0031-3998/88/2401-0006$02.00/0
PEDIATRIC RESEARCH

Vol. 24, No. 1, 1988
Printed in U.S.A.

Useful Parameters To Predict the Eventual Mental Outcome of Hypothyroid Children

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ABSTRACT. The Quebec Network for Genetic Medicine has followed the development of some 100 hypothyroid children treated by 1 month of age and evaluated at 18 months, 3 and 5 yr and the Griffiths Mental Development Scales, then at 7 and 9 yr with the Wechsler Intelligence Scale for Children Revised. Results show that the children as a group reach scores within the normal range of the tests. However, a few patients have low scores at each evaluation. Previously, we showed a correlation between a low serum thyroxine concentration, or a relatively retarded bone maturation before treatment, and low mental scores. To better characterize the significance of this relationship we correlated these pretreatment factors and the Wechsler Intelligence Scale for Children Revised results of 43 subjects reaching the age of 7 yr. Again, the same correlation was observed. Calculating a predictive factor (low thyroxine, <2 μg/dl and retarded bone surface, <0.05 cm²) from data recorded before therapy initiation, 10 of 13 children were correctly predicted to have I.Q. values <90. The use of these parameters might permit early intervention, and allow specific guidance of the more affected subjects. (*Pediatr Res* 24: 6–8, 1988)

Abbreviations

T_4, thyroxine
DQ, developmental quotient
CH, congenital hypothyroidism
W.I.S.C.R., Wechsler Intelligence Scale for Children Revised

Ten years of follow-up of congenitally hypothyroid children detected by newborn screening programs have confirmed the effectiveness of early treatment in normalizing mental development (1). I.Q. values at 5–7 yr of age are in the normal range in most patients. However, significant differences between subjects and controls, or siblings, have been observed (2–6). The Quebec Network for Genetic Medicine screened 250 congenital hypothyroid patients between 1975 and 1985, and 105 infants were recruited for a longitudinal study. All were French Canadian Caucasians, without any other known deficit or disease, coming from stable families, and they responded well to therapy. Description of biological (7) and psychological (3) characteristics of the group have already been reported showing a significant correlation between I.Q., a low serum T_4 concentration and a delayed bone maturation (8–11). A careful assessment of individual scores allowed identification of a few children who scored consistently low throughout the evaluations. Herein, we examined pretreatment factors that might permit early detection of these subjects.

Received March 23, 1987; accepted February 25, 1988.
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PATIENTS AND METHODS

Mental assessment was done using the Griffiths Mental Development Scales (12) at the age of 18 months and 3 and 5 yr. This test provides the global D.Q. and scales assessing locomotion, social development, hearing and speech, eye-hand coordination, performance, and depending the age of the patient, practical reasoning. It is an elaborate test well suited to determine possible differences within our group of patients. It is the only test covering child development from birth to the age of 7 yr. However, at the age of 7 and 9 yr we worked with the W.I.S.C.R. (13) as recommended in the guidelines for Neonatal Screening Programs (14). Biochemical values of the patients have been reported (7), and treatment (mean age 32 days) followed the recommended dosage of replacement hormone (8–10 μg/kg/day). The evolution of treatment was satisfactory but individual responses to therapy covered a wide spectrum (Table 1). The small number of subjects (17 at 5 yr, 18 at 7 yr) probably explain the fact that the first measures of T_4 (45 days and 3, 6, 12, and 18 months) never significantly correlated with the mental outcome, although the correlation coefficients between the T_4 at 3 months and DQ at 5 and 7 are very close to the 5% level of significance (0.479 and 0.406, respectively). Bone maturation was calculated by measuring the surface areas of the ossification centers of the knee using x-ray carried out following the method described by one of us (15).

RESULTS

We reported that the mental development of the children considered as a group was within the normal range at each assessment. We assessed the effects of various clinical, biological, and radiological parameters possibly linked to the later performance of the patients. The presence or absence of thyroid tissue, or delay in the initiation of therapy, did not relate to mental status. Initial T_4 and bone maturation were the best parameters explaining the patients developmental performance. Correlations of these parameters with intellectual assessment was always significant (Table 2). Taking both measures into consideration, we tried to develop a predictive index for eventual mental outcome. We arbitrarily defined a global score of 90 calculated with the W.I.S.C.R. at the age of 7 yr, as the superior limit of I.Q. for children with slow development, considering that data collected on 19 siblings from the original cohort gave a mean I.Q. of 106 (SD 16.7) with the same tests. Thirteen patients had scores under or equal to 90 and they were significantly different from the rest of the group only in their initial T_4 values ($p < 0.05$) and bone

