, 46% of the original cohort of patients born in 1981–1982 (Table 1, participants at 9.5 yr), and 35 controls were previously studied at 9.5 yr. IQ was measured with the Wechsler Intelligence Scale for Children–Revised (16), and motor skills were assessed with the test of motor impairment (TOMI) (17). The TOMI later evolved into the MABC and contains similar items. The TOMI score ranges from 0–20. By convention, 85% of the normal population have no motor problems (TOMI, <4), 10% have borderline motor problems (TOMI, 4–6), and 5% have definite motor problems (TOMI, >6).

**Statistical analysis**

One-sample t tests were used to determine whether the IQ scores in CH patients differed from the norm of 100. Binomial tests were conducted to test whether the percentages of CH patients in the different severity groups with an IQ score less than 85 or a total motor impairment score MABC greater than 9.5 differed from the percentages in the normal population.

Comparisons of IQ and motor scores were made among the following subgroups: severe vs. moderate vs. mild CH, early vs. late treatment, initiation with T4 supplementation vs. T3 supplementation, and patients who participated at 20 yr of age but not at 9.5 yr of age compared with those who participated at 9.5 yr of age.

**TABLE 1.** Characteristics of the 1981–1982 cohort

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Total</th>
<th>Nonparticipants</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Not suitable</td>
<td>Not willing</td>
</tr>
<tr>
<td>Thyroid agenesis</td>
<td>36</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Thyroid dysgenesis</td>
<td>59</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Thyroid dyshormogenesis</td>
<td>17</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Central CH</td>
<td>19</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>CH n.o.s.</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>24</td>
<td>42</td>
</tr>
</tbody>
</table>

Six groups are presented; the total group, the group of patients who did not participate divided in patients not suitable or not willing to participate, the group of patients who did participate at 21.5, 9.5, and at both 9.5 and 21.5 yr of age. For each group, the subdivision according to etiological classification is given. CH n.o.s., CH not otherwise specified.
ANOVA was used for group comparisons of continuous variables (post hoc group comparisons were performed with Bonferroni post hoc analysis), while χ² tests were used for categorical variables. For variables where the distributions of scores differed significantly from the normal distribution, nonparametric tests, such as the Mann-Whitney U tests, were used.

When multiple analyses were performed with the Mann-Whitney U, binomial, or χ² tests to compare scores, a correction for multiple testing was using by considering \( P < 0.01 \) significant.

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: parental educational level by severity: \( \chi^2 = 0.335; P = 0.846 \); parental educational level by initiation with T₄ or T₃: \( \chi^2 = 0.239; P = 0.625 \); parental educational level by early or late treatment: \( \chi^2 = 0.105; P = 0.746 \).

Linear regression models were fitted for IQ and motor scores, with severity (initial T₄ concentration) and starting day of T₄ supplementation as independent variables. In addition, bivariate correlation analyses between either severity of CH or the starting day of treatment and IQ and motor scores were performed. Similarly, bivariate correlations were calculated between full-scale IQ and total motor impairment score MABC.

For the longitudinal analysis of IQ scores obtained at 9.5 and 21.5 yr of age, the paired samples t-test (two-tailed) was used. Correlation analyses (Spearman) were conducted for the TOMI and MABC scores at the two ages.

### Results

#### Patient characteristics

The baseline characteristics of the participating CH patients are given in Table 2. Of the 70 patients (55 females, 79%), 35 had severe CH, of whom the majority (21 patients) had thyroid agenesis. Moderate and mild CH were seen in 16 (23%) and 19 (27%) patients respectively, of whom the majority had thyroid dysgenesis (9 and 17 patients, respectively).

The median age at start of T₄ supplementation was 28 d for the total group. In patients with severe and moderate CH, the median age at start of T₄ supplementation was younger than in those with mild CH (Table 2). In 28 patients, treatment started with T₃ supplementation, and in 39 patients treatment started with T₄ supplementation; in three patients, the initial treatment strategy could not be retrieved with certainty.

