INFLUENCE OF TIMING AND DOSE OF THYROID HORMONE REPLACEMENT ON MENTAL, PSYCHOMOTOR, AND BEHAVIORAL DEVELOPMENT IN CHILDREN WITH CONGENITAL HYPOTHYROIDISM

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Objectives To evaluate the influence of initial and postinitial treatment factors on cognitive, psychomotor, and psychological outcome in schoolchildren with congenital hypothyroidism (CH).

Study design We studied 45 patients (19 with severe CH and 26 with mild CH) and 37 control children by correlating initial and postinitial treatment factors (free thyroxine and thyroid-stimulating hormone [TSH] concentrations, and the percentage of overtreatment and undertreatment periods) with the results of neuropsychological tests and behavior (as reported on the Teacher Report Form [TRF]).

Results The global IQ of the children with CH was comparable to that of the controls; visuomotor and verbal scores were lower, and total TRF scores were higher. Ethnic group, previous development, and overtreatment predicted IQ and verbal scores, with higher scores seen for the overtreated patients than for the control children and those patients who had not been overtreated. As initial treatment was less satisfactory, total TRF scores were higher.

Conclusions Our study suggests that initial and postinitial suboptimal treatment of CH leads to abnormalities in IQ and specific fields. Overtreatment may advance cognitive development in 5-1/2- to 7-year-olds. Suboptimal initial treatment may lead to behavioral problems. We recommend that TSH concentrations be maintained within the normal range in patients with CH. *(J Pediatr 2005;147:768-74)*

Previous studies have indicated that schoolchildren who receive early treatment for congenital hypothyroidism (CH) have a normal or subnormal IQ combined with behavioral problems (especially regarding attention), and subtle defects in visuospatial skills, language, and memory.[1-10] The search for thyroid-related predictors of these developmental abnormalities has focused mainly on biological factors that play a role at the initiation of therapy; these include type of CH, thyroid hormone levels and bone age at diagnosis, and time to normalization of free thyroxine (T_4) concentrations. Non–thyroid-related predictors of these abnormalities include psychosocial and genetic factors.[7]

The influence of postinitial treatment is less well documented,[1-3,5,8,9] despite the fact that brain maturation continues until several years after birth and that such treatment almost certainly has several effects, especially on the maturation of higher functions. To date, most reports have focused on the negative effect of undertreatment.[1-3,5,8] Overtreatment has not been extensively studied,[9,10] despite its increasing prevalence in recent years, related to the common practice of maintaining free T_4 concentrations in the upper-normal range[1,2] to prevent periods of undertreatment, which inevitably leads to overtreatment. Whereas severe overtreatment and neonatal thyrotoxicosis are known for their sequelae, such as craniosynostosis and neurologic symptoms,[11-13] the effects of moderate overtreatment on central nervous system (CNS) maturation are largely unknown.

CBCL	Child Behavioral Check List	SES	Socioeconomic status
CH	Congenital hypothyroidism	T_4	Thyroxine
CNS	Central nervous system	TRF	Teacher Report Form
MDI	Mental Development Index	TSH	Thyroid-stimulating hormone
PDI	Psychomotor Development Index	VMI	Visual–motor integration

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In trying to determine optimal initial treatment conditions, we previously[14] investigated a group of 61 infants with CH treated either early (age < 13 days) or late (age ≥13 days) with either a high (> 9.5 μg/kg/day) or a low dosage (≤9.5 μg/kg/day) of levothyroxine. Bayley test[15] results indicated that mental and psychomotor development at age 10 to 30 months was closely related to age at initiation of medication therapy, initial levothryoxine dosage, and disease severity. Irrespective of the severity, the early/high-treated group displayed normal Mental Development Index (MDI) and Psychomotor Development Index (PDI) values, whereas the late/low-treated group had subnormal values.

In the present study, we reexamined 45 of these children with CH at age 5-1/2 to 7 years, using tests for IQ, language, visuospatial skills, and psychological development. Our objectives were to determine whether initial treatment factors are important for later cognitive, psychomotor, and psychological development and also to establish how such development is affected by postinitial treatment factors, such as thyroid hormone concentrations and periods of overtreatment or undertreatment.

