

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

Marlies J. E. Kempers, Liesbeth van der Sluijs Veer, Ria W. G. Nijhuis-van der Sanden, Caren I. Lanting, Libbe Kooistra, Brenda M. Wiedijk, Bob F. Last, Jan J. M. de Vijlder, Martha A. Grootenhuis, and Thomas Vulmsa

Emma Children's Hospital Academic Medical Center, University of Amsterdam, Departments of Pediatric Endocrinology (M.J.E.K., B.M.W., J.J.M.d.V., T.V.) and Pediatric Psychology (L.v.d.S.V., B.F.L., M.A.G.), 1100 DE Amsterdam, The Netherlands; Department of Pediatric Physical Therapy (R.W.G.N.-v.d.S.), Radboud University, Nijmegen Medical Center, 6525 GA Nijmegen, The Netherlands; Department of Prevention and Healthcare (C.I.L.), Netherlands Organization of Applied Scientific Research, Quality of Life, 2301 CE Leiden, The Netherlands; and Department of Paediatrics (L.K.), Behavioral Research Unit, Alberta Children's Hospital, Calgary, Canada T2T 5C7

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 to 1993 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)

IN CONGENITAL HYPOTHYROIDISM (CH), thyroid hormone deficiency is present from the prenatal period onward until, after birth, adequate T₄ supplementation is provided. Because the period of thyroid hormone deficiency coincides with a critical period of brain development, children with CH, if left untreated, are at risk for impaired brain development and subsequent cognitive and motor deficits. The aim of neonatal CH screening programs is to prevent cerebral damage through early initiation of T₄ supplementation, which shortens the period of postnatal hypothyroidism. In a previous nationwide study we followed patients with thyroidal CH (CH-T) born in 1981–1982, the first years of the Dutch screening. We found persistent subtle cognitive and motor deficits up to adulthood in these patients, for whom T₄ supplementation was initiated at a median age of

28 d after birth (1, 2). In 1981–1982, initial treatment strategy and starting day of treatment differed from current practice, which is characterized by treatment initiation at a younger age, with higher initial T₄ doses. Several studies evaluating the more recent practice have shown improved cognitive and motor outcome (3–6). However, due to small sample sizes and the relatively young age of the children, it is still unclear whether postnatal T₄ supplementation is capable of establishing completely normal intellectual, motor, and socioemotional development in patients with CH-T (7).

The Dutch screening procedure has been adapted several times since its introduction in 1981. One of the major changes is the advancement of the heel puncture sampling from 6–14 d initially to 6–8 d in the early 1990s and to d 4 from 1999 onward. This change in timing of the heel puncture sampling enabled us to investigate whether earlier treatment initiation had resulted in improved cognitive and motor outcome. We investigated cognitive and motor outcome at 10.5 yr of age in a nationwide cohort of CH patients born in 1992–1993, in whom treatment was initiated at a median age of 20 d. Outcome was analyzed in relation to etiology and severity of CH and in relation to treatment variables. Furthermore, the results of the present study were compared with those ob-

First Published Online December 12, 2006

Abbreviations: CH, Congenital hypothyroidism; CH-C, central CH; CH-T, thyroidal CH; FSIQ, full-scale intelligence quotient; FT₄, free T₄; MABC, Movement Assessment Battery for Children; PIQ, performance IQ; TOMI, Test of Motor Impairment; VIQ, verbal IQ; WISC, Wechsler Intelligence Scale for Children.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

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 SD score, is compared with the day mean. If T₄ was -0.8 SD or less, TSH was additionally measured. When T₄ was -3.0 SD or less or TSH was 50 μ U/ml or more, children were referred immediately. Children with a dubious result [$-3.0 < T_4 \leq -2.1$ SD, or $28 < TSH < 50$ μ U/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 μ g T₄/kg·d. 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 μ U/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 ad-

justments 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, $0.3 < \text{initial FT}_4 \leq 0.6$ ng/dl ($4.0 < \text{initial FT}_4 \leq 8.0$ 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 (SD 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 ($9.5 < \text{total MABC score} < 13.5$), 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