Table 1. *Thyroid function parameters in infants with congenital hypothyroidism detected by newborn screening and treated within 1 month of age*

Age at measurement	Number of infants and test: Serum T_4 (μg/dl) n	± sem	TSH* (μU/ml) n	± sem	T_3† (ng/dl) n	m ± sem
Pretreatment	43	1.4 ± 0.2‡	43	571 ± 37	33	74 ± 12
45 days	19	6.6 ± 0.4	13	31 ± 14	10	288 ± 47
3 mo	18	11.8 ± 1.5	8	16 ± 4.5	6	155 ± 13
6 mo	41	11.8 ± 0.7	39	17 ± 3.4	40	152 ± 8
12 mo	43	12.3 ± 0.8	32	12 ± 3.2	42	160 ± 7
18 mo	26	13.6 ± 0.9	25	11 ± 3	27	155 ± 27

* Thyrotropin-stimulating hormone.
† Triiodothyronine.
‡ Correlation with IQ at 7 yr, $p < 0.05$ (mean ± SEM).

Table 2. *Pretreatment parameters and mental outcome correlations in 43 infants with congenital hypothyroidism treated by 1 month of age*

Newborn parameters	Correlations with intellectual assessments: DQ 3 yr	DQ 5 yr	IQ 7 yr
Plasma T_4	0.33*	0.36*	0.36†
Bone surface	0.51*	0.52*	0.40†

* $p < 0.01$.
† $p < 0.05$.

surface measurement ($p < 0.06$). We then specified our risk criteria by selecting T_4 values < 2 μg/dl (mean of the total group is 1.7 μg/dl, SEM 0.8) and bone surfaces <0.05 cm^2 (taking into account the cumulated distribution of logarithmic data of the whole group). Applied to a total of 43 patients at the age of 7 yr this index correctly identifies 10 of the 13 children having an I.Q. score <90 (sensitivity of measure 77%). (Table 3). In other words, the prediction of a lower mental development score at the age of seven was accurate in only 63% of our sample. Those children had a mean I.Q. score of 81. However, six children with borderline scores were also selected; their mean I.Q. was 95. However, the risk criteria correctly predicted an I.Q. >90 for 24 of the 30 children remaining (specificity of measure 80%). The prediction of a higher mental score was accurate in 89% of our sample and the mean I.Q. of those patients was 105 (Table 3).

The effect of this discrimination factor on mental score at each assessment illustrates well the differences within our group of patients: the W.I.S.C.R. sub-test results were analysed by Student's *t* test. The mean verbal score was 83 for the selected group versus 99 for the less affected children ($p < 0.001$); the nonverbal scores were 92 and 107 ($p < 0.001$) and the global I.Q. values 86 and 102 ($p < 0.001$), respectively. The same discrimination was evident in the scores of the 19 oldest patients evaluated at the age of 9 yr: the verbal scores were 88 for the selected group *versus* 105 for the less affected children ($p < 0.003$); the nonverbal scores were 96 and 114 ($p < 0.002$) and the global I.Q. values 91 and 109 ($p < 0.001$), respectively. At the age of 5 yr, the scores reached by the two groups of patients in the six scales of the Griffiths test were analysed by Student's *t* test and showed important score differences. The locomotion was 81 for the selected group *versus* 106 for the less affected children ($p < 0.001$); the respective social development scores were 96 and 121 ($p < 0.001$), the speech scores 94 and 112 ($p < 0.003$), coordination scores 89 and 107 ($p < 0.001$), the performance scores 89 and 105 ($p < 0.01$), the practical reasoning scores 78 and 89 ($p < 0.005$) and the global I.Q. values 88 and 106 ($p < 0.001$). On the whole, the results of mental assessment showed a wider difference (Table 4) in the mean scores of the described subgroups of hypothyroid children than the discrimination previously found between the whole group of patients and controls (3). The predictive value of the proposed index holds significantly through time (correlation between scores of the 43 children at the age of 18 months and 7 yr: $r = 0.60$, $p < 0.01$).

The two subgroups did not differ in terms of age when therapy started, initial thyroid hormone dosage, or, as far as could be assessed, compliance. They were similar in their biochemical parameters at the age of 45 days and 3, 6, 12, and 18 months (Table 5).

