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

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Context: Long-term follow-up data on cognitive and motor functioning in adult patients with congenital hypothyroidism, diagnosed by neonatal screening, 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 2 yr after the introduction of the Dutch neonatal screening program.

Design/Setting/Patients: Seventy patients were tested (mean age, 21.5 yr); 49 of them were previously tested at 9.5 yr. The median age at the start of treatment was 28 d (range, 4–293 d). Congenital hypothyroidism was classified as severe, moderate, or mild, according to pretreatment T_4 concentrations.

Main Outcome Measurement: The main outcome measurement was the influence of the severity of congenital hypothyroidism and age at which T_4 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. **(*J Clin Endocrinol Metab* 91: 418–424, 2006)**

THYROID HORMONE PLAYS an essential role in brain development during pre- and postnatal life (1). Prenatally, 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 of the serious life-long cognitive and motor deficits seen before the advent of mass CH-screening programs (2, 3). The influence of impaired thyroid hormone production during 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 T_4 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 9.5 yr 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).

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Abbreviations: CH, Congenital hypothyroidism; IQ, intelligence quotient; MABC, movement assessment battery for children; TOMI, test of motor impairment.

Patients and Methods

Screening method and treatment strategy

The Dutch neonatal CH screening method is primarily based on the measurement of T_4. T_4, expressed as an SD score, is compared with the

day's mean. In the early 1980s, sampling was performed between 7 and 14 d after birth. If T_4 was −0.8 SD or less, TSH was additionally measured. If T_4 was −3.0 SD 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 ($-3.0 < T_4 \leq -2.1$ SD, or $25 \leq$ 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 T_3 supplementation. After 1 wk, T_4 was added (4 μg/kg·d), with a gradual increase to 8–10 μg/kg·d after 2 wk. With the start of T_4 supplementation the T_3 dose was gradually diminished and was stopped after 3 wk. In scheme 2, patients started with T_4 (6 μg/kg·d), which was increased to 8–10 μg/kg·d after 1 wk. Thereafter, T_4 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 T_4, less than 2.3 μg/dl (<30 nmol/liter); moderate CH: 2.3 or less than initial T_4 less than 4.7 μg/dl ($30 \leq$ initial $T_4 <60$ nmol/liter); or mild CH: initial T_4 4.7 μg/dl or more (≥60 nmol/liter). The T_4 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 T_4 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 T_4 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 T_3 supplementation *vs.* T_4 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

Etiology	Total	Nonparticipants		Participants		
		Not suitable	Not willing	At 21.5 yr	At 9.5 yr	At 9.5 & 21.5 yr
Thyroid agenesis	36	2	9	25	24	17
Thyroid dysgenesis	59	7	15	37	30	26
Thyroid dyshomonogenesis	17	3	6	8	9	6
Central CH	19	8	11	0	0	0
CH n.o.s.	5	4	1	0	0	0
Total	136	24	42	70	63	49

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 χ^2 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 χ^2 tests to compare scores, a correction for multiple testing was used 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 T_3 or T_4: $\chi^2 = 0.239$; $P = 0.625$; 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 T_4 concentration) and starting day of T_4 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 T_4 supplementation was 28 d for the total group. In patients with severe and moderate CH, the mean age at start of T_4 supplementation was younger than in those with mild CH (Table 2). In 28 patients, treatment started with T_3 supplementation, and in 39 patients treatment started with T_4 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 T_3

TABLE 2. Characteristics of the subgroups with different severities of CH

	Severe CH	Moderate CH	Mild CH
No. of patients (male:female)	35 (7:28)	16 (3:13)	19 (5:14)
Initial T_4 in μg/dl (95% CI)[a] [in nmol/liter (95% CI)]	1.1 (0.9–1.4) [14.5 (11.5–17.4)]	3.4 (3.1–3.7) [43.6 (39.5–47.6)]	7.6 (6.2–8.9) [97.2 (79.8–114.6)]
Initial TSH in μU/ml (95% CI)[b]	497 (298–696)	496 (336–656)	142 (50–234)
Total defects			
Agenesis	21	4	0
Dyshormonogenesis	3	1	0
Partial defects			
Dysgenesis	11	9	17
Dyshormonogenesis	0	2	2
Age at start of T_4 supplementation in d (range)	27 (8–47)	27 (4–47)[c]	74 (18–293)

T_4 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*.

