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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Supported by grants from the Theia Foundation, the Jan Dekker & Ludgardine Bouwman Foundation, and the Erasmus University Rotterdam Association Trust Fund.

Submitted for publication Dec 29, 2004; last revision received Aug 30, 2005; accepted Sep 28, 2005.

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0022-3476/$ - see front matter

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10.1016/j.jpeds.2005.09.031

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

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