METHODS

Subjects

The experimental group comprised 45 children with CH born between February 1993 and July 1996. All of these children belonged to the CH group (n = 61) examined for development at age 10 to 30 months in a previous study.[14] This original cohort contained no infants of mothers with known thyroid abnormalities; 16 children from the original cohort were not reexamined, because of relocation abroad (n = 1), parental refusal (n = 8), or difficulties in organizing the visits (n = 7), the latter because the children came from all over the country and were under the care of local pediatricians.

The control group comprised 37 children recruited from regular primary schools and matched for age and socioeconomic status (SES).[16] Children with perinatal problems (prematurity, dysmaturity, and asphyxia), previous meningitis, neurologic abnormalities, abnormal CH screening, and major diseases affecting the CNS (eg, metabolic diseases, syndromes, chromosomal defects) were excluded.

Written informed consent was obtained from the parents of all children examined. The study was approved by the medical-ethical committee of Erasmus Medical Center, Rotterdam.

Characteristics of the Groups

The experimental and control groups did not differ in age at time of testing (72.5 ± 6.6 vs 71.1 ± 3.3 months [mean ± 1 standard deviation]) and SES (3.8 ± 1.5 vs 4.2 ± 0.9). The percentage of males was lower in the experimental group (36%) than in the control group (55%). The CH group included 6 patients from ethnic minorities (Moroccan and Turkish, nonethnic Dutch); the control group had 4 nonethnic Dutch members. In the CH group, 19 patients had severe CH (with initial free T_4 concentrations of 2.7 ± 2.2 pmol/L) and 26 had mild CH (with initial free T_4 concentrations of 8.7 ± 4.1 pmol/L) ($P < .001$).

The qualification severe/mild was related to etiology, which was determined on the basis of the following: serum TSH, T_4, thyroxine-binding globulin, thyroglobulin, urine low-molecular-weight iodinated material, thyroid ultrasound investigation, and thyroid scan, combined with a perchlorate test if indicated.[14] Severe CH was defined as a complete deficiency of T_4 production (athyroidism or total dyshormonogenesis); mild CH, as a partial deficiency of T_4 production (ectopia, thyroid dysgenesis, or partial dyshormonogenesis).

Initial treatment groups (Table I) were formed according to time of start of substitution after birth as early (< 13 days) or late (≥13 days), and also according to initial dosage of levothyroxine as high (≥9.5 μg/kg/day) or low (< 9.5 μg/kg/day). The 4 initial treatment groups formed in this way (ie, early/high, early/low, late/high, and late/low) differed in terms of initial dosage of levothyroxine and day of substitution, but not in serum free T_4 level at diagnosis.

Control Measurements in Children With CH

Free T_4 and TSH results were gathered for all but 3 of the 45 patients with CH. During the first weeks of treatment, serum free T_4 and TSH had been measured twice a week, then once a month. From the beginning of the second year of treatment, they had been measured once every 3 months, and from the beginning of the third year, they had been measured once every 6 months. During the first year of treatment, 14.7 ± 4.4 blood control tests had been performed, but from the end of the first year to the end of the sixth year, only another 17.9 ± 5.0 blood control tests had been done. All decisions about treatment regimen had been made by the local pediatrician. For the first weeks, a dosage reduction of levothyroxine (commercially available tablets only) by 1 μg/kg/day had been recommended when free T_4 was > 35 pmol/L with TSH < 10 mU/L. After that, free T_4 had to be kept in the upper-normal range, with TSH between 0.5 and 10 mU/L.