#### Intellectual and motor outcome at adult age

Mean IQ scores of the total CH group were significantly lower than the population mean (full-scale IQ: \( P = 0.017 \); \( t = -2.450 \); verbal IQ: \( P = 0.042 \); \( t = -2.450 \); performance IQ: \( P = 0.012 \); \( t = -2.568 \); Table 3). Compared with the controls, the total CH group scored significantly worse on motor scores, except for manual dexterity (\( P < 0.001 \); Table 4). Full-scale IQ and total motor impairment score MABC were significantly correlated (\( r = -0.442; P < 0.001 \)).

Mean full-scale and performance IQ scores differed significantly between the severity groups [full-scale IQ: F(2,67) = 3.754; \( P = 0.028 \); performance IQ: F(2,67) = 5.112; \( P = 0.009 \); Table 3 and Fig. 1]. Post hoc analysis showed that the differences in mean full-scale and performance IQs were significant between severe CH and mild CH (\( P = 0.043 \) and \( P = 0.037 \), respectively). There was also a significant difference in mean performance IQ between severe CH and moderate CH (\( P = 0.031 \); Table 3).

Among patients with severe CH, 37% had a full-scale IQ score less than 85. This percentage was significantly higher than that in the normal population (\( P = 0.002 \)). In the moderate and mild CH groups, the percentages of children with a full-scale IQ score less than 85 (19% and 5%, respectively) were not significantly different from those in the normal population.

Patients with severe CH performed significantly worse on the total motor impairment score MABC and manual dexterity than patients with moderate CH (\( P = 0.004 \) and \( P = 0.007 \), respectively; Table 4). In the control group, the percentage of subjects with a subnormal total motor impairment score MABC (12% >9.5) was slightly, but not significantly, lower than that in the normal population (15% >9.5). Among patients with severe CH, 49% had a subnormal total motor impairment score MABC, which was significantly higher than the percentage in the normal population or controls (\( P < 0.001 \)). In the moderate and mild CH groups, the percentages of children with a total motor impairment score MABC above 9.5 (14% and 21%, respectively) were not significantly different from those in the normal population or controls.

IQ and motor scores of those patients who started with T₃

### Table 2

<table>
<thead>
<tr>
<th>Characteristics of the subgroups with different severities of CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe CH</td>
</tr>
<tr>
<td>No. of patients (male:female)</td>
</tr>
<tr>
<td>Initial T₄ in μg/dl (95% CI)* [in nmol/liter (95% CI)]</td>
</tr>
<tr>
<td>Initial TSH in μU/ml (95% CI)*</td>
</tr>
<tr>
<td>Total defects</td>
</tr>
<tr>
<td>Agenesis</td>
</tr>
<tr>
<td>Dysmorphogenesis</td>
</tr>
<tr>
<td>Partial defects</td>
</tr>
<tr>
<td>Dysgenesis</td>
</tr>
<tr>
<td>Age at start of T₄ supplementation in d (range)</td>
</tr>
</tbody>
</table>

T₄ and TSH concentrations are expressed as the mean, with the 95% confidence interval (CI) in brackets. For the etiology subgroups the number of patients is presented. The age at the start of treatment is presented as the mean, with the range in parentheses.

* Reference range for T₄ in children aged 2–6 wk, 6.5–16.3 μg/dl (84–210 nmol/liter) (12).

* Reference range for TSH in children aged 2–6 wk, 1.7–9.1 μU/ml (12).

* One patient, in whom T₄ supplementation was started at the age of 4 d, was already diagnosed before CH screening because of familial CH.
supplementation did not differ significantly from those who started with \( T_4 \) supplementation, nor were the scores different for patients in whom treatment was initiated before or after the age of 27 d.

In a bivariate correlation analysis, the initial \( T_4 \) concentration appeared to be associated with full-scale IQ (\( r = 0.278; P = 0.020 \)), performance IQ (\( r = 0.330; P = 0.005 \)), total motor impairment score MABC (\( r = -0.337; P = 0.005 \)), ball skills (\( r = -0.299; P = 0.013 \)), and balance (\( r = -0.278; P = 0.021 \)). Correlation analyses showed no correlation between starting day and IQ or motor scores.