[a] Reference range for T_4 in children aged 2–6 wk, 6.5–16.3 μg/dl (84–210 nmol/liter) (12).

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

[c] One patient, in whom T_4 supplementation was started at the age of 4 d, was already diagnosed before CH screening because of familial CH.

TABLE 3. IQ scores of the CH patients at 21.5 yr of age

	Full-scale IQ	Verbal IQ	Performance IQ
Severe CH (n = 35)	91.3 (86.3–96.3)[a]	92.9 (88.1–97.8)	90.4 (85.2–95.6)[b]
Moderate CH (n = 16)	99.1 (91.1–107.1)	97.8 (89.2–106.3)	101.3 (94.8–107.7)
Mild CH (n = 19)	101.3 (95.7–106.9)	101.8 (96.1–107.5)	100.4 (94.7–106.1)
Total CH (n = 70)	95.8 (92.3–99.2)[c]	96.4 (93.0–99.9)[d]	95.6 (92.3–99.2)[e]

IQ scores (expressed as the mean with confidence interval in *parentheses*) are presented for the total CH group and the severity subgroups.
[a] $P = 0.043$ *vs.* mild CH.
[b] $P = 0.031$ *vs.* moderate CH; $P = 0.037$ *vs.* mild CH.
[c] $P = 0.017$ ($t = -2.450$) *vs.* normal population.
[d] $P = 0.042$ ($t = -2.077$) *vs.* normal population.
[e] $P = 0.012$ ($t = -2.568$) *vs.* normal population.

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 concordant normal (45%) or abnormal (18%). However, in 36% of patients, total motor impairment scores at both ages were discordant (14% from subnormal at TOMI to normal at MABC, 22% from normal at TOMI to subnormal at MABC).

IQ and motor scores at 21.5 yr for those patients who did and those who did not participate at 9.5 yr of age did not differ significantly.

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.

TABLE 4. Motor scores of the CH patients at 21.5 yr of age

	Total motor impairment score MABC	Manual dexterity score	Ball skills score	Balance score
Severe CH (n = 35)	9.8 (7.6–11.9)[a]	2.1 (1.4–2.8)[b]	2.6 (1.8–3.4)	5.1 (3.6–6.6)
Moderate CH (n = 16)	4.3 (2.1–6.5)	0.5 (0.0–0.9)	1.5 (0.3–2.6)	2.4 (1.1–3.7)
Mild CH (n = 19)	6.7 (3.5–9.9)	1.8 (0.3–3.4)	1.4 (0.6–2.2)	3.4 (1.6–5.3)
Total CH (n = 70)	7.8 (6.3–9.3)[c]	1.7 (1.1–2.3)	2.0 (1.5–2.5)[c]	4.1 (3.1–5.0)[c]
Controls (n = 66)	3.2 (2.3–4.2)	1.4 (0.9–1.8)	0.7 (0.4–1.1)	1.1 (0.6–1.7)

Motor scores (expressed as the mean with confidence interval in *parentheses*) are presented for the total CH group, the severity subgroups, and the controls.
[a] $P = 0.004$ *vs.* moderate CH.
[b] $P = 0.007$ *vs.* moderate CH.
[c] $P < 0.001$ *vs.* control group.