We defined undertreatment as TSH ≥10 mU/L and overtreatment as TSH ≤0.5 mU/L. An undertreatment or overtreatment period was defined as the period between a previous control measurement and the point at which undertreatment or overtreatment was subsequently identified. Free T_4 and TSH concentrations during periods of undertreatment (n = 208; duration 1.9 ± 1.5 months) were 19.2 ± 4.8 pmol/L and 19.9 ± 12.4 mU/L. During periods with normal TSH (n = 713), these levels were 21.9 ± 4.3 pmol/L and 3.7 ± 2.4 mU/L ($P < .001$). During periods of overtreatment (n = 188; duration 3.0 ± 2.6 months), they were 25.4 ± 5.1 pmol/L and 0.2 ± 0.15 mU/L ($P < .001$). A patient was considered undertreated or overtreated if the percentage of these episodes from age 6 weeks until the age of testing (10 to 30 months or 5-1/2 to 7 years) was > 15% of the total number of control measurements. The value of 15% (equivalent to 4 undertreatment or overtreatment periods in our study) was chosen because it was previously demonstrated that 3 or more periods of undertreatment can lead to lower IQ.[1,5] Two pairs of

Table I. Composition of initial treatment groups, according to day on which therapy started and levothyroxine dosage

	N	Severe/ mild CH	Initial free T_4 (pmol/L)	Starting dose levothyroxine (μg/kg/day)	Start of therapy (day)
Early/high	11	6/5	5.7 ± 4.2	10.6 ± 1.1	10.8 ± 1.3
Early/low	8	4/4	5.0 ± 3.7	7.0 ± 1.8	10.8 ± 1.6
Late/high	13	6/7	6.4 ± 5.0	10.4 ± 0.7	18.1 ± 5.2
Late/low	13	3/10	6.8 ± 4.1	7.1 ± 1.7	15.6 ± 3.0
P			NS	< .001	< .001
Total	45	19/26	6.0 ± 2.6	12.5 ± 3.3	14.1 ± 5.6

NS, not significant.

Table II. Composition of the postinitial treatment groups, according to the percentage of undertreatment and overtreatment periods

	N	Severe/ mild CH	SES	Ethnic Dutch/nonethnic Dutch	N° control Measurement	Percent episodes of TSH≥10	Percent episodes of TSH≤0.5
TSH≥10	22	10/12	4.1 ± 1.3	18/4	27.4 ± 6.5	28.9 ± 10.6	13.1 ± 11.7
TSH<10	20	6/14	3.4 ± 1.6	18/2	24.9 ± 6.1	6.7 ± 4.7	21.8 ± 17.8
P		NS	NS	NS	NS	< .001	NS
TSH≤.5	19	7/12	4.1 ± 1.5	16/3	26.3 ± 6.2	13.0 ± 11.7	31.0 ± 12.5
TSH>.5	23	9/14	3.6 ± 1.5	20/3	25.2 ± 6.4	22.6 ± 14.3	5.8 ± 3.4
P		NS	NS	NS	NS	NS	< .001
Total	42	16/26	3.8 ± 1.5	36/6	26.5 ± 6.3	18.3 ± 13.9	17.2 ± 15.4

NS, not significant.

postinitial treatment groups were formed (Table II): TSH≥10 (n = 22) and TSH<10 (n = 20), and TSH≤.5 (n = 19) and TSH>.5 (n = 23).

Tests

Children with CH were tested either in Sophia Children's Hospital or their local hospital; the control children were tested at school. Three psychologists performed the tests; they were not familiar with the etiology or the CH treatment schedules.

At 21.7 ± 5.3 months, a Bayley test[15] was performed; the results are expressed as MDI and PDI. Normal MDI and PDI at 18 months were 110 ± 18 and 109 ± 15, respectively.[14]

For the present study, we used the following tests:

- The short version of the Revised Amsterdam Child Intelligence Test (Rakit),[17] consisting of 7 subtests: (1) exclusion (ie, picking the odd one out), (2) memory (reproducing after 5 seconds' observation the order in which 5 pictures appear), (3) word significance (choosing the correct picture out of 4 after hearing a word), (4) disc placement (placing discs with 1 to 4 holes on the corresponding places on a pegboard), (5) learning names (memorizing 12 animal names that have been taught before, on the basis of pictures), (6) hidden figures (recognizing 1 of 6 simple figures in a complex drawing), and (7) idea production (producing within a restricted time the highest possible number of words associated with a given category)
- The Beery-Buktenica Developmental Test for Visual-Motor Integration (VMI)[18]
- Two subtests of the Language Test for Children (in Dutch)[19] (word conjugation and sentence completion)
- The Perdue Pegboard Test,[20] which measures the development of fine motor functions.