Etiology	Total group	Participants	Nonparticipants	
			Not willing	Not suitable
Thyroid agenesis	24	17	1	6 (moved abroad, 1; syndrome, 1; syndrome suspected, 2; T ₄ dose not adequate, 2)
Thyroid dysgenesis	51	48	1	2 (T ₄ dose not adequate, 1; euthyroid without T ₄ supplementation, 1)
Thyroid dysmorphogenesis	24	17	4	3 (syndrome, 1; mother treated with T ₄ during pregnancy, 2)
CH-T not otherwise specified	26	11	11	15 (moved abroad, 3; patient died, 3; euthyroid without T ₄ supplementation, 3; syndrome, 5; tumor, 1)
CH-C	16	5	1	10 (blindness, 1; encephalopathy, 3; syndrome suspected, 3; late initiation of treatment, 3)
Total	141	87	18	36

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 ($4 \leq$ total TOMI score < 6), and 5% have definite motor problems (total TOMI score \geq 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. χ^2 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 T_4 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 T_4 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 ($\chi^2 = 1.260$; $P = 0.868$) and parental educational level by early or late treatment ($\chi^2 = 2.435$; $P = 0.296$).

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 T_4 supplementation was younger than in patients with mild CH-T. The median age at initiation of T_4 supplementation for the total CH-T group was 20 d (mean, 22 d).

TABLE 2. Characteristics of the participants

	Severe CH-T	Moderate CH-T	Mild CH-T	CH-C
No. of patients (male:female)	41 (13:28)	19 (6:13)	22 (10:12)	5 (4:1)
Initial FT4 (ng/dl) (range) ^a	0.1 (0.0–0.3)	0.4 (0.3–0.6)	1.0 (0.7–1.6)	0.6 (0.4–0.7)
[pmol/liter (range)]	[1.8 (0.0–4.0)]	[5.6 (4.2–7.1)]	[12.8 (9.0–20.2)]	[7.7 (5.4–9.6)]
Initial TSH (μ U/ml) (range) ^b	693 (254–1500)	493 (163–760)	120 (28–502)	4 (2–5)
Total defects ^c				
Agenesis	16	1		
Dyshormonogenesis	7			
Partial defects ^c				
Dysgenesis	16	17	15	
Dyshormonogenesis	2	1	7	
Age at start of T_4 supplementation (d) (range)	19 (10–43)	19 (9–41)	31 (2–73)	34 (14–58)
Initial T_4 dose (μ g/kg·d) (range)	7.0 (3.2–12.9)	6.6 (4.0–10.3)	5.0 (2.8–9.0)	8.1 (4.2–11.1)

Initial plasma FT4 and TSH concentrations, the age at start of treatment, and the initial T_4 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 μ U/m (8).

^c Only for patients with CH-T.

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 3. IQ scores of the CH-T group

	FSIQ	<i>P</i> (t)	Verbal IQ	<i>P</i> (t)	Performance IQ	<i>P</i> (t)
Severe CH-T (n = 41)	93.7 (89.5–97.9) ^{a,c}	0.004 (–3.0)	94.9 (90.1–99.7) ^b	0.039 (–2.1)	93.9 (90.0–97.8) ^{a,c}	0.003 (–3.1)
Moderate CH-T (n = 19)	96.2 (88.9–103.5)	0.290 (–1.1)	95.4 (87.9–102.9)	0.210 (–1.3)	98.0 (91.1–104.9)	0.550 (–0.6)
Mild CH-T (n = 22)	105.0 (99.5–110.4)	0.073 (1.9)	103.6 (98.2–109.1)	0.182 (1.4)	105.3 (99.3–111.3)	0.082 (1.8)
Total (n = 82)	97.3 (94.2–100.4)	0.088 (–1.7)	97.4 (94.1–100.6)	0.113 (–1.6)	97.9 (94.8–100.9)	0.172 (–1.4)
Range	57–129		65–138		58–134	

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.

^a *P* < 0.01 compared to the population mean.

^b *P* < 0.05 compared to the population mean.

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

–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.

FSIQ and total MABC score were not significantly correlated (*r* = –0.204; *P* = 0.073).