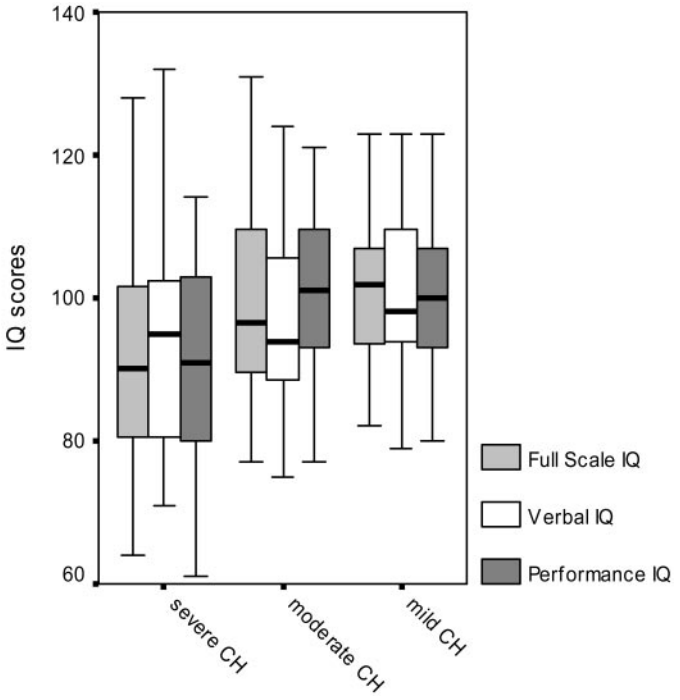

FIG. 1. Full-scale IQ, verbal IQ, and performance IQ scores of the CH patients at 21.5 yr of age. The box plot shows the full-scale IQ, verbal IQ, and performance IQ scores of the CH severity subgroups. The *box* incorporates 50% of all observations, the *das*h represents the median IQ score, and the *whiskers* represent the highest and lowest scores.

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 T_4 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 T_4. 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, T_4 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 T_4 supplementation is started, plasma free T_4 concentrations increase rapidly (22).

Only in our patients diagnosed with severe CH (pretreatment T_4 concentrations, <2.3 μg/dl) were significant cognitive and motor deficits found. This underlines that the severity of CH is an important factor determining cognitive

TABLE 5. Multiple regression analysis, IQ scores

T_4	Full-scale IQ	Verbal IQ	Performance IQ	Total MABC	Manual dexterity	Ball skills	Balance
Initial T4 concentration							
B	0.121	0.074	0.163	−0.052	−0.012	−0.014	−0.026
β	0.341	0.213	0.456	−0.337	−0.203	−0.272	−0.264
P	0.022	0.154	0.002	0.023	0.178	0.064	0.075
Starting day of treatment							
B	−0.028	0.002	−0.065	−0.003	0.004	−0.004	−0.003
β	−0.090	0.008	−0.205	−0.024	0.076	−0.081	−0.037
P	0.538	0.959	0.149	0.869	0.613	0.576	0.803
R^2 adjusted	0.061	0.018	0.117	0.095	−0.001	0.077	0.053
Model significance	F(2,64) = 3.149	F(2,64) = 1.594	F(2,64) = 5.389	F(2,62) = 4.366	F(2,64) = 0.979	F(2,63) = 3.720	F(2,63) = 2.824
	P = 0.050	*P* = 0.211	*P* = 0.007	*P* = 0.017	*P* = 0.381	*P* = 0.030	*P* = 0.067

Results of multiple regression analysis are given with initial T_4 concentration and starting day of treatment as independent variables and IQ scores and motor scores as dependent variable.