The results of the Rakit, VMI, Language, and Pegboard tests are expressed as scores standardized for age. For the Pegboard test, our analysis used the mean score of the 3 subtests (dominant hand, nondominant hand, and both hands) per child.

A visuomotor score was calculated for each child by combining the disc placement subtest with the VMI and Pegboard tests, whose scores were standardized according to the mean score of the control group, which was set at 100. In the same way, a verbal score was calculated by combining the scores of word significance (Rakit test) and word conjugation (Language test).

To evaluate the children's psychological development, parents and teachers filled in the Dutch version of the Child Behavioral Check List (CBCL)[21,22] and Teacher Report Form (TRF), whose results are expressed in T-scores for age. The T-scores for the 8 domains of behavior (socially withdrawn, somatic complaints, anxious/depressed, social problems, thought

problems, attention problems, delinquency, and aggression) were determined, together with the total scores. A higher score indicates a greater number or intensity of behavior problems.

SES was assessed on the basis of the fathers' and mothers' educational and occupational levels (on a 6-point scale ranging from unskilled to postgraduate).[16]

Statistical Analysis

Statistical analysis was done with SPSS package for Windows version 11.5 (SPSS, Chicago). To compare mean values of 2 groups, we used the Student *t* test or, if there were more than 2 groups, a 1-way analysis of variance. Values are given as mean ± standard deviation. Univariate and partial correlations were assessed using Pearson's test. For all tests, a 2-tailed significance value of $P < .05$ was chosen. Factor analysis was performed using multiple regression analysis.

RESULTS

Control Group

In the control group, test results showed no significant differences regarding gender or test age (data not shown), although there were significant differences in IQ between ethnic Dutch children (107.5 ± 14.7) and those from ethnic minorities (84.5 ± 8.2; $P = .004$). There were also significant differences in verbal scores (104.6 ± 22.4 for ethnic Dutch vs 61.8 ± 11.1 for nonethnic Dutch; $P = .001$). However, visuomotor score and total TRF score did not differ between these 2 groups.

CH Group Versus Controls

IQ scores of the children with CH (104.7 ± 16.2) did not differ significantly from those of the control group (105.0 ± 15.8) (Table III). Neither did the scores on the 7 subtests: exclusion (16.0 ± 4.9 vs 15.5 ± 4.8), memory (16.1 ± 4.4 vs 17.0 ± 5.4), word significance (15.9 ± 5.9 vs 17.5 ± 5.4), disc placement (14.8 ± 5.4 vs 15.2 ± 5.0), learning names (16.7 ± 5.0 vs 16.8 ± 5.3), hidden figures (18.0 ± 5.8 vs 17.1 ± 6.0), and idea production (14.3 ± 4.4 vs 14.7 ± 4.7). VMI results differed significantly between the CH and control groups (100.2 ± 12.0 vs 107.1 ± 9.1; $P = .024$), but Pegboard scores did not (35.9 ± 8.3 vs 39.9 ± 6.6). Word conjugation was performed less well by the children with CH than by the controls (5.3 ± 2.0 vs 6.2 ± 1.5; $P = .012$); sentence completion did not differ between the 2 groups, however (6.0 ± 1.5 vs 5.8 ± 1.9). Visuomotor and verbal scores of the CH children were significantly lower than those of the control children.

None of the test results were significantly influenced by thyroid status at testing. TSH was ≥10 mU/L in 4 patients, ≤.05 mU/L in 6 patients, and normal in the remaining patients.

Initial Treatment Factors

Children with severe and mild CH differed significantly in visuomotor score (86.3 ± 16.6 vs 96.5 ± 15.9), but not in IQ and verbal score. Although there were no differences in IQ and visuomotor scores among the 4 initial treatment groups, there was a significant difference with regard to verbal scores, with the late/low group scoring much lower than the controls and the other groups. Within the 4 initial treatment groups, a further subdivision into severe and mild CH could not be made, because these groups would then have become too small for statistical analysis.