Comparison of the 1992–1993 and 1981–1982 cohorts

Mean FSIQ and the percentage of patients with motor problems of patients born in 1992–1993 and in 1981–1982 with severe, moderate, and mild CH-T are presented in Table 6. In patients with severe and mild CH-T, the age at start of T₄ supplementation was significantly different between the 1981–1982 cohort and the 1992–1993 cohort (*P* < 0.001, *P* = 0.003, respectively), but not in 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 FT₄ concentration between that of patients with moderate and mild CH-T (Table 2); none of the CH-C patients had an initial FT₄ 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 4. Motor scores of the CH-T group

	Total MABC score	Manual dexterity	Ball skills	Balance
Severe CH-T (n = 41)	14.37 (11.8–16.8) ^{a,c}	8.2 (7.0–9.5) ^b	2.4 (1.5–3.3)	4.1 (3.2–5.0)
Moderate CH-T (n = 19)	9.7 (6.8–12.5) ^a	5.1 (3.5–6.6)	1.6 (0.6–2.6)	3.0 (1.9–4.1)
Mild CH-T (n = 22)	11.6 (8.7–14.6) ^a	6.0 (4.1–7.8)	1.6 (0.7–2.6)	4.0 (2.7–5.4)
Total (n = 82)	12.4 (10.8–14.0) ^a	6.8 (6.0–7.7)	2.0 (1.4–2.6)	3.8 (3.2–4.5)

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

^a *P* < 0.01 compared to the normative population.

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

^c *P* < 0.05 compared to moderate CH-T.

TABLE 5. Multiple regression analysis for IQ and motor scores

		FSIQ	Verbal IQ	Performance IQ	Total MABC	Manual dexterity	Ball skills	Balance
Initial plasma FT4 concentration	B	0.816	0.760	0.753	-0.202	-0.121	-0.082	-0.023
	β	0.296	0.277	0.262	-0.142	-0.156	-0.156	-0.039
	<i>P</i>	0.034	0.051	0.057	0.324	0.276	0.268	0.786
Starting day of T ₄ supplementation	B	0.005	-0.110	0.124	-0.062	-0.018	-0.017	-0.036
	β	0.005	-0.101	0.110	-0.110	-0.060	-0.084	-0.156
	<i>P</i>	0.973	0.470	0.420	0.443	0.674	0.549	0.276
R ² adjusted		0.060	0.030	0.080	0.015	0.006	0.014	0.000
Model significance		F(2,63) = 3.077, <i>P</i> = 0.053	F(2,63) = 2.014, <i>P</i> = 0.142	F(2,63) = 3.817, <i>P</i> = 0.027	F(2,60) = 1.471, <i>P</i> = 0.238	F(2,62) = 1.179, <i>P</i> = 0.314	F(2,63) = 1.457, <i>P</i> = 0.241	F(2,62) = 1.008, <i>P</i> = 0.371

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.

prenatal period. The importance of the *in utero* thyroid hormone state has been illustrated by the fact that maternal hypothyroidism during pregnancy is known to result in cognitive and motor deficits in the offspring (15). One has to keep in mind that CH is already expressed in fetal life and that maternal T₄, transferred via the placenta, is not sufficient to fill the gap in fetal T₄ production.

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 techniques (Guthrie card and radioimmunoassays) became available. 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 initiation 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 similar 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 intellectual 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 $\mu\text{g}/\text{kg}\cdot\text{d}$, 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 $\mu\text{g}/\text{kg}\cdot\text{d}$, 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.

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 $\mu\text{g}/\text{kg}\cdot\text{d}$ 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 $\mu\text{g}/\text{kg}\cdot\text{d}$, as relatively high, found that patients with CH, receiving 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-

TABLE 6. FSIQ scores and percentages of CH-T patients with motor problems born in 1992–1993 and 1981–1982

	FSIQ score		Percentage of patients with motor problems	
	CH-T group 1992–1993	CH-T group 1981–1982	CH-T group 1992–1993	CH-T group 1981–1982
Age (yr)	10.5	9.9	10.5	9.9
Severe CH-T ($n = 41^a$ and 27^b)	93.7 (89.5–97.9)	94.3 (87.9–100.8)	71	52
Age at start of T ₄ supplementation (d)	19	29	19	29
Initial T ₄ dose ($\mu\text{g}/\text{kg}\cdot\text{d}$)	7.0	5.4	7.0	5.4
Moderate CH-T ($n = 19^a$ and 17^b)	96.2 (88.9–103.5)	98.9 (91.6–106.3)	37	41
Age at start of T ₄ supplementation (d)	19	27	19	27
Initial T ₄ dose ($\mu\text{g}/\text{kg}\cdot\text{d}$)	6.6	7.4	6.6	7.4
Mild CH-T ($n = 22^a$ and 14^b)	105.0 (99.5–110.4)	98.7 (89.2–108.2)	59	15
Age at start of T ₄ supplementation (d)	31	68	31	68
Initial T ₄ dose ($\mu\text{g}/\text{kg}\cdot\text{d}$)	5.0	5.2	5.0	5.2
Total group	97.3 (94.2–100.4)	96.8 (92.7–100.9)	60	40

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 supplementations 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, improvement of cognitive or motor outcome failed to occur. Although it is possible that with further advancement of treatment initiation or adaptations in T₄ dose intellectual and motor deficits will disappear, the observed deficits might also be the consequence of the prenatal hypothyroid state.