TABLE 6. IQ scores of the CH patients tested at 9.5 and 21.5 yr of age

	Severe CH (n = 22)		Moderate CH (n = 14)		Mild CH (n = 13)	
	9.5 yr	21.5 yr	9.5 yr	21.5 yr	9.5 yr	21.5 yr
Full-scale IQ	91.1 (85.2–97.0)	90.6 (84.2–97.1)	99.7 (91.9–107.5)	100.2 (91.7–108.8)	101.9 (91.8–112.1)	102.5 (96.1–109.0)
Verbal IQ	91.3 (85.3–97.2)	92.8 (86.2–99.4)	96.4 (89.2–103.5)	98.9 (89.4–108.5)	98.5 (90.2–106.8)	102.1 (95.8–108.3)
Performance IQ	92.6 (87.1–98.1)	89.0 (82.3–95.7)	103.9 (95.7–112.0)	102.3 (96.1–108.5)	105.3 (94.0–116.6)	102.7 (96.3–109.1)

IQ scores (expressed as the mean with confidence interval in *parentheses*) are given for the 49 patients tested at 9.5 and 21.5 yr of age.

and motor outcomes (4, 6, 8, 18, 23). The question is whether earlier initiated postnatal T_4 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 T_4 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 T_4 doses (25, 26). However, others did not find a beneficial effect on developmental outcome of higher ($\geq$6 μg/kg·d) compared with lower ($<$6 μg/kg·d) initial T_4 doses, in patients treated before the age of 3 wk (27), nor could we demonstrate in a previous study that variations in the initial T_4 dose influenced the time needed to reach a plasma free T_4 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 T_4 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 T_4 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 T_4 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 T_4 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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References