Table III. Effect of CH, initial and postinitial treatment factors on IQ, visuomotor, and verbal scores

	N	IQ Rakit	Visuomotor score	Verbal score
Controls	37	105.0 ± 15.8	100.5 ± 15.8	100.2 ± 23.4
CH	45	104.7 ± 16.2	92.5 ± 15.2	86.0 ± 29.4
P		NS	*.037*	*.024*
Initial treatment factors				
Severe CH	19	99.4 ± 14.8	86.3 ± 16.6	82.8 ± 30.7
Mild CH	26	108.5 ± 16.4	96.5 ± 15.9	88.4 ± 28.8
P		NS	.048	NS
Early/High	11	104.6 ± 12.3	96.3 ± 15.0	91.0 ± 24.2
Early/Low	8	106.5 ± 20.5	89.0 ± 15.6	92.7 ± 33.0
Late/High	13	108.2 ± 17.4	93.3 ± 17.5	99.4 ± 27.5
Late/Low	13	100.1 ± 15.8	90.9 ± 19.2	64.3 ± 23.3
P		NS	NS	.001
Postinitial treatment factors				
TSH≥10	22	104.4 ± 16.1	96.0 ± 13.3	86.5 ± 30.4
TSH<10	20	107.6 ± 14.9	96.2 ± 17.7	94.2 ± 28.4
P		NS	NS	NS
TSH≤0.5	19	111.1 ± 17.7	99.4 ± 15.5	100.0 ± 34.0
TSH>0.5	23	101.5 ± 11.8	93.2 ± 15.2	81.9 ± 22.0
P		.047	NS	.049
FT_4 3-12 M	45	NS	−.37*	NS
Correlations (r values)				
SES	82	.23*	NS	.40†
Ethnic group	82	.45†	NS	.49†
MDI	45	.46†	.34*	.50†
PDI	45	.37*	NS	NS

NS, not significant.
*$P < .05$.
†$P < .01$.

Postinitial Treatment Factors

Mean free T_4 concentration of 3 to 12 months correlated positively with visuomotor score, but not with IQ or verbal score. There was no other significant correlation between outcome variables and free T_4 or TSH concentrations during any other tested period. Although the TSH≥10 and TSH<10 groups showed no significant difference in IQ, verbal, or visuomotor score, the TSH≤.5 group had higher IQ and verbal scores than the TSH>.5 group (with no significant difference in visuomotor score).

Table IV. Multiple regression analysis of MDI and IQ with the various factors

	MDI		IQ Rakit	
Dependent factor	***t***	***P***	***t***	***P***
Ethnic group		NS	−3.835	.001
SES	2.267	.029		NS
Initial free T_4	2.657	.012		NS
Initial treatment	−2.057	.047		NS
Free T_4 3 to 12 mol		NS		NS
MDI			2.618	.013
Overtreatment		NS	3.835	.001
Undertreatment		NS	−1.781	NS
(Constant)	10.420	< .001	3.500	.001
R^2	.594	.002	.585	< .001

With regard to ethnic Dutch children alone, the IQ values of the TSH≤.5 group (n = 16; 117.6 ± 9.5) were higher than those of the TSH>.5 group (n = 20; 103.3 ± 12.3; P = .001) and of controls (n = 33; 107.5 ± 14.7; P = .016). MDI values of the TSH≤.5 group (n = 16; 120.6 ± 10.8) were also higher than those of the TSH>.5 group (n = 20; 111.3 ± 20.0), but not significantly so. IQ values of the ethnic Dutch children with CH correlated positively with the number of overtreatment periods (n = 36; r = .57; P = .001).

Relations With Other Variables

IQ and verbal score were related to SES, ethnic group, and previous development (MDI); IQ was also related to PDI. Visuomotor score was found to correlate with MDI. IQ was significantly lower in patients of nonethnic Dutch origin than in patients of Dutch origin (86.2 ± 13.1 vs 107.5 ± 14.8; P = .002). In the same group, verbal score was also significantly lower in ethnic minorities than in ethnic Dutch (47.5 ± 24.2 vs 94.7 ± 26.1; P < .001). The differences in visuomotor score were not significant.