Acknowledgments

We are indebted to all patients and their parents for their participation in this study and to their pediatricians for their cooperation; to Anneloes L.

van Baar for her support with the design of the study; to José A. Willemsen and Astrid A. M. Huiberts for their support with the data management; and to Heleen Stam for her support with the statistical analysis.

Received July 14, 2006. Accepted December 4, 2006.

Address all correspondence and requests for reprints to: Marlies J. E. Kempers, Department of Pediatric Endocrinology, Emma Children's Hospital Academic Medical Center, University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands. E-mail: m.j.kempers@amc.uva.nl.

This work was supported by Grant 22000144 (to M.J.E.K. and T.V.) from The Netherlands Organization for Health Research and Development (ZON-MW; The Hague, The Netherlands).

Disclosure Statement: The authors have nothing to declare.

References

- 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
- Kempers MJ, van der Sluijs Veer L, Nijhuis-van der Sanden MW, Kooistra L, Wiedijk BM, Faber I, Last BF, de Vijlder JJ, Grootenhuys MA, Vulsma T 2006 Intellectual and motor development of young adults with congenital hypothyroidism diagnosed by neonatal screening. *J Clin Endocrinol Metab* 91:418–424
- 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
- Bongers-Schokking JJ, Koot HM, Wiersma D, Verkerk PH, de Muinck Keizer-Schrama SM 2000 Influence of timing and dose of thyroid hormone replacement on development in infants with congenital hypothyroidism. *J Pediatr* 136:292–297
- Bongers-Schokking JJ, de Muinck Keizer-Schrama SM 2005 Influence of timing and dose of thyroid hormone replacement on mental, psychomotor, and behavioral development in children with congenital hypothyroidism. *J Pediatr* 147:768–774
- Selva KA, Harper A, Downs A, Blasco PA, LaFranchi SH 2005 Neurodevelopmental outcomes in congenital hypothyroidism: comparison of initial T₄ dose and time to reach target T₄ and TSH. *J Pediatr* 147:775–780
- Hindmarsh PC 2002 Optimization of thyroxine dose in congenital hypothyroidism. *Arch Dis Child* 86:73–75
- Fisher DA 1991 Clinical review 19. Management of congenital hypothyroidism. *J Clin Endocrinol Metab* 72:523–529
- Kort W, Compaan EL, Bleichrodt N, Resing WCM, Schittekatte M, Bosmans M, Vermeir G, Verhaeghe P 2002 WISC-III, 3rd edition NL. Wechsler D, ed. Handleiding. [Dutch manual] Amsterdam: Harcourt Test Publishers
- Haasen PP, de Bruyn EEJ, Pij YJ, Poortinga YH, Lutje Spelberg HC 1986 Wechsler Intelligence Scale for Children-Revised; Dutch edition. Lisse, The Netherlands: Swets, Zeitlinger
- Kort W, Schittekatte M, Dekker PH, Verhaeghe P, Compaan EL, Bosmans M, Vermeir G 2005 WISC-III, 3rd edition NL. Wechsler D. Handleiding en verantwoording [Technical manual] Amsterdam: Harcourt Test Publishers
- Henderson SE, Sugden DA 1992 Movement Assessment Battery for Children: manual. London: Psychological Corporation
- Smits-Engelsman BCM 1998 Movement ABC; Nederlandse Handleiding [Dutch manual Movement ABC]. Lisse, The Netherlands: Swets, Zeitlinger
- Stott DH, Moyes FA, Henderson SE 1984 Test of motor impairment. Guelph, Ontario, Canada: Brook Educational Publishing
- Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 341:549–555
- 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
- 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
- Hrytsiuk I, Gilbert R, Logan S, Pindoria S, Brook CG 2002 Starting dose of levothyroxine for the treatment of congenital hypothyroidism: a systematic review. *Arch Pediatr Adolesc Med* 156:485–491
- Bakker B, Kempers MJE, De Vijlder JMM, 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