Socially, the groups were different, having Hollingshead's scores of 54 *versus* 45 ($p < 0.07$). The more affected children came from less educated families. However, the correlation between I.Q. and Hollingshead's scores was much lower for the more affected children ($n = 16$, $r = -0.139$) than for the less affected patients ($n = 27$, $r = -0.647$). This difference is significant ($p < 0.067$), perhaps indicating that more affected patients do not benefit as much from the higher status of their parents because of specific physiological condition.

DISCUSSION

A relationship between the thyroidal status of CH patients at birth and their mental outcome has been suggested in several recent reports (17–19). Murphy *et al.* (17) showed that children who had a low T_4 and triiodothyronine did significantly less well on the McCarthy general cognitive index at 3 yr, and noticed that children with very delayed bone age also did relatively poorly (17). This was suggested long ago by Wolter *et al.* (18) and more recently confirmed by Rovet *et al.* (19). The use of the combined measures of serum T_4 and precise bone surface measure permit the selection of children who might benefit from psychological assessment. Their early identification would allow the physician to make a reasonable prediction of a lower range DQ outcome and permit early provision of specific support for optimal development. We would suggest that the parents be informed so that their cooperation can be maintained throughout childhood development; they might be more compliant with therapy and keep a positive attitude even if, as predicted, the performance of their child may not reach the level of his siblings or his peers.

Our results also emphasize the success of a decade of newborn

Table 3. *Global WISCR IQ value at age of 7 yr for 43 infants with congenital hypothyroidism treated by 1 month of age*

Newborn risk criteria	No. of children with I.Q. <90	>90
Bone surface < 0.05 cm^2 and T_4 <2 μg/dl	10	6
Bone surface > 0.05 cm^2 and/or T_4 >2 μg/dl	3	24
Total	13	30

Table 4. *Mental outcome in infants with congenital hypothyroidism relative to newborn risk criteria*

Age (yr) in year	T_4 and bone surface measures: T_4 <2 μg/dl and bone <0.05 cm^2 n	Mean IQ	IQ distribution	T_4 >2 μg/dl and/or bone >0.05 cm^2 n	Mean IQ	IQ distribution
3	17	91 ± 4*	(61–120)	40	103 ± 2	(81–140)
5	14	88 ± 3†	(60–109)	30	104 ± 2	(84–125)
7	16	86 ± 3†	(49–98)	27	102 ± 2	(75–128)

* $p < 0.01$ (SEM).
† $p < 0.001$ (SEM).

Table 5. *Comparison of follow-up thyroid function test results in less affected and more affected infants as assessed by newborn risk criteria*

Age at testing	Less affected infants						More affected infants					
	n	T_4 (μg/dl)	*n*	TSH* (μU/dl)	*n*	T_3† (ng/dl)	*n*	T_4 (μg/dl)	*n*	TSH (μU/ml)	*n*	T_3 (ng/dl)
Pretreatment	27	1.95 ± 0.3	27	565 ± 52	20	95 ± 15	16	0.50 ± 0.1‡	16	582 ± 5	13	43 ± 15§
45 days	11	6.8 ± 0.7	9	41 ± 20	6	260 ± 63	8	6.3 ± 0.5	4	9.3 ±	4	331 ± 77
3 mo	12	12.2 ± 1.6	6	20 ± 5	5	162 ± 14	6	11.2 ± 3	2	6.5 ± 0.8	1	118
6 mo	26	11.6 ± 0.9	24	19 ± 4	25	147 ± 11	15	12.1 ± 1.2	15	16 ± 6	15	161 ± 9
12 mo	27	12.8 ± 0.9	27	9 ± 2	23	165 ± 8	16	11.4 ± 1.4	15	17 ± 4.7	9	148 ± 16
18 mo	14	14.0 ± 1.0	15	16 ± 5	14	144 ± 9	12	13.2 ± 1.6	12	5 ± 1.1	11	170 ± 11

* $p < 0.001$; ** $p < 0.02$

* Thyrotropin stimulating hormone.

† Triiodothyronine.

‡ $p < 0.001$ (mean ± SEM).

§ $p < 0.02$ (mean ± SEM).

thyroid screening: the less affected children reached scores comparable to controls and siblings in most of the assessment, and there was no need for psychological follow-up. Even though the more affected patients might be slightly delayed in development, they reach better scores than those reported for nonscreened infants with CH. Hulse (20) reported a mean I.Q. of 79.5 for 99 children with CH diagnosed before screening and evaluated with the W.I.S.C.R. Close follow-up will permit us to further substantiate our data and to assess the importance of specific guidance intervention.

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