Multiple Regression Analysis

In terms of IQ, multiple regression analysis of the test results of the children with CH demonstrated a highly significant correlation, with significant contributions from ethnic group, MDI, and overtreatment (Table IV). With regard to MDI, the correlation was also significant: SES, initial free T_4, and initial treatment were the determinant factors.

CBCL and TRF Results

Total scores in the parental CBCL for the CH (with 31 forms returned) and control groups (36 forms returned) were comparable (Table V), as were the scores on the 8 domains of behavior (data not shown). However, the total TRF score of the CH group was significantly higher than that of the control group. Eight children in the CH group and 0 children in the control group had a T-score above the clinical reference value of 60 (χ^2 = 9.74; P = .008). This difference was due mainly to significantly higher scores on TRF domains of attention and aggression (Table V).

Table V. CBCL and TRF scores

	CH (n = 31)	Controls (n = 36)	*P*
Total score			
CBCL-mother	49.5 ± 9.4	46.9 ± 8.1	NS
CBCL-father	46.5 ± 9.7	45.9 ± 7.7	NS
TRF-teacher	52.1 ± 11.3	45.7 ± 8.8	.012
Attention			
CBCL-mother	54.9 ± 6.4	52.9 ± 5.0	NS
CBCL-father	53.8 ± 5.0	53.6 ± 6.1	NS
TRF-teacher	55.0 ± 6.3	51.8 ± 3.0	.009
Aggression			
CBCL-mother	53.5 ± 6.9	52.3 ± 3.7	NS
CBCL-father	51.7 ± 4.4	51.8 ± 3.9	NS
TRF-teacher	56.8 ± 9.5	52.0 ± 4.3	.007

Only those subscores reaching a significant difference are shown.

The CH group scored a little higher than the control group on the other 6 domains, but not significantly. Attention, aggression, and total score were related only to initial treatment. The late/low group had the highest scores for attention (57.0 ± 7.2), aggression (60.3 ± 13.0), and total score (54.7 ± 10.8). These values were significantly higher than the scores in both the early/high group (52.8 ± 6.2 for attention [P = .023], 54.2 ± 4.5 for aggression [P = .029], and 45.4 ± 9.7 for total score [P = .049]) and the control group (52.0 ± 4.3 for attention, 51.8 ± 3.0 for aggression, and 45.7 ± 8.8 for total score; P < .05 for all). There was no relation between attention, aggression, and total score and any other tested factor (ie, overtreatment/undertreatment, free T_4 and TSH concentrations during treatment and at the time of testing, type of CH, SES, ethnic group, MDI, or PDI).

DISCUSSION

The results of our study of the cognitive, psychomotor, and psychological development of children with early treated CH indicate that at age 5-1/2 to 7 years, global IQ is normal, with a wide range extending from subnormal to supranormal. There were specific defects in verbal and visuomotor development and in behavior, especially in attention and aggression. These results are in line with those of many previous studies in this field.[1-4,23] Thyroid hormone substitution therapy from 6 weeks until testing had a considerable effect on cognitive development. Overtreatment was related to supranormal IQ and verbal scores; mild undertreatment did not significantly alter scores. Initial treatment, if inadequate, negatively influenced early development (MDI) at 10 to 30 months, as well as verbal score and behavior at 5-1/2 to 7 years. It did not seem to influence IQ and visuomotor score at 5-1/2 to 7 years, although MDI and IQ scores were positively related. Ethnicity was an important factor for later cognitive and verbal development but not for early development, visuomotor score, or behavior.

Mild overtreatment during the first 6 years may lead to higher-than-normal IQ and verbal values. These results were surprising; we had expected to find lower values, similar to those in a previous study in which IQ values were higher in 9-year-old patients with CH treated during the first 24 months with high dosages of levothyroxine (thus leading to high T_4 concentrations) than in patients treated with lower dosages.[9] Eventually, perhaps, the children in our study will also have below-normal outcomes, because——as indicated by the longitudinal study of Rovet[6]—in children with CH, an above-normal IQ score in childhood does not automatically mean a normal outcome in puberty.