In a multiple regression analysis with severity of CH and starting day of \( T_4 \) supplementation as independent variables, the severity of CH appeared to be a significant predictor of full-scale IQ (\( P = 0.022 \)), performance IQ (\( P = 0.002 \)), and total motor impairment score MABC (\( P = 0.023 \)); the starting day of treatment did not predict IQ or motor scores (Table 5).

### Intellectual and motor outcome: longitudinal assessment

The IQ scores of the 49 patients tested at 9.5 as well as 21.5 yr are shown in Table 6. The paired samples \( t \) test showed no significant differences in IQ scores at 9.5 and 21.5 yr of age and a significant correlation among full-scale, verbal and performance IQ scores at 9.5 and 21.5 yr (\( r = 0.799, P < 0.001; r = 0.820, P < 0.001; r = 0.678, P < 0.001 \), respectively).

There was a significant correlation between motor scores at 9.5 and 21.5 yr: total motor impairment score MABC (\( r = 0.339; P < 0.017 \)), ball skills (\( r = 0.316; P = 0.025 \)), and balance (\( r = 0.431; P = 0.002 \)). For the majority of patients, the classification of the total motor impairment scores at both ages were discordant (14% from normal at TOMI to normal at MABC, 22% from normal at TOMI to subnormal at MABC).

### Discussion

The aim of neonatal screening is to prevent cerebral damage due to lack of thyroid hormone by enabling early and adequate \( T_4 \) supplementation. However, we found persistent cognitive and motor deficits in young adults with CH born in the first 2 yr after the nationwide introduction of screening. Cognitive deficits were observed in both verbal and performance domains, and motor deficits were found in balance, fine motor, as well as ball skills. Deficits were most pronounced in patients with severe CH and were comparable to those measured during childhood.

Although several studies have shown subnormal cognitive and motor development during childhood (4, 5, 7, 18), our study is only the second one reporting on the persistence of these deficits into adulthood (10). Both studies are comparable with regard to the number of participating patients and the timing of initiation of treatment, but there are two major differences in the design. In our study, comparisons were made between severity subgroups and between CH patients and the normal population, whereas in the study of Oerbeck et al. (10), the total CH group was compared with siblings, and no differentiation in severity was made. Oerbeck et al. (10) found that only motor outcome correlated with the severity of CH. We found that also IQ scores correlated with the severity of CH.

The other major difference in the design is that we considered euthyroidism at the time of testing an essential condition for each individual patient. Therefore, we verified in all patients that, before the cognitive and motor assessments, plasma TSH concentrations were within the reference range.
In Oerbeck’s study (10), however, the mean TSH concentration at the time of testing was 12.2 μU/ml. The supposedly suboptimal treatment potentially influenced the patients’ cognitive functioning (i.e. attention, speed of processing, etc.) (19, 20), which impedes judgments on the effect of severity of hypothyroidism on outcome.

Because important steps in brain development take place from early gestation until several years after birth, outcome determinants of CH patients should be correlated to both pre- and early postnatal thyroid hormone concentrations. According to term cord plasma T4 concentrations, the prenatal thyroid hormone state in fetuses without (functioning) thyroid tissue is comparable to the postnatal thyroid hormone state in neonates with moderate CH (21). This must be the effect of a substantial, but limited, maternal-fetal transfer of T4. It is likely that this maternal contribution to the fetal thyroid hormone state is a major factor in protecting brain development, but it is not known whether it is always sufficient to completely preserve prenatal brain development. When, in particular in patients with severe CH, T4 concentrations rapidly decline after birth, this is undoubtedly a dangerous condition with respect to thyroid hormone-dependent brain development. Neonatal screening is only capable of shortening the period of postnatal thyroid hormone deficiency; once T4 supplementation is started, plasma free T4 concentrations increase rapidly (22).