1. **Bernal J, Guadano-Ferraz A, Morte B** 2003 Perspectives in the study of thyroid hormone action on brain development and function. Thyroid 13:1005–1012
2. **Raiti S, Newns GH** 1971 Cretinism: early diagnosis and its relation to mental prognosis. Arch Dis Child 46:692–694
3. **Klein AH, Meltzer S, Kenny FM** 1972 Improved prognosis in congenital hypothyroidism treated before age three months. J Pediatr 81:912–915
4. **Derksen-Lubsen G, Verkerk PH** 1996 Neuropsychologic development in early treated congenital hypothyroidism: analysis of literature data. Pediatr Res 39:561–566
5. **Kooistra L, Laane C, Vulsma T, Schellekens JM, van der Meere JJ, Kalverboer AF** 1994 Motor and cognitive development in children with congenital hypothyroidism: a long-term evaluation of the effects of neonatal treatment. J Pediatr 124:903–909
6. **Tillotson SL, Fuggle PW, Smith I, Ades AE, Grant DB** 1994 Relation between biochemical severity and intelligence in early treated congenital hypothyroidism: a threshold effect. Br Med J 309:440–445
7. **Rovet JF, Ehrlich RM, Sorbara DL** 1992 Neurodevelopment in infants and preschool children with congenital hypothyroidism: etiological and treatment factors affecting outcome. J Pediatr Psychol 17:187–213
8. **Salerno M, Militerni R, Di Maio S, Bravaccio C, Gasparini N, Tenore A** 1999 Intellectual outcome at 12 years of age in congenital hypothyroidism. Eur J Endocrinol 141:105–110
9. **Rovet JF** 1999 Long-term neuropsychological sequelae of early-treated congenital hypothyroidism: effects in adolescence. Acta Paediatr 432(Suppl): 88–95
10. **Oerbeck B, Sundet K, Kase BF, Heyerdahl S** 2003 Congenital hypothyroidism: Influence of disease severity and L-thyroxine treatment on intellectual, motor, and school-associated outcomes in young adults. Pediatrics 112:923–930
11. **Vulsma T** 1991 Etiology and pathogenesis of congenital hypothyroidism. Evaluation and examination of patients detected by neonatal screening in The Netherlands, academic thesis, University of Amsterdam
12. **Fisher DA** 1991 Clinical review 19. Management of congenital hypothyroidism. J Clin Endocrinol Metab 72:523–529
13. **Wechsler Adult Intelligence Scale III** 2000 Dutch manual. Lisse: Swetstest
14. **Henderson SE, Sugden DA** 1992 Movement assessment battery for children: manual. London: Psychological Corp
15. **Smits-Engelsman BCM** 1998 Dutch manual movement ABC. Lisse: Swets, Zeitlinger
16. **Haasen PP, de Bruyn EEJ, Pij YJ, Poortinga YH, Lutje Spelberg HC** 1986 Wechsler intelligence scale for children-revised; Dutch edition, Lisse, The Netherlands. Lisse: Swets, Zeitlinger
17. **Stott DH, Moyes FA, Henderson SE** 1984 Test of motor impairment. Guelph, Ontario: Brook Educational Publishing
18. **Simons WF, Fuggle PW, Grant DB, Smith I** 1997 Educational progress, behaviour, and motor skills at 10 years in early treated congenital hypothyroidism. Arch Dis Child 77:219–222
19. **Song SI, Daneman D, Rovet J** 2001 The influence of etiology and treatment factors on intellectual outcome in congenital hypothyroidism. J Dev Behav Pediatr 22:376–384
20. **Rovet J, Alvarez M** 1996 Thyroid hormone and attention in school-age children with congenital hypothyroidism. J Child Psychol Psychiatry 37:579–585
21. **Vulsma T, Gons MH, De Vijlder JJM** 1989 Maternal fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. N Engl J Med 321:13–16
22. **Bakker B, Kempers MJE, De Vijlder JJM, Van Tijn DA, Wiedijk BM, Van Bruggen M, Vulsma T** 2002 Dynamics of the plasma concentrations of TSH, FT4 and T3 following thyroxine supplementation in congenital hypothyroidism. Clin Endocrinol (Oxf) 57:529–537
23. **Fuggle PW, Grant DB, Smith I, Murphy G** 1991 Intelligence, motor skills and behaviour at 5 years in early-treated congenital hypothyroidism. Eur J Pediatr 150:570–574
24. **Toublanc JE** 1999 Guidelines for neonatal screening programs for congenital hypothyroidism. Working Group for Neonatal Screening in Paediatric Endocrinology of the European Society for Paediatric Endocrinology. Acta Paediatr 88(Suppl):13–14
25. **Bongers-Schokking JJ, Koot HM, Wiersma D, Verkerk PH, Keizer-Schrama SMPF** 2000 Influence of timing and dose of thyroid hormone replacement on development in infants with congenital hypothyroidism. J Pediatr 136:292–297
26. **Dubuis JM, Glorieux J, Richer F, Deal CL, Dussault JH, Van Vliet G** 1996 Outcome of severe congenital hypothyroidism: closing the developmental gap with early high dose levothyroxine treatment. J Clin Endocrinol Metab 81: 222–227
27. **Boileau P, Bain P, Rives S, Toublanc JE** 2004 Earlier onset of treatment or increment in LT4 dose in screened congenital hypothyroidism: Which was the more important factor for IQ at 7 years? Horm Res 61:228–233
28. **Rovet JF, Ehrlich R** 2000 Psychoeducational outcome in children with early-treated congenital hypothyroidism. Pediatrics 105:515–522
29. **Hindmarsh PC** 2002 Optimisation of thyroxine dose in congenital hypothyroidism. Arch Dis Child 86:73–75
30. **Heyerdahl S** 1996 Treatment variables as predictors of intellectual outcome in children with congenital hypothyroidism. Eur J Pediatr 155:357–361
31. **Simoneau-Roy J, Marti S, Deal C, Huot C, Robaey P, Van Vliet G** 2004 Cognition and behavior at school entry in children with congenital hypothyroidism treated early with high-dose levothyroxine. J Pediatr 144:747–752
32. **Kempers MJ, Van Trotsenburg AS, Van Tijn DA, Bakker E, Wiedijk BM, Endert E, De Vijlder JJM, Vulsma T** 2005 Disturbance of the fetal thyroid hormone state has long-term consequences for treatment of thyroidal and central congenital hypothyroidism. J Clin Endocrinol Metab 90:4094–4100

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