We know from previous clinical and animal studies[11-13,24-26] that physical and neurologic maturation initially can be advanced by prolonged periods of high T_4 concentrations in the postnatal period caused by neonatal thyrotoxicosis or severe overtreatment. Later, these concentrations will prematurely arrest development, reducing the number of neurons, oligodendrocytes, and neuronal fibers in specific areas and causing abnormal behavior and defects in myelination. In these clinical and animal studies, however, hyperthyroidism was severe and occurred *before* the end of the first year. In our study, overtreatment occurred mainly *after* the first year, when the cerebral architecture and its neurochemical maturation are largely complete. In view of the normal MDI at 22 months, a serious disturbance of these processes thus seems unlikely in our overtreated children.

Myelination still proceeds, however; controlled by thyroid hormones,[25-27] it continues until early adulthood[28] and is thought to be important for the higher cognitive functions.[29] The direct relationship between IQ values and the number of overtreatment periods suggests that the high IQ values reflect enhanced myelination. Another explanation for the better scores may be that they are related to hyperthyroid status at the time of testing. But this is unlikely, because in our own study and also in a previous study,[30] hyperthyroid children did not perform better than euthyroid children, probably due to poorer attention in the former related to hyperthyroid status. If myelination is the most important factor, then eventual outcome will depend on the progress of this myelin formation and its possible premature arrest, which then may lead to lower IQ value.

Overall, our results emphasize the important role played by postinitial treatment in the development of the higher cerebral functions. This would mean that the critical period of thyroid sensitivity of the CNS might last until adulthood. This overriding role of postinitial treatment probably made it impossible for us to establish a direct relation between IQ and initial treatment factors.

In contrast with previous studies,[1-3,5,8] we found no impairment of cognitive and verbal development resulting from frequent periods of undertreatment. This may be due to the relatively short duration (about 2 months) and mildness of hypothyroidism (free T_4 concentrations still in the high-normal range) during the undertreatment periods compared with the earlier studies[1-3] that found longer-lasting hypothyroid periods with lower T_4 values. Our findings do not indicate that undertreatment is not harmful for CNS development, but only that compensated hypothyroidism (TSH elevation only) may not be as harmful as was previously believed.

Behavioral problems, mainly aggression and attention problems, were more frequent in the children with CH than in the control children. These problems were reported more frequently by the children's teachers than by their parents. The association between CH and attention problems has been studied extensively by Rovet et al[31] and Alvarez et al,[30] who concluded that attention defects in children with CH were associated with higher circulating free T_4 concentrations at the time of testing and with late normalization of T_4 concentrations after the start of therapy. This is in line with results of a study in which rat pups exposed to propylthiouracil through maternal milk—which causes mild hypothyroidism—exhibited marked hyperactivity that did not resolve once thyroid function normalized after weaning.[32] The first weeks after birth seem important in the development of attention and aggression problems; these problems were seen predominantly in patients known to have undergone inadequate initial treatment.

Ethnicity proved to be an important factor for IQ and verbal scores. It does not seem to be related to CH, however. A Dutch survey of normal schoolchildren found lower IQ and verbal scores for Turkish and Moroccan children than for native children.[33] The differences were comparable to those found in our control group.

The main drawback of our study is its relatively limited sample size, preventing us from testing subgroups for the effects of several factors. We are currently testing the children again (who are now age 10 to 11 years) and hope to achieve at least a similar sample size. A further drawback is that the free T_4 and TSH measurements were performed by 27 different laboratories. But the quality of these measurements is determined by the national External Quality Scheme on Immunoassays surveys; because the normal adult values of these laboratories match very closely, we accepted the small differences in free T_4 and TSH concentrations caused by the different determination methods. Unfortunately, we asked the pediatricians only for their free T_4 and TSH data, so we do not have data on levothyroxine dosages.

Our results underline the importance of proper therapy, both initially and thereafter. Initial therapy should be started early with an adequate dosage of levothyroxine that is reduced once euthyroidism is reached. Subsequently, TSH should be maintained within the normal limits of 0.5 to 10 mU/L. This can be achieved only by frequent blood controls.

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