Only in our patients diagnosed with severe CH (pretreatment T4 concentrations, <2.3 μg/dl) were significant cognitive and motor deficits found. This underscores that the severity of CH is an important factor determining cognitive
and motor outcomes (4, 6, 8, 18, 23). The question is whether earlier initiated postnatal T₄ supplementation had been able to prevent the observed damage. In our study, we could not find any relation between the day treatment was initiated and IQ or motor scores, nor did we find within the severe CH group a beneficial effect of early treatment initiation. This might be influenced by the fact that treatment initiation was strongly correlated with the severity of CH or by too little variation in the day of the start of treatment.

An important consideration is that the patients in our study were among the first Dutch patients screened and were treated relatively late (mean, 27 d for severe and moderate CH; 74 d for mild CH), with lower T₄ doses than have been advised in more recent years (24). It is possible that the time frame for early and adequate treatment to prevent cerebral damage was before the age at which treatment was initiated in these patients. Indeed, some studies indicate that even patients with severe CH, assessed in the first 3 yr of life, had normal cognitive and motor outcomes if treatment started early and with high initial T₄ doses (25, 26). However, others did not find a beneficial effect on developmental outcome of higher (≥6 μg/kg-d) compared with lower (<6 μg/kg-d) initial T₄ doses, in patients treated before the age of 3 wk (27), nor could we demonstrate in a previous study that variations in the initial T₄ dose influenced the time needed to reach a plasma free T₄ concentration within the reference range (22). Furthermore, it still needs to be established whether improvements in IQ due to optimized timing and/or dose of treatment lead to improved well-being without detrimental effects on behavior or social emotional development (28, 29).

Several investigators have reported that the adequacy of long-term T₄ supplementation influences outcome (25, 30, 31). Yet, this variable was not studied explicitly in the Dutch cohort, because, in our opinion, treatment adequacy is difficult to assess by integrating the numerous plasma TSH and free T₄ concentrations from infancy to adulthood. As in healthy people, concentrations in well-treated patients may vary considerable (32), and mean values completely disregard intraindividual fluctuations and interindividual variations. The durations of phases of inadequate treatment (especially lack of compliance) cannot be established in retrospect. Besides, treatment of CH patients is remarkably uniform regardless of severity. All studied patients were treated according to criteria of good clinical practice by pediatricians who rely on (inter)national guidelines (preserving euthyroidism primarily by maintaining plasma TSH concentrations within the reference range with regular T₄ dose adjustments). Therefore, we had no reason to assume group differences in long-term treatment adequacy, including compliance. Patients with moderate or mild CH had IQ scores indistinguishable from those of the normal population, indicating implicitly that even if these patients had experienced phases of insufficient treatment, these had no consequences for intellectual outcome at adult age. This makes it unlikely that the IQ deficits observed in patients with severe CH had anything to do with long-term treatment insufficiency.

The use of the MABC in this study requires some comment. This test is developed to detect motor problems in children; consequently, normative data for adults are not available. Nevertheless, we applied this test to detect motor problems in adults with CH by using norms of 12-yr-old children. This might have resulted in an underestimation of motor problems in our patient group. Indeed, the percentage in the adult control group with a subnormal motor score (12%) was slightly, but not significantly, lower than that in the general population (15% by convention). However, even with a potential underestimation, the CH group had substantially more motor problems than the control group.

In conclusion, this study has shown that cognitive and motor deficits in CH patients, who started treatment at a median age of 28 d after birth, persist into adulthood. Mildly and moderately affected patients have a fair prognosis, whereas severely affected CH patients continue to experience IQ and motor problems in later life. Cognitive and motor outcomes could not be related to the age at which T₄ treatment was initiated. Apparently the postnatal treatment strategy used in The Netherlands in the early eighties was not capable of abolishing all negative effects of severe congenital hypothyroidism.

Regarding the directions for future research, it is important to move beyond the mere task of establishing levels of cognitive and motor functioning and also investigate the long-term social emotional and behavioral consequences of early-treated CH.

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